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TITLE: Effect of a Stress Reduction Intervention on Psycho-Immuno-Endocrine Parameters in Early Stage Breast Cancer

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13. ABSTRACT *(Maximum 200 words)*

This is a Career Development Award which provides salary support for research and training done under a separately-funded project, Grant Number DAMD 17-94-J-4475 (P.I. Dr. James R. Hebert), called the Breast Research Initiative for DetermininG Effective Skills (BRIDGES), which focuses on skills for coping with breast cancer, and consists of a prospective randomized intervention trial with women ages 65 or less, having stage 1 or 2 breast cancer, randomized to one of three arms: 1) a modified form of the University of Massachusetts Medical Center mindfulness meditation-based Stress Reduction and Relaxation Program (SR&RP); 2) a nutrition education program developed specifically for BRIDGES; and 3) a usual-care control group. Outcome parameters are: 1) psychological and behavioral indices of function and coping; 2) quality of life measures; 3) compliance with the interventions and medical treatment regimens; and 4) immunological/endocrinological measures consisting of cytokines and melatonin. Over the past year, I have been involved in the following aspects of the project: writing manuscripts, serving on the Executive and Steering Committees, data cleaning and analysis, hypothesis testing, overseeing sample collections and analysis for the melatonin assays, quality control of the melatonin assay, and taking a two-semester introductory/intermediate level biostatistics course in the Dept. of Public Health.

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Abstract presented at the American Psychiatric Association Annual Meeting (symposium) - May, 1997

Abstract of presentation at Univ. of Med. Center Breast Cancer Conference - September, 1997

Abstract presented at the Era of Hope Meeting - November, 1997

Book chapter: "Meditation, Melatonin, And Cancer"

## INTRODUCTION

This four-year Career Development Award provides me with salary support for a training practicum done as part of a separately funded research project, Grant # DAMD17-94-J-4475 titled "Effects of Meditation-Based Stress Reduction in Younger Women with Breast Cancer". The study is called the **Breast Research Initiative for DetermininG Effective Skills (BRIDGES)**, focusing on effective skills for coping with breast cancer. The Principal Investigator for that project, James R. Hebert, MSPH, Sc.D., is my mentor on the Career Development Award. Please note that my application for this award was originally written in association with another project application which was not funded. Therefore, the title for my DAMD # does not correspond with the title of the project listed under Dr. Hebert's DAMD #. The original Statement of Work was revised as part of the 1996 annual report in order to correspond with the work actually being done as part of the funded project. The section on Work Accomplished is structured according to the timeline for the project. The results of the project are included in Dr. Hebert's annual report. I have extracted portions of that report which apply to the work I have done.

Following is a summary of the background and overall goal for my Career Development Award. The background is extracted from the project grant. Also included are the specific aims and hypotheses from the project grant.

### Background

An increasing body of research literature has shown that psychological states have clear impact on recovery and quality of life in women with breast cancer. Psychosocial variables such as emotional expression, coping style, and factors related to social support appear to have the most promise for improving quality of life and increasing the probability of prolonged survival. Also, there is a small body of evidence indicating that women with breast cancer receiving psychosocial interventions may derive a beneficial effect in respect to improved response and disease-free survival.

In light of these findings, there is an important need for the development of cost-effective psychosocial interventions for women with breast cancer. A successful intervention will be one that can reduce emotional distress, promote effective coping, and be useful and adaptable to the diverse population of women with breast cancer. The BRIDGES study seeks to adapt the University of Massachusetts Medical Center's Stress Reduction and Relaxation Program (SR&RP) for women with breast cancer. The SR&RP is a well-established intervention program with demonstrated effectiveness in improving emotional status and quality of life in individuals with a variety of serious medical problems. The program is educational in format. It has been offered to diverse populations, including general hospital setting, an inner city clinic and a prison population.

The BRIDGES study addresses aspects of two of the fundamental research issues in

psychosocial aspects of breast cancer: 1) the psychosocial impact of breast cancer, particularly on quality of life and ability to cope; and 2) identifying techniques for delivering cost-effective care to facilitate recovery, improve quality of life, and possibly improve immune response after receiving a diagnosis of breast cancer. The study is designed to evaluate the effectiveness of the SR&RP, previously untested in this population of patients, and compare it to a usual-care group as well as a nutrition education program which is an inactive attention control relative to the SR&RP but may have active therapeutic aspects as well.

#### Overall goal of the Career Development Award

My overall goal is to investigate a well-established short-duration psychosocial intervention, the University of Massachusetts Medical Center (UMMC) SR&RP for use with women with breast cancer. Outcome measures of particular interest are those relating to adjustment to illness, quality of life, ability to comply with medical recommendations, immune parameters related to tumor surveillance and potentially to the intervention, and an endocrine parameter, melatonin, which is believed to be an oncostatic agent involved in the immunological response to breast cancer and may potentiate the response to chemotherapy, thus representing a biologic predictor of good prognosis. My particular focus is on the psycho-physiologic interactions involved in coping with breast cancer, and on using the associated outcome measures to test the study hypotheses. This goal is achieved by working on the BRIDGES research project as a practicum experience. My mentor is Dr. James R. Hebert, the Project P.I. As noted above, the project is separately funded by your agency.

#### Specific Goals of the Career Development Award:

To gain experience and training in the following aspects of conducting this kind of research, which is a trial of a randomized psychosocial clinical intervention using psychosocial and biological outcome parameters: 1) research study design; 2) start-up planning; 3) recruitment; 4) delivering the intervention(s); 5) data collection and analysis; 6) hypothesis testing; and 7) reporting results via manuscripts.

#### Overall Goal of the BRIDGES study

The primary goal of this study is to test the efficacy of the well-established short-duration mindfulness meditation-based Stress Reduction and Relaxation Program (SR&RP) in women 65 years or less who have stage I or II breast cancer diagnosed within the past two years. The SR&RP intervention aims to influence a number of well-defined psychosocial factors which are suggested by a growing body of evidence as critically important for adjustment to a potentially life-threatening diagnosis: enhancement of quality of life and potentially enhancement of resistance to disease progression and survival in women with breast cancer. The study consists of a prospective randomized three-arm design with a target goal of 60 women enrolled into each arm: 1) the SR&RP intervention, tailored to focus on issues specific to breast cancer; 2) a nutrition education program which will serve as an inactive attention control with regard to the psychosocial outcome measures and as a potentially active intervention with regard to effect on some outcome measures, such as immune parameters (see

Aim 2); and 3) a usual-care control group.

### Specific Aims and Hypotheses of the BRIDGES study

Aim 1: to test the effect of the SR&RP on quality of life (QOL), emotional awareness and expression, coping strategies and related perceptual and behavioral factors, and compliance with the intervention and medical treatment recommendations in women  $\leq 65$  years who have been diagnosed with Stage I or II breast cancer within the past two years. Because the SR&RP and NEP groups will have an equivalent time commitment and the NEP will provide none of the essential components of the SR&RP, we will be able to examine the effect of the SR&RP intervention as distinguished from non-specific group/therapist factors.

Primary Hypothesis: the SR&RP intervention will result in improved QOL and ability to cope, compared to either the NEP or usual care alone.

Secondary Hypothesis: the SR&RP intervention will result in : a) improved perception of self and self in relationship to the world, as measured by increased self-esteem, sense of coherence, and decreased loneliness; b) a corresponding reduction in mood disturbance (e.g., anxiety and depression); c) increased use of active-behavioral and active-cognitive coping strategies, as measured by the Dealing with Illness Coping Inventory; and d) increased compliance with treatment regimens as compared to usual care alone.

Aim 2: to test the relative effect of the SR&RP versus NEP and usual care on endocrine/immune parameters specifically related to cytokines that activate Natural Killer (NK) cells and melatonin levels, which may in turn affect the response to breast cancer. Because NK activity may be related to recurrence, we have previously shown that low-fat diets enhance NK activity <sup>1</sup> and we have preliminary data that meditation may affect melatonin levels <sup>2</sup>. Therefore, we are particularly interested in the relative differences between the two intervention groups, SR&RP and NEP, relative to usual care alone.

Specific Hypothesis: Relative to usual care, the SR&RP intervention will be associated with enhanced immune responsiveness and enhanced melatonin levels in women with Stage I or II breast cancer enrolled in this study. This will be reflected by an increase in the production of cytokines, e.g. Interleukins 2 and 4, which activate NK cells, and Interferon, which activates macrophages, and melatonin levels as measured by the primary urinary melatonin metabolite, 6-sulfatoxymelatonin.

Aim 3: to determine if the study effects (described in Aims 1 and 2), along with maintenance of the intervention practices, persist over 1-2 years of follow-up.

Specific Hypothesis: psychosocial and immunological changes will be maintained over time and related to on-going practice of the SR&RP self-regulatory strategies and

behaviors, and NEP dietary practices.

## **WORK ACCOMPLISHED**

### **Task One: Run-in Phase, Months 1-3**

a. Conduct additional focus groups and preliminary data as needed. Analyze preliminary data previously gathered in support of this study and in preparation for the study.

A preliminary focus group was conducted with a community-based breast cancer support group in order to gather data that would inform certain decisions such as timing of recruitment, and timing and length of the intervention itself. I conducted the focus group with another co-Principal Investigator. This data was then used in developing the recruitment protocol as well as the intervention protocol.

b. Based on focus group interviews and preliminary studies, the existing SR&RP intervention will be adapted and expanded so that the content of the program will be most useful to women with early stage breast cancer.

I was involved in the development of the modified SR&RP intervention, which consisted of adding 6 additional sessions, one session before and five after the standard SR&RP program which is 8 weeks long. The 8 sessions, provided as part of the standard stress reduction program already offered at the University of Massachusetts Medical Center, are larger groups composed of 30-40 people with a wide variety of medical or psychiatric problems, not just breast cancer. The 6 sessions were "wrapped around" the standard program and were given only to the women in the BRIDGES study. These were small group sessions composed of 6-12 women. The purpose of these sessions is to reinforce the practices taught in the program and give the women a chance to talk about issues specific to breast cancer.

c. Participate in finalizing and pilot-testing instrument materials.

I was involved in developing sections of the baseline questionnaire, particularly pertaining to medical and psychiatric information, as well as finalizing the acquisition and preparation of all of the psychosocial instruments for use in the study.

d. Develop the protocol for collection and of the 24-urine samples for the melatonin assays and for analyzing the results. Develop a familiarity with the technical aspects of conducting this assay and any possible confounding variables, such as oral agents which elevate melatonin levels.

I researched and developed the procedure for collection of 24-hour urine specimens, delivery of the specimens to the laboratory which is conducting the melatonin assays for the study, storage of specimens, and data analysis of the results. Also, I oversaw a trial run of assays

which was conducted by the laboratory using samples from a preliminary study which I conducted with another co-investigator. This included working with the laboratory technician and Project Director to ensure that the assay procedure was feasible and to resolve any potential problems with it. I continue to oversee any issues which arise in relation to the assay and sample collection for it. This includes checking the results and monitoring for any factors which might confound the results (such as oral agents which elevate melatonin levels).

e. Participate in developing and creating the recruitment videotape and other recruitment materials (e.g. brochures), along with Drs. James Hebert, Judith Ockene, Jon Kabat-Zinn, and the Project Director, Susan Druker.

I attended weekly meetings during the first approximately 6 months of the study. The meetings were attended at various times by site coordinators from the four participating sites, the Principal Investigator, Project Director, and other investigators. I also chaired or participated in sub-committees involved in: 1) developing screening questions and baseline questionnaires to be used in recruiting and at the baseline assessment; 2) writing the script for the recruiting videotape and being involved in producing the videotape which was then used at the participating sites; 3) writing and producing other recruitment materials such as the brochure and descriptions of the individual interventions themselves; and 4) developing the actual recruitment procedure with specific modifications for each site.

f. Develop the recruitment protocol, along with Drs. Hebert, Kabat-Zinn, Clemow, and the Project Director, Susan Druker.

As part of developing the recruitment protocols, I researched the effectiveness of recruitment methods used in other studies similar to ours and contacted other investigators involved with those studies who were able to provide valuable information. I was part of a working group, composed of Dr. Hebert and the Project Director, Susan Druker, which developed the procedure for recruiting subjects at each of the study sites. I had the specific task of researching recruitment strategies which were specific for two of the sites, Medical Center of Central Massachusetts and Fallon Clinic. This involved interfacing with the various medical/surgical specialty clinics involved in seeing women with breast cancer, as well as the departments involved in keeping databases which could identify potential subjects for the study. I worked with Susan Druker on integrating all of the strategies for all the sites in the study.

Also, I was involved in developing the screening questionnaire used during the recruitment process.

g. Participate in training and supervising the Site Coordinators who will be conducting telephone and in-person interviews of the subjects. This will be done with Dr. Lynn Clemow, Co-Principal Investigator, and Susan Druker, Project Director.

I was involved in supervising and training Susan Druker and the Site Coordinators in developing the procedures for telephone and in-person interviews, along with Dr. Clemow. Also, I continue to be available for on-going consultation in screening and other clinical issues as needed.

h. Participate in setting up the database and analysis on run-in phase data, along with Dr. James Hebert and the biostatisticians on the project.

I have been involved in setting up the database and conducting process-related analyses (to ensure that data collections steps have occurred) and simple univariate analyses, under the supervision of Dr. Hebert and along with the study biostatisticians. I attend regular data analysis meetings to set up and develop the database and database management plan.

### **Task Two: Recruitment, Months 4-21**

a. Serve as a member of the Executive Committee, composed of myself, Dr. Hebert and Susan Druker, Project Director, to track the recruitment process and deal with any issues that may arise. Investigate any potential new recruitment sites as needed. Work on maximizing opportunities for recruiting subjects and improving the effectiveness of the recruitment process.

I have performed this task as described above. These meetings will be ongoing throughout the study. One of the decisions made by the committee, after consulting with other study investigators, was to raise the age inclusion criteria to extend to women ages 65 or less. The rationale for this decision is explained in Dr. Hebert's report. Also, we extended the criteria for period of diagnosis to include women diagnosed within the past two years.

During 1995-1996 I explored options for other potential recruitment sites, particularly at three facilities in the nearby area. I was responsible for all of the initial contact work with the physicians and appropriate personnel at those facilities. I went with Dr. Hebert and the Project Director, Susan K. Druker, to make presentations at two of the facilities and meet with personnel who would be involved in recruiting. The two facilities, Burbank Hospital (an affiliate of UMMC and Bay State Medical Center in Springfield, MA.), have agreed to informally recruit subjects for the study. The decision was made to leave the agreement informal rather than set up formal sub-contract sites.

178 women have been enrolled into the study, representing 99% of the recruitment goal (which was 180). Eighteen (10%) have dropped out of the study as of 10-1-97, representing a 90% retention rate. We estimated that our retention rate would be 80%. We feel our high retention rate is due to the positive response of our patients to this study, our recruitment methods, and the expertise of our Project Coordinator and site coordinators.

b. Serve as a member of the Steering Committee, which meets quarterly and is attended by nearly all personnel involved in the study. These meetings are held to make some study

decisions and maintain communication and cohesiveness among study personnel.

I have been involved in planning and participating in quarterly Steering Committee meetings as described above. These meetings will be ongoing throughout the study.

**Task Three: Intervention, months 6-27:**

a. Provide the six "booster" or "wrap-around sessions as part of the modified SR&RP intervention. These 6 sessions occur one before and five after the standard 8 week SR&RP program given at UMMC.

During the first intervention cycle, I and another co-investigator provided the 6 "wrap-around" or booster sessions for the women randomized to the stress reduction intervention arm. Beginning with the second intervention cycle, I began providing the 6 sessions alone. These 6 sessions occur before and after the standard stress reduction program, as explained above. All six intervention cycles have been completed, each lasting 14 weeks total (8 standard sessions plus 6 "wrap-around" sessions). In general, the women have been reporting that the intervention has been quite beneficial.

For quality control purposes, two senior instructors from the Stress Reduction and Relaxation Clinic, who teach in the 8-week program, sat in and observed some of the sessions provided by me in the sixth intervention cycle. They also reviewed audiotapes from two other sessions, also occurring in the sixth cycle. They met with me to provide comments and to discuss how the two segments of the intervention are integrated. In general, we have agreed that the integration has worked well and have been able to further conceptualize the model we are using.

b. Take a two-month internship training program in giving the SR&RP as an intervention. This is provided by the Stress Reduction Clinic at UMMC, under the direction of Saki Santorelli, EdD.

In 1996, I took a two-month training program in giving the SR&RP as an intervention.

c. Follow the progress of the nutrition education program (NEP) through the Executive and Steering committee meetings, where the nutritionist who gives the NEP will present progress reports.

I am aware of the progress of the nutrition education program (NEP) through the regular Executive Committee meetings and Steering Committee meetings, where the nutritionist who gives the NEP presents progress reports.

d. Continue to serve on the Executive and Steering Committees to deal with ongoing administrative study decisions and issues.

As noted above, these are ongoing meetings. The study is primarily administrated by virtue of the functioning of the Executive Committee, a working committee composed of myself, Dr. Hebert, and Susan Druker, the Project Director. Dr. Clemow and the study biostatisticians also attend as needed.

**Task Four: Follow-up, months 8-46**

a. Continue to oversee the melatonin sample collection and assay, as well as storage of samples, along with Susan Druker, Project Director.

This is being done as described. The assays are done in a batch when approximately 50 samples have been accumulated. I have been involved in quality control issues to maintain consistency and accuracy of the assay results and to insure that there is adherence to the assay protocol. This has involved periodic consultation with Stockgrand, Ltd., Surrey, England, the company which developed the assay and provides us with the kits. Over the past year, there have been some particular technical issues with regard to quality control of the assays which have been resolved by working closely with the laboratory at Univ. of Massachusetts and with Stockgrand, Ltd.

b. Participate in tracking ongoing data collection, validating the data according to each individual instrument and begin preliminary testing of study hypotheses.

Currently, I and other members of the research group are involved in validating the data according to each individual instrument to make sure that the data makes sense and is consistent. Also, along with Dr. Hebert and the study biostatisticians, I am involved in conducting descriptive, univariate data analyses and preliminary testing of study hypotheses. Also, in the past year I have been involved in data cleaning and updating data files.

c. As noted above, continue to oversee study progress by serving on the Executive and Steering Committee meetings, and being involved in administrative/study decisions.

This is being done as described above.

d. Additional education

In September 1997, I began taking an introductory course in biostatistics at Univ. of Massachusetts, with the goal of enhancing my ability to participate in data analysis and testing of study hypotheses in this project. I completed the second semester or intermediate level of this course in Spring, 1998. This was an additional activity which was not specified in the revised Statement of Work.

**Task Five: Final Data Analysis, Months 47-51**

Along with Drs. Hebert and Clemow and the study biostatisticians, the following tasks will be done:

- a. Participate in performing exploratory analyses to test for adherence to model assumptions.
- b. Participate in testing study hypotheses.
- c. Participate in conducting post-hoc analyses of study data.
- d. Work with other study investigators and personnel in preparing manuscripts.

Up to and including the past year, I have been involved in performing exploratory analyses to test study hypotheses and analyzing preliminary data which were used in manuscripts and presentations as follows:

Previously, I co-authored a paper reporting on preliminary data gathered prior to submitting the original grant application <sup>2</sup> in which we discussed one of the study hypotheses, namely that the SR&RP intervention would be associated with enhanced melatonin levels.

During 1996-1997, I was the first author of a second paper on another preliminary study conducted prior to the BRIDGES study, which related to and supported the same hypothesis. That study is in submission and has not been published yet.

During 1996, I co-authored two book chapters (first and second author), both of which discussed the BRIDGES study. The first chapter <sup>3</sup> discussed the use of the SR&RP intervention as an intervention for cancer patients. The chapter was primarily descriptive and briefly mentioned BRIDGES. No data was presented.

The second book chapter <sup>4</sup> discussed our hypothesis about meditation and melatonin. BRIDGES was discussed and preliminary data on melatonin levels from 82 subjects at baseline and 4-month follow-up (approximately 2-3 weeks after the intervention) was presented: crude mean difference for each group in  $\mu\text{g}$  per 24 hours, with the standard deviation of the difference (not the overall standard deviation) shown in parentheses was: SR&RP = +1.58 (11.87); NEP = +3.26 (9.03); and usual-care = -1.06 (10.30). Note that the standard deviation of the difference is approximately 1½ times as large as the standard deviation for the cross-sectional difference.

Due to the large variability in the data, the overall effect was not statistically significant ( $p = 0.33$ ), nor was the effect due to either of the interventions relative to usual care: NEP ( $p = 0.15$ ) and the SR&RP ( $p = 0.34$ ). However, we believe the results are suggestive because they were obtained in a randomized trial where background factors are controlled by design and in which we would expect less of an effect than in a highly self-motivated group of experienced meditators - hence more relevance to the experience of average people. Also, these results were obtained on less than half of the projected sample and cover only the first four months.

I have been either first author or co-author for three 1997 presentations:

a) co-author on paper presented at Society for Behavioral Medicine annual meeting in March, 1997. This was a preliminary report (n=75) of baseline and four month scores on psychosocial measures.

b) first author on symposium presentation at the American Psychiatric Association annual meeting in May, 1997. This was a preliminary report of baseline and four month data on psychosocial measures for a subset of the total sample.

c) co-author of presentation at breast cancer conference held at Univ. of Mass. Medical Center on September 23, 1997. This was presented by a co-P.I., Dr. Lynn Clemow, and involved presentation of preliminary data of baseline, four month and one-year data on psychosocial measures and dietary behavior, using a subset of the total sample.

d) co-author of poster to be presented at "Era of Hope" meeting on 11-3-97, which will involve baseline and four-month data of a subset of the sample (n=107).

Over the past year, I and the other members of the research group have been involved in data cleaning, updating data files, and conducting additional hypothesis testing of preliminary data.

We are nearly ready to begin manuscript writing for the dietary and psychosocial data. Also, I have been involved in preliminary analyses of the melatonin data. There are still two more assays of melatonin samples to be conducted. These and other analyses are on-going.

For the 1999 Society of Behavioral Medicine meeting, we have submitted two abstracts, one on change in dietary fat intake and body weight, and the other concerning effects on health-related quality of life and psychological factors.

## **RESULTS**

**Psychosocial Well-Being:** To date, the Stress Reduction and Relaxation Program (SR&RP) intervention appears to produce the most consistent improvements in psychosocial well-being. The usual treatment group (UC) appears to be associated with a slight deterioration and the Nutrition Education Intervention (NEP) is associated with psychosocial outcomes intermediate between the SR&RP and UC groups. For example, we observed an increase of 1.4 vs. very little change (+0.7) in NEP and a reduction of -1.9 in UC ( $p=0.0007$ ) in active-cognitive coping as assessed by the Dealing With Illness questionnaire (a coping inventory). Other variables which showed similar significant results for the SR&RP are Depression (Beck and SCL-90-R), Spirituality (FACT-B), Helpless/hopeless thoughts (Mental Adjustment to Cancer questionnaire), Emotional Expression (Courtauld scale), and emotional distress (SCL-90-R GSI and five subscales). Social support and Active-cognitive coping were significantly better in the NEP than UC group. The usual effect size (pre-post GSI on the SCL-90-R) for the standard SR&RP offered clinically at Univ. of Massachusetts ranges from -0.25 to -0.57 (34-54%). These data come from published studies in a variety of populations of self-selected

participants (immediate treatment vs. wait-list controls) <sup>5-8</sup>. In this study, using an augmented version of the same program, the intervention produced a reduction of 0.12 (roughly 25% change) suggesting that the treatment effect might be larger in a design with Breast Cancer patients who select SR&RP instead of being randomly assigned to it.

At one-year follow-up, we found significant sustained benefits of the SR&RP intervention for the overall sample on the Spirituality and Emotional Well-Being subscales of our quality of life (QOL) instrument, the FACT, and Active-Behavioral Coping from the Dealing with Illness questionnaire <sup>9</sup>. In an effort to explore the individual differences that may have modified the intervention effects (particularly those that might bear on the process of self-selection) we have conducted some preliminary subset analyses. Women with high baseline emotional distress (Beck Depression scores > median) were much more likely to benefit significantly at post-treatment and to have a more enduring effect after one year of the SR&RP vs. the two comparison groups on a variety of psychosocial measures including : Higher Active-behavioral ( $p=.01$ ) and Active Cognitive Coping ( $p=.03$ ) and lower Avoidant Coping ( $p=.008$ ); Less Helpless-Hopelessness ( $p=.04$ ); higher Spirituality ( $p=.01$ ) and Emotional QOL ( $p=.005$ ), higher social support ( $p=.003$ ), and less distress on the GSI and six subscales of the SCL-90-R. ( $p=.05-.01$ ).

**Diet-Related Outcomes:** Of all women randomized, 154 had complete baseline, 4-month (immediately post-intervention), and 12-month dietary data and 159 had body weight data for each time point. Though not focused on weight loss, we sought to examine change in weight partly because of the importance of weight as a prognostic indicator and partly as a construct validation of the dietary data. Changes in percent of energy as fat (%EF) and body weight (kg) were analyzed using PROC GLM in SAS, controlling for baseline value of the dependent variable. At 4 months, there were decreases of 5.6%EF and 1.3 kg in weight in the NEP versus slight increases in the SR&RP and UC ( $p=0.0002$ ). At 12 months there was a slight rebound in fat intake in the NEP (4.5%EF less than baseline versus no change in the SR&RP or UC,  $p=0.008$ ) but women had returned to their baseline weight. In 50% of women with high expectation there was a larger reduction in fat (-6.0%EF and -5.0%EF at 4 and 12 months, respectively,  $p<0.01$ ), but the same pattern in terms of body weight change. The results of this study show that large reductions in dietary fat can be achieved in such a randomized controlled trial and that the effect is larger in women who expect more of an effect from the intervention, indicating effect modification of the intervention by expectancy. Weight shows a pattern typical of many diet interventions, but it is notable that the weight gain typical of early-stage breast cancer patients was not observed <sup>10</sup>. Both of these findings could translate to improved survival over time <sup>11</sup>.

**Melatonin Excretion:** Because we do not have complete data from the 4-month measurement point and no data, as yet, from the 2-year point, the following results are not presented as a formal test of the hypothesis that melatonin production (as estimated by excretion of its primary metabolite, urinary 6-sulphatoxymelatonin) changes with NEP or SR&RP, but in a

more descriptive sense, broadly in support of pursuing the same study in the context of a self-selection trial. The assays are done in batches and as a result, 4-month samples from the last two intervention cycles have not been assayed as yet. Values presented are the least squares means of the change in melatonin (total  $\mu\text{g}/24$  hours) between baseline and 4-months on the 125 women with paired data obtained using PROC GLM in SAS. All analyses controlled for baseline melatonin value. Overall, results were consistent with an increase in both the SRC (+1.21  $\mu\text{g}/\text{day}$ ) and NEP (+1.54) and a decrease in the UC (-0.38), but not close to "statistically significant" ( $p=0.49$ ). In terms of magnitude of change, they are about one quarter to one half the size observed in our previous studies.

Additional analyses also considered surgical status (lumpectomy versus mastectomy), level of depression according to scores on the Beck Depression Inventory (BDI), Global Severity Index (GSI) from the SCL-90-R, and level of expectancy. Of the 105 women on whom we have paired melatonin data and data on surgical status, 84 (80%) had lumpectomies and 21 (20%) had mastectomies. While the relative (though technically non-significant) intervention effects persisted, the change in melatonin level between baseline and 4-months was significantly different between those with mastectomy (-2.50) and those with lumpectomy (+1.46) ( $p = 0.05$ ). For women who were in the lower half of depression, those in the SR&RP group appeared to have a larger change in melatonin level over the course of the intervention period than those in the other two groups: SR&RP = +3.55, NEP = -0.11, and UC = -1.16 ( $p = 0.34$ ). Women above the 50<sup>th</sup> percentile score on the GSI (greater severity of symptoms), all showed either a decrease or minimal change in melatonin between baseline and 4 months, regardless of intervention group: SR&RP = -0.39, NEP = -2.13, and UC = -0.78 ( $p = 0.82$ ). In this group, there appeared to be even larger differences according to surgical status: mastectomy = -3.50, lumpectomy = +1.29 ( $p = 0.05$ ). These results suggest that women given the SR&RP who have lower levels of depression are able to increase their melatonin production while the other two groups, NEP and UC, were not. Furthermore, the direction of change in melatonin according to intervention group was consistent with our hypothesis of increased melatonin for the SR&RP and NEP groups compared to the UC group and with results from two previous preliminary studies. In both of those studies, meditation practice was associated with a higher level of melatonin excretion. The magnitude of change observed here was less than half what was observed in those studies (about 1.2 vs. 2.3 to 5.8  $\mu\text{g}/\text{day}$ ), that a self-selection study in which the participants would presumably have higher motivation and level of practice, could show a greater change in melatonin level over the course of the intervention.

As part of the BRIDGES data management and analysis plan, we are in the process of assaying the remaining urine samples and developing additional analyses to take into account other variables, such as compliance with meditation practice and quality of life.

## **CONCLUSIONS**

In summary, we feel our progress on this grant has been excellent. As a group, we have been successful in recruiting 99% of our targeted total for subjects, with only 10% dropping out. Recruitment ended in December 1996 with a total of 178 subjects. The work accomplished has closely adhered to the Statement of Work outlined in the project grant.

We have received a no-cost extension for the following year. During this time period, we will continue to analyze the data, and in particular will perform the assays and analyses on the cytokines as well as completing the remaining melatonin assays with the corresponding analyses.

My experience working on the BRIDGES study by virtue of this Career Development Award has been invaluable. I have been involved in a substantial portion of the project at every stage of progress, and have had direct impact on the majority of the major executive decisions and design issues. The training and experience I am receiving can be generalized to other clinical psychosocial interventions with psychosocial and biological outcome parameters. I have had the pleasure of working with a superb, enthusiastic research group and have been extremely fortunate in having Dr. Hebert as a mentor. He has tremendous expertise, has been a marvelous teacher and his guidance as well as his presence have been a special gift.

I am very grateful to have had the opportunity to receive the training experience provided by the Career Development Award. I feel that this enabled me to develop the tools for doing meaningful research work that hopefully will have lasting benefit in terms of health and healing.

## REFERENCES

1. Hebert J, Barone J, Reddy M, Backlund J. Natural killer cell activity in a dietary fat intervention trial. *Clin Immunol Immunopathol*. 1990;54:103-116.
2. Massion A, Teas J, Hebert J, Wertheimer M, Kabat-Zinn J. Meditation, melatonin and breast/prostate cancer: hypothesis and preliminary data. *Medical Hypotheses*. 1995;44:39-46.
3. Kabat-Zinn J, Massion AO, Hebert JR, Rosenbaum E. Meditation. In: Holland JC, ed. *Textbook of Psycho-oncology*. New York: Oxford University Press; 1998:767-779.
4. Massion AO, Teas J, Hebert JR. Meditation, melatonin, and cancer. In: Shafii M, Shafii S, eds. *Melatonin in Psychiatric and Neoplastic Disorders*. Washington, D.C.: American Psychiatric Press, Inc.; 1998:261-294.
5. Kabat-Zinn J. An out-patient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *Gen Hosp Psychiatry*. 1982;4:33-47.
6. Kabat-Zinn J, Lipworth L, Burney R, Sellers W. Four year follow-up of a meditation-based program for the self-regulation of chronic pain: treatment outcomes and compliance. *Clin J Pain*. 1986;2:159-173.
7. Kabat-Zinn J, Massion A, Kristeller J, Peterson L, Fletcher K, Pbert L, Lenderking W, Santorelli S. Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. *Am J Psychiatry*. 1992;149:936-943.
8. Miller J, Fletcher K, Kabat-Zinn J. Three-year follow-up and clinical implications of a mindfulness meditation-based stress reduction intervention in the treatment of anxiety disorders. *Gen Hosp Psychiatry*. 1995;17:192-200.
9. Clemow L, Hebert J, Massion A, Fowke J, Druker S, Kabat-Zinn J. A meditation-based stress reduction intervention for women with breast cancer: outcome and one-year follow-up. *Ann Behav Med*. 1998;20:52S.
10. Demark-Wahnefried W, Rimer BK, Winer EP. Weight gain in women diagnosed with breast cancer. *J Am Diet Assoc*. 1997;97:519-526, 529.
11. Hebert JR, Hurley TG, Ma Y, Hampl JS. The effect of dietary exposure on recurrence and mortality in early stage breast cancer. *Breast Cancer Res Treat*. 1998 (in press).

PA 19B

A MEDITATION-BASED STRESS REDUCTION  
INTERVENTION FOR YOUNGER WOMEN  
WITH BREAST CANCER

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This is a preliminary report (n=75) of an intervention for women <age 60 with Stage I or II breast cancer. Women were randomly assigned to one of 3 groups: 1) Stress Reduction group, based on the U. Mass. Stress Reduction and Relaxation Program, plus 6 group therapy sessions; 2) Dietary Intervention Group; and 3) Standard Care. The two group interventions have equivalent contact time, elements of group support, and are equally well-received by patients.

Comparisons were made between baseline scores on psychosocial measures and 4-months later (immediate post-treatment for the treatment groups), with repeated-measures ANOVAS. Significant (<.05) Group X Time interactions were found, showing an advantage for the stress reduction group on the following variables: Dealing with Illness Active/Cognitive Coping, and Avoidant Coping; the Spirituality scale of Quality of Life (as measured by FACT-B); and the SCL-90 hostility scale. In addition, in preliminary analyses, similar trends (p=0.1 or less) were found for physical and functional dimensions of Quality of Life and SCL-90-R scales measuring anxiety, depression, interpersonal sensitivity and overall distress (GSI). Overall, the measures suggest some specific beneficial effects of a psychological/stress reduction intervention over a credible group dietary intervention with younger women with breast cancer.

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ogy. This review will discuss studies on the emotional consequences of the following tests specific to breast cancer: 1) risk assessment for the BRCA1 gene, 2) screening mammography, 3) follow-up testing for recurrence of disease.

Patients tend to overestimate the utility of screening and diagnostic tests, and often incorrectly perceive the significance of a "normal" test. Individual variations in coping style appear to be a key factor in determining different psychological responses to receiving information. Prospective evaluations of quality of life and patients' perceptions of diagnostic interventions are needed, as well as physician training to assess and address the specific psychological needs of patients.

#### No. 14B FERTILITY ISSUES IN WOMEN TREATED FOR BREAST CANCER

Randy S. Glassman, M.D., *Department of Psychiatry, Brigham & Women's Hospital, 75 Francis Street, Boston MA 02115*; Alison Fife, M.D.

##### SUMMARY:

For a woman of child-bearing age, a diagnosis of breast cancer carries both a physical and an emotional burden. The physical side effects of chemotherapy are numerous, and include potential effects on ovarian function, which affects fertility and sexual function, and may have implications for fetal anomalies. For example, female patients who have undergone bone marrow transplantation for acute myeloid leukemia have gone on to have successful pregnancies. Others developed ovarian failure and were unable to become pregnant. Infertility becomes an issue for these women, and carries with it the potential for comorbid psychological dysfunction for the patient, her partner, and family.

We review here the medical, ob-gyn, and psychiatric literature on fertility and the psychological and psychiatric issues in women who are anticipating or who have undergone treatment for breast cancer. The known effects of chemotherapy on ovarian function, and the available data on pregnancy outcomes will be reviewed. Additionally, the newer infertility treatments will be reviewed as they relate to decision making and psychological status. The potential for freezing embryos and possibly unfertilized eggs in the future will present women with new opportunities, but difficult and emotionally laden choices.

We will present information from interviews with women who have received chemotherapy for breast cancer, and who have either considered pregnancy or who have become pregnant. Psychiatric issues, comorbidity, and implications for treatment will be addressed.

#### No. 14C MEASURING DEPRESSION IN WOMEN WITH BREAST CANCER

Mary Jane Massie, M.D., *Department of Psychiatry, Memorial Sloan-Ketter, 1275 York Avenue, New York NY 10021-6007*; David K. Payne, Ph.D., Maria Theodoulou, M.D.

##### SUMMARY:

The most common types of psychological distress in women with breast cancer are depression and anxiety. Oncology staff members often ask consulting psychiatrists to recommend brief screening instruments that can be used to measure depression and anxiety and to assist them in learning how to rapidly identify patients most in need of psychiatric consultation. We have explored the use of two screening instruments (the Hospital Anxiety and Depression Scale [HADS] and a 100m visual analogue scale [VAS]) to measure psychological distress in 103 women with breast cancer and have ex-

plored correlations between patients' perceptions of their psychological distress and oncological staff members' perceptions of patients' psychological distress. The HADS tapped significant levels of distress that correlate with patients' subjective assessments of distress. The VAS correlated well with both the medical oncologist's and oncology nurse's ratings of the patients' distress, as well as with the HADS. The usefulness and limitations of brief screening measures to identify women with breast cancer who could benefit from psychiatric consultation will be described.

#### No. 14D NEW RESEARCH IN PSYCHOSOCIAL INTERVENTIONS FOR WOMEN WITH EARLY- STAGE BREAST CANCER: THE BRIDGES STUDY

Ann O. Massion, M.D., *Department of Psychiatry, University of Mass Medical Ctr, 55 Lake Avenue North, Worcester MA 01655*; James R. Herbert, Sc.D., Lynn Clemow, Ph.D., M.D. Wertheimer, M.D., Jon Kabat-Zinn, Ph.D.

##### SUMMARY:

An increasing body of literature indicates that coping skills and psychosocial function can have an impact on quality of life and possibly recovery for women with breast cancer. There is a need to identify effective coping skills and cost-effective psychosocial interventions to facilitate coping with breast cancer. The BRIDGES study at the University of Massachusetts Medical Center was designed to address these issues. The study involves randomization to one of three arms: a meditation-based stress reduction intervention, a nutrition education intervention, and an individual approach group, which essentially is a usual-treatment group. Inclusion criteria are stage 1 or 2 breast cancer, age 65 or less, and within two years of diagnosis. Outcome variables include psychosocial measures (coping skills, quality of life, anxiety, and depression) and biological measures (immunological consisting of soluble Interleukin-2 receptor, Interleukin 4, and Interferon-gamma; and endocrinological consisting of the urinary melatonin metabolite, 6-sulphatoxymelatonin).

The presentation will include a brief literature review and presentation of preliminary data from the BRIDGES study (baseline and 4-month follow-up).

#### No. 14E TREATING FAMILIES OF WOMEN WITH BREAST CANCER

Bonnie B. Greenberg, M.S.W., *Department of Social Work, Dana-Farber Cancer Institute, 44 Binney Street, Boston MA 02115*

##### SUMMARY:

Women being treated for breast cancer are faced with many challenges. Success in meeting these challenges is impacted by the reaction and involvement of the surrounding family/social system. This presentation will explore in detail the dimensions of family psychosocial assessment, unique breast cancer related issues, and appropriate psychosocial interventions.

A thorough, accurate assessment of the family's structure and dynamics is essential to effective intervention. Important areas of focus in assessing families with cancer include communication patterns, coping mechanisms, ability of members to support one another, individual and collective definitions of hope, potential role realignments, and pre-existing areas of family stress.

Family interventions should include the spouse/significant other, children, and/or parents/extended family, as much as is logistically possible. Treatment needs to be tailored to both the unique issues and developmental stages of the individual members as well as the

Dr. Lynn Clemow

The Effects of a Meditation-Based Stress Reduction Program  
in Women with Early-stage Breast Cancer

Lynn Clemow, Ph.D.

for the BRIDGES Study Group, James Hebert, Sc.D., PI

The Breast Research Initiative for determining Effective Strategies (BRIDGES) for coping with Breast Cancer is a 51-month randomized multi-center trial to test the effect of the UMass Stress Reduction Clinic (SRC) program and an attentionally equivalent Nutrition Education Program (NEP) on quality of life, a variety of psychosocial factors, dietary intake, melatonin, excretion, and circulating levels of cytokines. Recruitment ended in December, 1996 with a total of 178 subjects, 99% of the recruitment goal of 180 younger women (under age 65 years) newly diagnosed with early-stage (I or II) breast cancer, and a retention rate >90% thus far. Results presented here are the psychosocial and nutritional data, based on data from the entire sample who completed the 4-month assessment, and a series of the first 97 participants for whom we have 1-year assessments.

Overall thus far, the SRC intervention appears to produce improvements in a number of psychosocial factors. The no-treatment control group (UC) appears to be associated with a slight deterioration and the NEP produces results intermediate between the SRC and UC. These variables (from the 4-month data) include Active Cognitive Coping ( $p=.005$ ), Spirituality ( $p=.0007$ ), Beck Depression scores ( $p=.02$ ), as well as several indices of emotional distress measured by the SCL-90-R, including anxiety ( $p=.04$ ), Depression ( $p=.01$ ), Hostility ( $p=.01$ ), and the overall emotional distress scale ( $p=.01$ ). Many of these beneficial differences hold up significantly at 1-year, as well.

Large dietary changes were confined to the NEP: for example, there was a reduction of 7.2% of energy as fat in the NEP vs no change in either the SRC or the UC ( $p<0.001$ ). Though not meant to be a weight loss program, the NEP was associated with a loss of 1.59 kg ( $p=0.02$ ). This corresponds to a decrease in body fat equivalent to about 120 kcal of total dietary energy per day (about 60% of the reduction in total energy reported).

Results were consistent with the hypothesis that the SRC meditation approach would affect a range of psychosocial variables. The NEP intervention not only produces impressive results in terms of dietary change but is associated with results intermediate between the UC and SRC on several of the relevant psychological variables.

## **THE EFFECTS OF A MEDITATION-BASED STRESS REDUCTION PROGRAM IN WOMEN WITH EARLY-STAGE BREAST CANCER**

**Dr. James R. Hebert, Dr. Ann O. Massion, Dr. Lynn Clemow, Mr. Jay H. Fowke, Ms. Susan K. Druker, Dr. Judith K. Ockene, Dr. Jon Kabat-Zinn**

University of Massachusetts Medical School  
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The Breast Research Initiative for DetermininG Effective Strategies (BRIDGES) for coping with breast cancer is a 51-month randomized multi-center trial to test the effect of the UMass Stress Reduction Clinic (SRC) program on quality of life, a variety of psychosocial factors, dietary intake, melatonin excretion, and circulating levels of cytokines. The three-arm study also consists of a no-treatment control group (UC) and a Nutrition Education Program (NEP), attentionally equivalent to the SRC and designed specifically for BRIDGES. The NEP excludes all aspects of meditation that form the basis of the SRC but includes aspects of group support, education, and dietary change that could influence some or all of the outcome variables. Recruitment ended in December 1996 with a total of 178 subjects, 99% of the recruitment goal of 180 younger women (to age 65 years) newly diagnosed with early-stage (I or II) breast cancer, and a retention rate >90% thus far. Subjects were randomized in equal numbers to each of the three study arms. Randomization was blocked by: stage of disease (I or II); age (<45, 46 to 52, or 53 to 65 years); and medical center. The last of six intervention cycles of the NEP and SRC were completed in April of 1997.

Data on study outcomes and a number of relevant background factors and potential confounders or effect modifiers of intervention effects were collected at baseline, 4 months (just after the end of the interventions), 12 months, and 24 months. Currently, we have data on 107 women who have completed the 4-month assessment point. Salient results are summarized in Table 1.

**Keywords: Dietary Fat, Randomized Clinical Trial, Quality of Life, Affective Symptoms, Meditation**

This work was supported by the U.S. Army Medical Research and Materiel Command under DAMD17-94-J-4475 and DAMD17-94-J-4261.

Table 1: Summary of Changes by Intervention

Psychosocial Variables:	UC		NEP		SRC		p-values <sup>†</sup>			
	base-line	Δ*	base-line	Δ*	base-line	Δ*	Overall	UC vs NEP	UC vs SRC	NEP vs SRC
Active-Cognitive Coping (Dealing with Illness)	62.1	-2.7	62.5	0	62.4	+1.0	0.005	0.03	<0.001	0.43
Quality of Life (FACT-B)	118.9	-1.0	117.5	-0.2	111.2	+3.6	0.60	0.87	0.33	0.45
Spirituality	29.1	-1.5	27.4	-0.3	26.3	+3.4	0.004	0.58	<0.001	0.01
Depression (Beck)	7.7	-1.6	6.1	-0.3	8.9	-	0.11	0.45	0.15	0.04
						2.8				
Sense of Coherence	155.5	-4.1	155.2	-2.6	148.2	+3.2	0.21	0.70	0.09	0.22
Hostility (SCL-90)	0.26	+0.09	0.23	-0.02	0.29	-0.11	0.03	0.13	0.01	0.31
General Symptom Index (SCL-90)	0.38	-0.03	0.30	-0.01	0.47	-0.13	0.42	0.89	0.22	0.31
Nutritional Variables:										
fat (g/day)	69.7	-1.7	80.8	-21.1	71.6	+2.7	0.05	0.08	0.51	0.02
fat (% of energy)	33.75	-0.26	35.28	-7.26		+0.87	<0.001	<0.001	0.34	<0.001
					4.85					
energy (kcal/day)	1825	-48	2064	-199	1826	-2	0.42	0.78	0.76	0.57
weight (kg)	69.59	0.48	72.51	-1.59		-0.27	0.02	0.006	0.28	0.08
					2.85					

\* differences are the crude differences observed

† p-values are based on the difference adjusted for the baseline values

Thus far, the SRC intervention appears to produce an improvement in the psychosocial factors. UC generally appears to be associated with a slight deterioration, and the NEP is associated with results intermediate between the SRC and UC. As can be seen in the table, large dietary changes were confined to the NEP. Though the NEP was not meant to be a weight loss program, successful low-fat interventions usually result in some weight loss. The loss of 1.59 kg (3.51 lbs) in the NEP would correspond to a decrease of about 13.3g of body fat per day, the equivalent of about 120 kcal of total dietary energy per day (about 60% of the reduction reported).

Results are consistent with the hypothesis that the SRC meditation approach would affect a range of psychosocial variables. The NEP intervention not only produces impressive results in terms of dietary change but is associated with results intermediate between the UC and SRC on several of the psychological variables. There appears to be no effect of age on any study outcome, indicating that the effects of the interventions apply to older women in whom the incidence rate of breast cancer is the highest. Other studies have shown that effects of such interventions may increase over time. Therefore, there will be considerable interest in monitoring intervention effects at the one- and two-year time points. Results presented will extend and expand upon those shown here and we will discuss their implications.

# *Melatonin in Psychiatric and Neoplastic Disorders*

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## Chapter 11

### *Meditation, Melatonin, and Cancer*

Ann O. Massion, M.D., Jane Teas, Ph.D., and  
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**M**editation generally can be described as the process of intentionally focusing attention on the present moment with nonjudgmental awareness (Kabat-Zinn 1982, 1990, 1994). In this chapter, we will expand on the definition of meditation, using additional details on the types of meditation used in our studies, with emphasis on mindfulness meditation.

#### **Components of Meditation Practice**

Most meditative traditions include two, not necessarily exclusive, categories or components of practice: concentration and mindfulness (Kabat-Zinn et al., in press). Concentrative practices are used to develop one-pointed attention. Mindfulness practices begin

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with one-pointedness and then expand the field of awareness to include a range of inner and outer experience of the present moment that shifts from moment to moment (Kabat-Zinn et al., in press).

### Concentrative and Mindful Meditation

The following is an excerpt on the differences between concentrative and mindfulness practices from work we and other colleagues published elsewhere:

Examples of concentrative practices include: the use of mantras (sounds or phrases used repetitively to concentrate attention); koans (phrases or questions in the Zen tradition that are aimed at cutting through discursive thinking); and the breath, when . . . [these] serve as the singular, invariant focus of attention. Concentration practices can bring about profound states of calmness, inner stillness and nonreactivity of mind.

Mindfulness practices, exemplified in the vipassana (Goldstein 1976; Goldstein and Kornfield 1987; Kornfield 1993; Levine 1979; Thera 1962) and Soto Zen (C. Beck 1989, 1993; Suzuki 1970) traditions, cultivate an intentionally nonreactive, nonjudgmental moment-to-moment awareness of a changing field of objects [of attention]. Rather than becoming absorbed, as in concentrative practices which to a degree shut out the world, the practitioner attends to the full range of whatever is present in the field of his or her unfolding experience, no matter what it is. This makes mindfulness a highly practical inner orientation for people with busy, engaged lives, especially if they are faced with a life-threatening illness and all its accompanying emotional turbulence in addition to other life stressors. Mindful attention helps in facing and embracing all aspects of life, however painful or frightening, with increasing degrees of equanimity and wisdom. These qualities develop as the practitioner spends time each day in periods of silence and nondoing (formal meditation practice), with the focus on present-moment experience as it unfolds and then as the practitioner carries that moment-to-moment awareness into various aspects of daily living (informal practice). (Kabat-Zinn et al., in press, *italics in original*)

At some point, concentration and mindfulness may merge and become indistinguishable, as does the distinction between the meditator and the object of attention. As a result, meditation becomes a direct experience in the moment and *of* the moment, a way of being fully present, which can expand beyond the period of formal meditation to simply a way of being. In fact, one insight that can arise from the practice is the experience of connectedness, the sense of separation dissolving, whether it be between the "I" who is meditating and the object of attention (Kabat-Zinn et al., in press) or between the individual and the entire universe of beings, both animate and inanimate. Some teachers talk about reaching the space between thoughts. This dissipation of emotional reactivity, self-absorption, and self-preoccupation can give rise to profound feelings of well-being and unity (Epstein 1995; Kabat-Zinn et al., in press).

### **Transcendental Meditation**

Although the transcendental meditation (TM) technique may or may not be the same as mindfulness, some aspects of both concentrative meditation and mindfulness appear to be present in this technique. In TM, derived by Maharishi Mahesh Yogi from the Vedic tradition (Roth 1994; Maharishi 1990), the mantra is used in a way that frees the mind from a specific focus, which Maharishi (1990) described as allowing the attention to turn "inwards towards the subtler levels of a thought until the mind transcends the experience of the thought and arrives at the source of the thought" (p. 470). He noted that his systematic technique is "neither a matter of contemplation nor of concentration," asserting that both these activities "hold the mind on the conscious thinking level, whereas Transcendental Meditation systematically takes the mind to the source of thought, the pure field of creative intelligence" (Maharishi 1990, p. 471). Another description given by an experienced teacher trained by Maharishi is that the TM technique "allows mental activity to settle down to a silent state of awareness where the mind is calm, collected, yet fully expanded, fully awake, ... the simplest form of human awareness" (Roth 1994, p. 11).

In other schools of meditation, the practitioner may be trained first to stabilize attention through concentrative practice and then expand awareness through mindfulness practice.

### Goal- and Non-Goal-Directed Meditation

Confusion often arises around the question of whether meditation has a goal, largely because the answer is a paradox. In forms of meditation such as mindfulness and Zen, there is no particular state or goal to be achieved in meditation. The overall orientation is one of nonstriving and nondoing (Kabat-Zinn 1994; Kabat-Zinn et al., in press) in the context of being fully present and nonjudgmentally aware from moment to moment. This means observing and experiencing the full range of *all* sensations, emotions, thoughts, and states as they arise. The process is one of embracing experience rather than detaching from it, creating distance by judging it, or diminishing it by harnessing the present to the goals of the future.

The paradox lies in the fact that people *do* have various goals and motivations for learning meditation and for life in general. They may want to reduce their pain or anxiety, achieve a relaxed state, or develop an improved ability to cope with stress. They may even achieve some of these goals as part of their practice. However, part of meditation practice involves the insight that goals can come and go like "thought formations, something like clouds in the sky, beyond their personal meaning and content, just like all other thoughts in the field of awareness" (Kabat-Zinn et al., in press). As described by one meditation teacher (M. Blacker, personal communication, March 1996), goals can be "lightly held," in the sense that they are held for a time and then released when their time is over, in a tapestry of permutation and change. Just noticing that one has goals and at times is attached to them can be part of the practice. A revered Thai meditation teacher, Achaan Chah, was quoted as saying "Your only job is to stay in your seat (meditation seat). You will see it all arise and pass, and out of this, wisdom and understanding will come" (Kornfield 1993, p. 31).

Certainly, there are specific meditation practices that involve embodying or developing specific states or qualities, such as loving-kindness or compassion. But none of these are presented as the overall goal of practice. The TM technique involves the experience of transcendent or higher states of consciousness, but these are said to develop spontaneously and naturally as a result of the practice, not from individual effort to bring them about (Alexander et al. 1990).

Nondoing can be best explained as intention without effort. An example is the drowning person and the rescuer. The more the drowning person flails about in the water, trying harder and harder to stay afloat, the more he or she is in danger of drowning both himself or herself and the rescuer. However, in actuality, all the person needs to do is float, which requires no rescue at all but simply the intention to float and the disbanding of effort. Some action still is required in order to float, but it is different from trying harder.

Meditation is often taught through the use of paradox embedded in stories, particularly stories that end with a riddle or seemingly impossible question. One such story comes from the Zen tradition:

A young man went to the sensei (Zen master) at a monastery and said, "I wish to study to become like you, master. How long must I study?"

"Ten years," replied the sensei.

"Ten years! But what if I study twice as hard as the other students, master?"

"Well, then it will take you 20 years," replied the master.

"Twenty years! But what if I study night and day, master?"

"Then it will take you 30 years," replied the master.

"I don't understand," said the young man. "Why does it take longer if I work harder?"

"Because the task is not to work harder but to work *softer*. If you keep one eye fixed on your destination, it will take you twice as long, because then you will have only one eye left with which to find your way."

## Orientations of Meditation Practice

Along with the two components of practice, most meditative traditions have two possible orientations: meditation for the benefit, awakening, or enlightenment of oneself and meditation with the intention to transmit the benefit from oneself to all beings. There may be an emphasis of one over the other or a progression from one to the other. These two orientations, relationship to oneself and to others, are linked through the practice itself or the teaching. They are closely related to the "three jewels" of the Buddhist tradition (Gyatso 1985, p. 56): 1) the sense of being fully awakened (*buddha*), 2) the teaching (*dharma*), and 3) the community of beings (*sangha*) (Yeshe 1979). These three jewels can be seen as woven into the universal aspects of all human experience.

First is the direct experience of one's inherent wisdom and through that the realization of the vast potential inherent in all human beings. The word *buddha* actually refers to a "totally opened mind" (Yeshe 1979, p. 11), with the understanding that that capacity already exists in everyone and simply needs to be realized or revealed.

Second are the teachings that underlie the practice. The word *dharma* refers simply to understanding reality (Yeshe 1979), including understanding the nature of impermanence, of suffering, and of the ways to stop suffering. The literal meaning of *dharma*, a Sanskrit term, is "that which holds" (Gyatso 1984, p. 1). In this sense, *dharma* can be viewed as outer teachings that become inner realizations that hold, protect, and sustain the individual in daily life. For a person with cancer, it might mean the realization that he or she is more than someone with a disease, that the illness really is more background than foreground. Or it might mean the understanding that pain is not the same as suffering (i.e., that pain is the physical sensation and suffering is the perception of it), that the pain may be chronic but not necessarily the suffering. In understanding the nature of change and impermanence, a person with panic attacks may be able to let go of the need for controlling

the attacks and instead learn to cope by "floating" through them (Weekes 1969, p. 35).

Third is a sense of connection with a larger community beyond oneself and of being supported by this community. "Sangha consists of those who are endowed with wisdom and can help us along the way" (Yeshe 1979, p. 11). This term might mean people who support one another in their practice and are committed to fostering each other's personal growth, or it might mean a group of friends, doctors, nurses, or other health care professionals who help an individual cope with or recover from his or her illness (Yeshe 1979).

Meditation is sometimes mistaken for a solitary experience, as in the ascetic hermit meditating for years in a cave to the point of being unaware that bugs are eating his skin. Solitary experiences can be true in some cases or some traditions, but most traditions contain various aspects of the three elements described above. In this context, meditation is very much a practice done *in* the world, and the experience of practice can have therapeutic benefits similar to psychotherapy. In the following discussion, meditation is compared with relaxation strategies, such as biofeedback, progressive muscle relaxation, and visual imagery, and to two specific psychotherapies, cognitive-behavior and supportive-expressive therapy.

The major differences between schools of meditation practice often are more stylistic differences in the *emphasis* placed on one of the two components or orientations, or differences in the *order* of their presentation during meditation training. Other differences often can be explained by cultural and historical factors.

Finally, most meditative traditions have some schema or description of different stages or levels of consciousness that may be experienced at various stages of practice. These include the more commonly known levels of consciousness, such as waking, sleeping, and half-awake or hypnagogic states, but with additional levels beyond these, which are seen as evolving states according to the length or depth of practice.

In terms of meditation research, different effects may be seen depending on the particular stage of training of the subjects, the

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particular orientation at the time the measurements are taken, and the particular level or state of consciousness.

### **Meditation Compared With Self-Regulatory/Relaxation Strategies and With Other Psychotherapies**

Meditation, as used in clinical settings, can be distinguished from self-regulatory or relaxation strategies, such as biofeedback, progressive muscle relaxation, or visual imagery, primarily by the fact that in meditation there is no explicit goal, for relaxation or anything else. The actual practice may look similar; the focus on the breath, for example, might be done both as part of a meditation practice and as part of relaxation training.

Breathing retraining also is taught as part of cognitive-behavior therapy used to treat anxiety disorders (Moras et al. 1990). The difference is that, as with relaxation training, there is an explicit goal, namely to reduce anxiety or bring about a change in avoidance or phobic behavior. Also, breathing retraining, as taught in either relaxation strategies or cognitive-behavior therapy, usually is not presented as a way of being or general lifestyle, nor is it presented in the larger context of meditative practice as described previously.

Supportive-expressive group therapy (Classen et al. 1994; Spiegel and Spira 1991) originally was developed as a way to cope with recurrent cancer, again an explicit goal. However, part of the approach is to encourage patients to live as fully as possible, which has some similarity to the approach taught in mindfulness meditation. In addition, a breathing technique based on self-hypnosis is taught. This technique shares some features with meditation practice in the focus on the breath, but in supportive-expressive group therapy it is taught mostly for pain control. There is a large component of group support in supportive-expressive therapy, although in this case the community is defined by the illness. In meditation practice, group support is inherent in the concept of community but with a different focus than that of coping with cancer. In

mindfulness-based stress reduction programs, often taught in clinical settings in a group format, group support may occur but is not the predominant focus or stated goal.

Other differences between meditation and self-regulatory/relaxation strategies are presented in Table 11-1. Differences among meditation, cognitive-behavior therapy, and supportive-expressive group therapy are presented in Table 11-2. Both tables were adapted from work published by us and other colleagues (Kabat-Zinn et al., in press).

## **Meditation, Melatonin, and Cancer**

Because the many functions of melatonin have been well covered in the other chapters of this book, we will confine this discussion to our proposed relationship between melatonin and meditation, with the exception of a brief section on melatonin and cancer. Previously, we published our hypothesis and preliminary data suggesting that the pineal gland not only is photosensitive but also psychosensitive (Massion et al. 1995). The correlate would be that a psychosocial intervention such as meditation could influence melatonin levels. It should be noted that increased melatonin production might not necessarily reflect pineal activity alone, as there is some indication in the literature that some melatonin may be produced in extrapineal sites such as the gastrointestinal tract (Huether 1993, 1994).

### **Melatonin and Meditation Studies**

Various studies from the literature on either meditation or melatonin indicate that the two share several physiological effects, which are summarized in Table 11-3. For at least three of these effects, pain reduction, insomnia reduction, and anxiety reduction, a common underlying mechanism is suggested by the literature. Some of melatonin's effects have been shown to be mediated through the opioid system (Guerrero and Reiter 1992; Maestroni and Conti 1993). The mindfulness-based Stress Reduction and Relaxation Program (SR and RP) (Kabat-Zinn 1990, 1994; Kabat-

**Table 11-1. Meditation versus self-regulatory/relaxation strategies: major differences**

Meditation	Other self-regulatory/relaxation strategies
Orientation of nondoing, nonstriving, nonattachment to specific goals	Relaxation or coping with some specific condition is targeted as the goal (e.g., reducing anxiety, coping with cancer, visualizing overcoming cancer cells)
Experiencing whatever is present in the moment, allowing present sensations, thoughts, and feelings to be as they are, without having to hold on to them or push them away	Attempting to create a change in the present and future (e.g., by creating relaxation or reducing anxiety or pain)
Practiced as a way of being rather than a technique; a way to live fully and include all experience, pleasant or unpleasant	Usually presented as a technique for solving or coping with a condition
Practiced daily, for its own sake, as part of learning to be awake and nonjudgmentally aware; not based on an attempt to induce a change in state	Often practiced as needed, to relieve or cope with a particular condition or mood state (e.g., tension, anxiety, or pain)

Zinn et al., in press), first developed by Jon Kabat-Zinn, Ph.D., at the Stress Reduction Clinic of the University of Massachusetts Medical Center (UMMC), has been shown to be effective for chronic pain (Kabat-Zinn 1982; Kabat-Zinn et al. 1985, 1986). Amelioration of pain is known to involve the opioid system. Therefore, the opioid system may be the common mechanism for both meditation and melatonin.

The SR and RP also was found to be effective for patients with panic disorder and generalized anxiety disorder (Kabat-Zinn et al. 1992; Miller et al. 1995). The etiology of generalized anxiety disorder has been shown to be related to the  $\gamma$ -aminobutyric acid (GABA) receptor (Dubovsky 1990). One of the main pharmacological treatments for both generalized anxiety disorder and insomnia

Table 11-2. Comparison of meditation with other psychosocial interventions<sup>a</sup>

Meditation	Cognitive-behavior therapy <sup>b</sup>	Supportive-expressive therapy <sup>c</sup>
<p><b>Goal</b></p> <p>Presented as a way of being or general lifestyle approach. Group support is present but is not a stated goal or predominant focus. Emphasis is on living life fully and being in touch with the full range of emotions. Nonattachment to goals is taught (e.g., lightly held goals).</p> <p><b>Individual/group format</b></p> <p>Can be taught in large or small groups of people with either homogeneous or diverse problems and concerns.</p> <p>Taught as a class to large or small groups (up to 40 people).</p>	<p>Generally presented as a way to cope with a particular mood, feeling state, or illness (e.g., depression, anxiety, or cancer). Group support usually occurs spontaneously and may or may not be a stated goal.</p>	<p>Goals are to 1) facilitate full expression of emotions and thoughts about the illness, based on the assumption that this will be therapeutic; 2) provide a support system to alleviate social isolation; and 3) live life as fully as possible.</p>
<p><b>Individual/group format</b></p> <p>Can be taught in large or small groups of people with either homogeneous or diverse problems and concerns.</p> <p>Taught as a class to large or small groups (up to 40 people).</p>	<p>Usually presented to individuals or groups with one overall concern (e.g., depression or anxiety).</p> <p>Provided as individual or small-group therapy (6-10 people).</p>	<p>Usually provided in small intimate groups that are homogeneous for a particular illness or common concern.</p> <p>Provided as group therapy, usually with smaller groups (8-10 people).</p>

(continued)

Table 11-2. Comparison of meditation with other psychosocial interventions (continued)

Meditation	Cognitive-behavior therapy	Supportive-expressive therapy
<p data-bbox="591 1354 1040 1801"><b>Skills/practices presented</b> Coping skills are presented in the larger framework of everyday life, as a practice for living, using formal and informal practices and demonstrating how these are mirrored in everyday life. The practices are used for the purpose of cultivating greater present-moment awareness and self-acceptance rather than as technique-based coping strategies.</p>	<p data-bbox="639 877 805 1339">Coping skills are presented largely in relation to the mood or feeling state to be dealt with and may be secondarily related to a more general lifestyle change.</p>	<p data-bbox="639 277 932 850">Coping strategies specific to the common illness or concern are learned by hearing what other group members have found helpful, by suggestions from the group leaders, or both. Uses a breathing technique based on self-hypnosis that shares some features with sitting meditation practice, including a primary focus on the breath.</p>
<p data-bbox="1068 1354 1365 1801">No attempt is made either to monitor or reframe particular thoughts or feeling states. Whatever appears in awareness is simply held as the salient aspect of the present-moment experience. If there is a change in perception, it emerges spontaneously.</p>	<p data-bbox="1068 877 1393 1339">Thoughts and reactions to physical sensations are monitored, reframed, and sometimes induced (e.g., symptoms of panic attacks). Through systematically looking at thought patterns or attributions to sensations, a change in perception is facilitated that may be associated with improvement (e.g., less anxiety or depression,</p>	<p data-bbox="1068 277 1328 850">A forum for expressing feelings and concerns is presented, usually oriented around a specific illness; thoughts and feelings are not specifically induced or systematically monitored and reframed. Changes in lifestyle or perception usually are related to coping with the illness.</p>

greater ability to cope with the illness) and may secondarily include greater self-acceptance.

<sup>a</sup>Adapted from Kabal-Zinn et al., in press.

<sup>b</sup>A. Beck et al. 1979; Greer et al. 1992; Moorey and Greer 1989; Moorey et al. 1994; Moras et al. 1990.

<sup>c</sup>Classen et al. 1994; Spiegel and Spira 1991.

is the benzodiazepines, which interact at this receptor (Dubovsky 1990). The pineal gland has GABA<sub>A</sub> receptors and actively synthesizes and metabolizes GABA (Demisch 1993). Also, melatonin has been shown to significantly increase the inhibitory effect of GABA and to have a benzodiazepine-like activity (Stankov et al. 1993). This finding suggests that the GABA system might be one common mechanism by which meditation and melatonin exert their anti-anxiety and anti-insomnia effects.

To the best of our knowledge, melatonin has not been used as an outcome measure for any psychosocial intervention in a published peer-reviewed study before the 1995 preliminary study described in the discussion in the following section "Research on Meditation, Melatonin, and Cancer." The most closely related study was one using regular practitioners of the TM technique, showing higher daytime levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) compared with that in control subjects and showing that the levels increased following meditation (Bujatti and Riederer 1976). However, the report was based on 5-HIAA urine concentration for a 2-hour period rather than total excretion. In a separate review that commented on this study, the author hypothesized that the reported rise in serotonin was due to enhanced pineal activity (Romijn 1978).

### Melatonin and Cancer

Melatonin has been shown to have oncostatic properties and to inhibit the growth of a wide range of neoplasms in animal and human in vivo and in vitro models, with the most compelling evidence being in the area of breast cancer (see Hill et al., Chapter 9, and Blask, Chapter 10, in this volume).

Based on the theory of pineal/melatonin involvement in the etiology of certain cancers, a group of Italian investigators has conducted several preliminary and two randomized trials of groups of patients with a variety of cancers, administering either oral melatonin alone or melatonin with a series of interleukin-2 (IL-2) injections (Lissoni et al. 1989, 1991, 1992a, 1992b, 1992c, 1993, 1994a, 1994b). Most of the patients were unresponsive to standard

Table 11-3. Similarities in effects of meditation and melatonin based on literature review

Effect	Meditation	Melatonin
Analgesia	Kabat-Zinn et al. 1985, 1986	Maestroni and Conti 1993
Antistress	<i>Pain:</i> Kabat-Zinn et al. 1985, 1986 <i>General:</i> Kabat-Zinn et al. 1989	<i>Psychological:</i> Katz et al. 1995 <i>Physical:</i> Khan et al. 1990, Maestroni and Conti 1993, Monteleone et al. 1992, 1993
Anti-insomnia/ hypnotic	Woolfolk et al. 1976	Dollins et al. 1994
Decreased anxiety	Kabat-Zinn et al. 1992	<i>Based on GABA receptor:</i> Stankov et al.
Decreased heart rate	Delmonte 1984	Chuang et al. 1993
Decreased blood pressure	Alexander et al. 1996, Delmonte 1984, Schneider et al. 1995	Chuang et al. (1993)

Note. GABA =  $\gamma$ -aminobutyric acid.

chemotherapy or other anticancer therapies. In one of the randomized studies on patients with brain metastases due to solid neoplasms, those treated with melatonin, compared with supportive care alone, had a significantly greater survival at 1 year, longer free-from-brain-progression period, and longer mean survival time, along with significant improvement in their Karnofsky Performance Status Score (Lissoni et al. 1994b). In the second randomized study, melatonin combined with IL-2 was associated with a significant improvement in immune parameters and a higher rate of survival at 1 year, compared with IL-2 given alone (Lissoni et al. 1994a). In a separate study, increasing melatonin levels were predictive of a favorable response to chemotherapy in a group of cancer patients, some of whom had breast cancer (Lissoni et al. 1988).

### Psychosocial Interventions and Cancer

We were unable to find a published study using meditation as the primary component in a psychosocial intervention for cancer patients. However, at least two randomized studies have used psychosocial interventions in which relaxation/self-regulatory strategies were one component: one study in women with metastatic breast cancer followed for 10 years (Spiegel et al. 1989) and the other study in postsurgical patients with malignant melanoma followed for 6 years (Fawzy et al. 1990a, 1990b, 1993). Both showed improved survival associated with the psychosocial interventions.

In the following discussion, we present preliminary data from an ongoing randomized study of women with stages I and II breast cancer, using a modified form of the SR and RP as one of two interventions and melatonin as one of the biological outcome parameters.

### Research on Meditation, Melatonin, and Cancer

In 1995, we published preliminary studies showing that regular practice of meditation may be associated with increased levels of melatonin as measured in the urine. In this preliminary cross-sectional study we compared 12-hour overnight (8 P.M.–8 A.M.) levels of the urinary metabolite of melatonin, 6-sulfatoxymelatonin ( $\alpha$ MT6s), in healthy women, eight of whom regularly meditated and eight who did not (Massion et al. 1995). After controlling for age and the nonsignificant effect of menstrual period interval, the meditators were found to have significantly higher  $\alpha$ MT6s levels ( $t = 2.60$ ,  $P = .02$ ). We suggested that melatonin would be a relevant outcome variable in assessing psychosocial interventions, particularly for subjects with breast or prostate cancer.

Since that time, we conducted another preliminary study of healthy men and women before and after an intensive meditation retreat (A. O. Massion et al., unpublished observations, 1995). We also began a larger randomized study of women with stage I or II breast cancer, using a modified form of the SR and RP as one of the

intervention arms and melatonin as one of the biological outcome variables.

In the meditation retreat study, 12-hour overnight (8 P.M.–8 A.M.) urinary  $\alpha$ MT6s levels were measured on the first and last days of either an 11-day or 21-day mindfulness meditation retreat in late May to June 1994, in Barre, Massachusetts. Samples were collected from 11 retreat participants (six from the 11-day retreat and five from the 21-day retreat) and from 9 staff members. The staff were practicing the same form of meditation on a less intensive schedule and living at the same location, with a similar lifestyle and food intake (mainly vegetarian), but were not participating in the retreat schedule. Subjects were healthy men and women, all of whom agreed to go to bed by midnight.

The retreats were overlapping so that the two retreat groups were together for the last 11 days. The majority of the retreat was conducted in silence, with walking and sitting meditations beginning at approximately 5:45 A.M. and ending at approximately 9 P.M. In contrast, the staff were meditating on their own for an average of 50 minutes per day.

A general linear model (linear regression), with the general linear models procedure (PROC GLM) in the *Statistical Analysis System (SAS) Users Guide* (1993), was used for this study. The change in  $\alpha$ MT6s total excretion amount was the dependent variable (the change score was calculated by subtracting the baseline value from the value on the last day of the retreat). The covariates or independent variables were groups (fitting indicator variables for retreat groups together and separately in two separate models), sex, age, daily rate (in minutes per day) of average meditation practice prior to the retreat, and baseline level of  $\alpha$ MT6s excretion. Also modeled as independent variables were the interactions between retreat group and both gender and rate of meditation practice prior to the retreat.

Exploratory analyses showed that there were no significant differences between  $\alpha$ MT6s levels or other differences between the two retreat groups, so they were combined in subsequent analyses. After we controlled for covariates, the results showed a significant increase in  $\alpha$ MT6s excretion between pre- and post-

measurements for the retreat group but not the staff. However, the difference between the retreat group and the staff group was not significant. The results are summarized in Table 11-4.

Of the covariates fitted, only the daily rate of average meditation practice before the retreat was predictive of the change in  $\alpha$ MT6s excretion. The association was inverse, with greater practice before the retreat being predictive of a smaller change during the retreat (i.e.,  $-0.015 \mu\text{g}$  of  $\alpha$ MT6s/minute of meditation/week,  $t = 2.15$ ,  $P = .05$ ).

The significant difference between pre- and post- $\alpha$ MT6s levels in the retreat group seems especially notable given the small sample size. For the staff group, there was a suggestion but no significant difference between pre- and post-rates of excretion. Because both groups were eating essentially the same food and going to bed by midnight, the differences between groups are unlikely to be explained by sleep or dietary factors. The results are consistent with a dose-dependent effect of meditation because 1) the staff were involved in some aspects of the retreat and doing some meditating on their own for much shorter periods than the retreat participants, and 2) the difference in  $\alpha$ MT6s levels was approximately twofold higher for the retreat participants, although this difference was not significant. The lack of statistical significance between the retreat group and staff group appears to be a consequence of the small sample size in relation to the magnitude of the difference in  $\alpha$ MT6s, which may in turn reflect the difference in meditation time.

The fact that the maximal change apparently was reached by the end of the 11-day retreat suggests a plateau effect for at least the period of meditation represented in the study. Regular meditation over a period of years also may show such an effect.

### Increase of Serum Melatonin After Meditation

A study in Australia by G. A. Tooley et al. (unpublished observations) measured serum melatonin levels taken serially at six time points before and after a period of meditation beginning at midnight and lasting up to 60 minutes. They hypothesized that medi-

**Table 11-4.** Differences in pre- and posttreat total 12-hour (8 P.M.-8 A.M.) 6-sulfatoxymelatonin ( $\alpha$ MT6s) excretion in retreat group versus staff in the Meditation Retreat Study, Barre-Worcester, Massachusetts, 1994

	Retreat group ( $n = 11$ )		Staff ( $n = 9$ )		Intergroup comparison	
	Mean	(SE)	Mean	(SE)	$P^a$	$P^b$
Baseline $\alpha$ MT6s ( $\mu\text{g}/12$ hours)	9.96	(5.03)	10.36	(6.79)		.88
Follow-up $\alpha$ MT6s ( $\mu\text{g}/12$ hours)	15.49	(8.45)	12.86	(10.65)		.57
Crude difference <sup>c</sup> ( $\mu\text{g}/12$ hours)	5.73	(1.67)	2.70	(1.76)	.008	.17
Adjusted difference <sup>d</sup> ( $\mu\text{g}/12$ hours)	5.78	(1.56)	2.90	(1.73)	.004	.24

<sup>a</sup>  $P$  value for the test of the hypothesis that the difference between baseline and follow-up = 0.

<sup>b</sup>  $P$  value for the test of the hypothesis that the group mean values are the same, based on two-sample  $t$  test for continuous variables.

<sup>c</sup> Based on the simple intergroup difference (i.e., subtracting the baseline from the value obtained at the end of the intervention). This value represents all those subjects for whom we had complete data to compute an adjusted score.

<sup>d</sup> The adjusted difference is obtained as the least means square (LSMEANS) using the general linear model in the *Statistical Analysis System* (PROC GLM). This difference is based on the same simple intergroup difference as above in c. The value is adjusted for previous rate of meditation (minutes/week), gender, baseline production of melatonin (to control for regression to the mean), and interactions between retreat group and both sex and previous rate of meditation. None of these covariates was independently predictive of changes in melatonin amount.

tation would be associated with an acute rise in serum melatonin. There were three groups of healthy subjects: 1) 11 long-term TM practitioners, 2) 7 practitioners of an internationally well-known form of meditative-based yoga who participated on the condition that their organization was not identified, and 3) 10 volunteers with no prior meditation or yoga experience (nonmeditator group). Both the TM and yoga groups were long-term practitioners (mean of  $12.3 \pm 6.43$  years for the TM group;  $5.77 \pm 4.45$  years for the yoga group). During the study, the TM group meditated for an hour and the yoga group for approximately 45 minutes. A repeated-measures crossover design was used, with random allocation to control or intervention conditions on two separate nights 2 weeks apart. The TM and yoga groups were randomly assigned to meditate beginning at midnight on one night and to the control condition (no meditation) on the alternate night. Instead of meditating, the nonmeditator group was instructed to sit with their eyes closed for 1 hour beginning at midnight on the intervention night. On the control night, all groups were asked to sit quietly but otherwise could engage in any activities they chose, such as talking or watching television.

Lighting levels were monitored throughout the experiment and did not exceed 15 lux, which was below the level known to influence melatonin secretion (Lewy et al. 1980; McIntyre et al. 1988). Blood was sampled via a butterfly needle inserted in a vein in the cubital fossa region of the forearm at the following times: 1) four samples before meditation at 10 P.M., 11 P.M., 11:30 P.M., and midnight and 2) six samples taken 20 minutes apart postmeditation (10 samples total).

The mean paired differences between meditation and control night melatonin levels were significant for both the TM and yoga groups for both major outcome measures, the maximum melatonin peak after baseline ( $P < .05$ ) and total cumulative melatonin production ( $P < .05$ ). The results indicated that the average post-baseline melatonin levels peaked higher on the meditation compared with the control night and that more melatonin was secreted overall during the postbaseline sampling period on the meditation night. For the nonmeditator group, no differences

were noted between intervention and control nights. Although both the TM and yoga groups appeared to show a decline from the peak after approximately 1 A.M., in the nonmeditator group the peak appeared to be higher than the TM and yoga groups and not completely defined in that it occurred toward the end of the interval. Of note, the nonmeditator group was, on average, more than 12 years younger than the other two groups, which may account for the apparent higher average peak production in the nonmeditator group. Also, the last sample was taken at 2:40 A.M., which is earlier than the end of the normal range for the circadian melatonin peak, namely, between midnight and 3 A.M., with considerable interindividual variability (McIntyre et al. 1987; Reiter 1991). Taking the last sample before 3 A.M. may explain why the peak was not completely captured. Finally, midnight is an unusual time for people to meditate and was chosen mainly to maximize the influence on peak melatonin production. However, the main finding was that both the TM and yoga groups had a significant acute increase in melatonin levels on the meditation nights compared with the control nights and the nonmeditator group did not, which would seem to rule out an effect due to simple rest or relaxation.

### **Acute and Chronic Stress and Melatonin**

A second study, by K. G. Walton et al. (1990; unpublished observations) compared long-term TM-practicing college students (mean years of practice  $8.5 \pm 5.1$  years) from Maharishi University of Management with a group of nonmeditating college students from a different university, both universities being in Iowa. Apparently unlike the previous studies, K. G. Walton et al. (1990; unpublished observations) assessed the students during a relatively stressful time, approximately 2 weeks before final examinations. The investigators proposed that because meditation has been reported to reduce psychological and biochemical indicators of acute and chronic stress and because it has been postulated that melatonin increases with acute stress, that the long-term TM group would have lower indicators of chronic stress and corre-

spondingly reduced indicators of melatonin level or turnover. Melatonin levels were measured using 24-hour urinary  $\alpha$ MT6s excretion. Indicators of chronic stress were excretion rates of cortisol, vanillylmandelic acid, and sodium, along with scores on the Profile of Mood States (POMS; McNair et al. 1971) and State-Trait Anxiety Inventory (STAI; Spielberger and Sydeman 1994). On the basis of these indicators, the 22 college students in the TM group were found to have lower stress (designated as the LS group) than the 31 nonmeditating college students who were felt to have average stress levels (designated as the AS group). Ages were similar in both groups.  $\alpha$ MT6s excretion rates were significantly higher for the AS group (nonmeditators) compared with the LS group (TM practitioners), as reflected by the 24-hour urine samples (AS =  $508 \pm 49$  ng/h and LS =  $318 \pm 58$  ng/h;  $F = 6.11$ ,  $P = .017$ ). These results were independent of the use of alcohol, nicotine, and caffeine. Higher  $\alpha$ MT6s excretion correlated directly with higher stress indicators, both within each group and across all subjects.

The results of this latter study appear to be inconsistent with the first three studies in that the meditating groups had higher rather than lower melatonin levels in the two studies by Massion et al. (1995, in submission) and the study by G. A. Tooley et al. (unpublished observations). The difference in types of meditation (TM and mindfulness) does not account for the results because G. A. Tooley et al. and K. G. Walton et al. (1990; unpublished observations) both used subjects practicing the TM technique, as well as the more advanced TM-Sidhi program. Because the study by Walton et al. was cross-sectional, it is possible that variables other than TM practice, such as lifestyle or dietary factors, were responsible for the difference in melatonin levels. Also, Walton et al. used college students in a situation that would be experienced as stressful by most people, a condition apparently absent from the other studies. Furthermore, the college students may have been experiencing both acute and chronic stress simultaneously, which makes the issue more complicated, especially considering the reported variability of the effects of stress on human melatonin levels according to the nature and timing of the stress. As a case in point, a study of 23 pregnant women showed higher  $\alpha$ MT6s levels on

work versus nonwork days based on within-subjects comparisons (Katz et al. 1995), which would seem to be an indicator of acute psychological stress.

Other reports have suggested that the human pineal is unresponsive to acute physical stress induced either during the day or 3 hours after the beginning of darkness but does respond to acute physical stress induced in the second half of the dark phase (Monteleone et al. 1992, 1993). Reports on circulating melatonin levels in various groups of cancer patients, presumably under chronic stress levels ranging from mild to severe, have shown both increased and decreased levels (Blask 1993).

Obviously, all of the previously mentioned meditation studies need to be replicated, preferably with larger samples. The only conclusion that can be made at this point is that meditation does seem to influence melatonin levels; the majority of the studies suggest enhanced or increased melatonin levels, but certainly the direction of the effect is not well established at this point.

None of these were randomized studies. Although randomized studies are testing hypotheses and estimating effects, this approach seems unusually difficult for examining the relationship between melatonin and meditation because self-selection factors play such an important role in the motivation to practice intensive meditation, particularly of the kind used in these studies. The disadvantages of a randomized clinical trial are that subjects are asked to sustain effort, attention, and practice for concentrated or prolonged periods and that they are likely to have strong treatment preferences (Brewin and Bradley 1989). Motivation plays a crucial role in compliance with the intervention.

### **Breast Cancer, Meditation, and Melatonin**

Despite this difficulty with randomized studies, we and other colleagues in a multidisciplinary research group at the University of Massachusetts Medical Center (UMMC) did design and initiate a larger multisite study—the BRIDGES (*Breast Research Initiative for Developing Effective Skills*) study—of women, ages 20–65 years, with stages I or II breast cancer and within 2 years of

diagnosis. The aims of the study are to identify effective skills for coping with breast cancer and measure psychosocial and biological outcome parameters over 2 years of follow-up. Outcome measures include psychosocial variables (quality of life, coping methods, anxiety, depression), immunological parameters (interferon- $\gamma$  [IFN- $\gamma$ ], soluble IL-2 receptor, and interleukin-4 [IL-4]), and melatonin.

Study participants are randomized to one of three arms: 1) a modified form of the SR and RP, expanded to address issues specific to breast cancer; 2) a nutrition education intervention originally intended to act as an attention control but also with the hypothesis that it might have therapeutic effects; and 3) a usual-treatment control group. Subjects have had no prior experience in either intervention. They are randomized according to strata of age (< 55 years or  $\geq$  55 years), disease status (stage I or II), and institution. Each subject is followed for 2 years. A description of the SR and RP has been provided elsewhere (Kabat-Zinn 1990, 1994; Kabat-Zinn et al., in press), but briefly, this is a well-developed psychosocial intervention that has been in operation for the past 17 years as an outpatient service of the UMMC Stress Reduction Clinic in the Department of Medicine, Division of Preventive and Behavioral Medicine. More than 8,000 patients with a wide range of chronic medical conditions, many life threatening, have been physician-referred to the program. Research on the SR and RP has shown clinically significant short- and long-term improvement in physical and psychological symptoms, as well as enhanced psychological well-being, in patients with chronic conditions, including chronic pain (Kabat-Zinn 1982; Kabat-Zinn et al. 1985, 1986), anxiety disorders (Kabat-Zinn et al. 1992; Miller et al. 1995), and psoriasis (Bernhard et al. 1988).

The program is structured as an 8-week course given to heterogeneous groups of 25-40 people referred for problems, including cancer, hypertension, gastrointestinal problems, chronic pain, and anxiety. Classes meet for 2 1/2 hours once a week and one intensive daylong silent meditation retreat on the weekend during the sixth week. The core curriculum is intensive training in mindfulness meditation (formal practice) and its applications to daily living

(informal practice). Classes include training in sitting and walking meditation, hatha-yoga, experiential exercises, and discussion.

The SR and RP was modified for use in the BRIDGES study by adding six sessions, one before and five after the standard 8-week SR and RP. Only women with breast cancer who are in the study attend these six sessions. The sessions are used to reinforce the meditation training and practice, and to address issues specific to breast cancer.

The nutrition education program (NEP) was designed to reduce dietary fat to 20% or less. The NEP is presented as 14 weekly class sessions and one all-day session in order to be attentionally equivalent to the SR and RP. The NEP is used to introduce participants to nutritional concepts, techniques, and group cooking/eating experiences that broaden rather than restrict dietary options. Although the NEP is equivalent in time commitment to the SR and RP and includes an important aspect of group support, it includes no element of mindfulness meditation. The usual care group may include attendance in community support groups but otherwise has none of the elements of either the SR and RP or the NEP.

Currently, we have 160 women enrolled in the study. Preliminary data on 24-hour  $\alpha$ MT6s levels have been collected on 84 subjects for the baseline and 4-month (2–3 weeks postintervention) assessment points. These data do not include the immunological parameters because those assays will not be done until the final year of the study for quality control reasons.

A total of 84 women had complete data at both the baseline and 4-month assessment points. Of these, two had taken melatonin supplementation at some time during this study interval. Although we chose to analyze the data according to the intention-to-treat paradigm of randomized clinical trials, we decided to exclude the two users of melatonin from these analyses because of the direct relationship between the intake of melatonin supplements and increased excretion of  $\alpha$ MT6s. Because of the stratified method of randomization by age and severity of disease, these factors were controlled by design. Of the 82 subjects on whom we had complete data for this analysis, 23 had completed the NEP, 30 were in the SR and RP arm, and 29 were assigned to usual care.

We found that there was a suggestion that both the NEP and SR and RP were associated with increases in  $\alpha$ MT6s excretion in the study period. In the usual-care group, we observed a mean *decrease* of 1.06  $\mu$ g/24 hours, whereas in the SR and RP and the NEP groups, we observed mean *increases* of 1.58  $\mu$ g/24 hours and 3.26  $\mu$ g/24 hours, respectively. Mean baseline and 4-month values are shown in Table 11-5.

Because of the relatively large variability in the data, the overall effect was not statistically significant ( $P = .33$ ), nor was the effect due to either of the interventions relative to usual care (NEP [ $P = .15$ ] and SR and RP [ $P = .34$ ]). We believe these results warrant as much attention as the statistically significant results of the previous studies because they were obtained in a randomized trial in which background factors are controlled by design and in which we would expect less of an effect than in a highly self-motivated group of experienced meditators; hence, there is more relevance to the experience of average people. In addition, an effect of this magnitude would be statistically significant in even a slightly larger sample and probably is of clinical significance. Finally, these results cover only the first 4 months of follow-up and may reflect more immediate postintervention changes. These results may

**Table 11-5.** BRIDGES study: baseline and 4-month (postintervention) 24-hour 6-sulfatoxymelatonin ( $\alpha$ MT6s) values ( $\mu$ g/24 hours)

Group	N	Mean baseline (SD)	Mean 4-month (SD)	Mean difference (SD) <sup>a</sup>	Effect relative to usual care (P value)
SR and RP	30	9.83 (9.23)	11.41 (10.99)	+ 1.58 (11.87)	.34
NEP	23	9.63 (6.08)	12.89 (12.50)	+ 3.26 (9.03)	.15
Usual care	29	11.20 (10.15)	10.16 (5.68)	- 1.06 (10.30)	

*Note.* SR and RP = Stress Reduction and Relaxation Program; NEP = Nutrition Education Program.

<sup>a</sup>Crude mean difference for each group with the standard deviation of the difference (not the overall standard deviation) shown in parentheses.

change over the course of the 2-year follow-up period.

Table 11-6 summarizes the results of the meditation/melatonin studies discussed in this chapter. All but one study showed increased melatonin levels associated with meditation practice. In terms of pineal function, an elevation in endogenous melatonin could reflect a change in circadian amplitude, circadian phase, or liver metabolism. However, all the studies had healthy subjects without liver disease; the only exception was the BRIDGES study in which the subjects had early stage breast cancer. Therefore, an effect on liver metabolism seems unlikely. All but one of the studies used total excretion of urinary  $\alpha$ MT6s and therefore were not able to address directly the question of amplitude versus phase. G. A. Tooley et al. (unpublished observations) did use serum melatonin levels and characterized the circadian phase, but not definitively because the sample collection ended shortly before 3 A.M. Overall, the results appear to favor a change in circadian amplitude as the most likely explanation.

## Conclusions

In general, the results of the preliminary studies reported in this chapter suggest that meditation practice is associated with enhanced endogenous melatonin levels. The results need to be replicated with larger samples and/or a randomized trial. A number of related questions are still to be answered, such as whether this effect 1) holds true for both long-term and short-term meditation practitioners, 2) persists over long-term follow-up, and 3) can be explained by a change in circadian amplitude or phase. If meditation can influence pineal activity, this in turn could influence the course of certain diseases for which melatonin plays a role, such as breast or prostate cancer. The potential value of meditation for people with such conditions remains to be investigated.

Recently, there has been a great deal of interest in the use of oral melatonin supplements for disorders such as insomnia and jet lag (see Lewy et al., Chapter 4, in this volume). Often, these supplements are taken in doses resulting in blood levels that are higher

Table 11-6. Summary of preliminary meditation/melatonin studies

Author/study	Type of meditation	Short- or long-term practice	Population	Melatonin measurement	N	Melatonin levels <sup>a</sup>
Massion et al. (1995), cross-sectional, nonrandomized	Mindfulness	Long-term	Healthy women	12-hour <sup>b</sup> $\alpha$ MT6s, urine	16	Increased
Massion et al. (in submission), retreat study, nonrandomized	Mindfulness	Variable	Healthy men/women	12-hour <sup>b</sup> $\alpha$ MT6s, urine	20	Increased
Tooley et al. (in submission), post on two nights, nonrandomized	Transcendental meditation	Long-term	Healthy men/women	Serum	25	Increased
K. G. Walton et al. (1990; unpublished observations)	Transcendental meditation	Long-term	Healthy men/women	24-hour $\alpha$ MT6s, urine	53	Decreased
Preliminary analysis 1996, BRIDGES study, pre-post over 4 months, randomized	Mindfulness	Short-term	Women with breast cancer	24-hour $\alpha$ MT6s, urine	82	Increased

Note.  $\alpha$ MT6s = 6-sulfatoxymelatonin; BRIDGES = Breast Research Initiative for Developing Effective Skills.

<sup>a</sup>Melatonin levels in meditators relative to comparison or control groups; all results were statistically significant except for BRIDGES study.

<sup>b</sup>Overnight collection from 8 P.M. to 8 A.M.

than the physiological range. Our hope is that this chapter has at least raised the thought-provoking possibility of influencing melatonin production by using capacities that are inherent in all people and that act within our own physiological and psychological homeostatic resources for being in the world. Certainly, melatonin is not the only biological outcome measure that could be used in meditation research, but it is one porthole into the fascinating interface between psyche and soma.

## References

- Alexander CN, Davies JL, Dixon CA, et al: Growth of higher states of consciousness: the Vedic psychology of human development, in *Higher States of Human Development: Perspectives on Adult Growth*. Edited by Alexander C, Langer E. New York, Oxford University Press, 1990, pp 286-340
- Alexander CN, Schneider RH, Staggers F, et al: Trial of stress reduction for hypertension in older African Americans. *Hypertension* 28:228-237, 1996
- Beck A, Rush A, Shaw B, et al: *Cognitive Therapy of Depression*. New York, Guilford, 1979
- Beck C: *Everyday Zen*. San Francisco, CA, HarperCollins, 1989
- Beck C: *Nothing Special*. San Francisco, CA, HarperCollins, 1993
- Bernhard JD, Kristeller J, Kabat-Zinn J: Effectiveness of relaxation and visualization techniques as an adjunct to phototherapy and photochemotherapy of psoriasis. *J Am Acad Dermatol* 19:572-573, 1988
- Blask DE: Melatonin in oncology, in *Melatonin: Biosynthesis, Physiological Effects, and Clinical Applications*. Edited by Yu H-S, Reiter R. Boca Raton, FL, CRC Press, 1993, pp 447-475
- Brewin CR, Bradley C: Patient preferences and randomised trials. *BMJ* 299:313-315, 1989
- Bujatti M, Riederer P: Serotonin, noradrenaline, dopamine metabolites in transcendental meditation-technique. *J Neural Transm* 39:257-267, 1976
- Chuang JI, Chen SS, Lin MT: Melatonin decreases brain serotonin release, arterial pressure and heart rate in rats. *Pharmacology* 47:91-97, 1993

- Classen C, Hermanson KS, Spiegel D: Psychotherapy, stress, and survival in breast cancer, in *The Psychoimmunology of Cancer*. Edited by Lewis C, O'Sullivan C, Barraclough J. Oxford, England, Oxford University Press, 1994, pp 123-162
- Delmonte MM: Physiological concomitants of meditation practice. *Int J Psychosom* 31:23-36, 1984
- Demisch L: Clinical pharmacology of melatonin regulation, in *Melatonin: Biosynthesis, Physiological Effects, and Clinical Applications*. Edited by Yu H-S, Reiter R. Boca Raton, FL, CRC Press, 1993, pp 513-540
- Dollins AB, Zhdanova IV, Wurtman RJ, et al: Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature and performance. *Proc Natl Acad Sci U S A* 91:1824-1828, 1994
- Dubovsky SL: Generalized anxiety disorder: new concepts and psychopharmacologic therapies. *J Clin Psychiatry* 51 (suppl 1):3-10, 1990
- Epstein M: *Thoughts Without a Thinker*. New York, Basic Books, 1995
- Fawzy FI, Cousins N, Fawzy NW, et al: A structured psychiatric intervention for cancer patients, I: changes over time in methods of coping and affective disturbance. *Arch Gen Psychiatry* 47:720-725, 1990a
- Fawzy FI, Kemeny ME, Fawzy NW, et al: A structured psychiatric intervention for cancer patients, II: changes over time in immunological measures. *Arch Gen Psychiatry* 47:729-735, 1990b
- Fawzy FI, Fawzy NW, Hyun CS, et al: Malignant melanoma: effects of an early structured psychiatric intervention, coping and affective state on recurrence and survival 6 years later. *Arch Gen Psychiatry* 50:681-689, 1993
- Goldstein J: *The Experience of Insight*. Boston, Shambhala, 1976
- Goldstein J, Kornfield J: *Seeking the Heart of Wisdom*. Boston, MA, Shambhala, 1987
- Greer S, Moorey S, Baruch et al: Adjuvant psychological therapy for patients with cancer: a prospective randomized trial. *BMJ* 304:675-680, 1992
- Guerrero J, Reiter R: A brief survey of pineal gland-immune system interrelationships. *Endocr Res* 18:91-113, 1992
- Gyatso GK: *Buddhism in the Tibetan Tradition: A Guide*. Boston, Routledge & Kegan Paul, 1984

- Gyatso GK: *Meaningful to Behold: A Commentary to Shantideva's Guide to the Bodhisattva's Way of Life*. London, Tharpa Publications, 1985
- Huether G: The contribution of extrapineal sites of melatonin synthesis to circulating melatonin levels in higher vertebrates. *Experientia* 49:665-670, 1993
- Huether G: Melatonin synthesis in the gastrointestinal tract and the impact of nutritional factors on circulating melatonin, in *The Aging Clock: The Pineal and Other Pacemakers in the Progression of Aging and Carcinogenesis* (Annals of the New York Academy of Sciences, Vol 719). Edited by Pierpaoli W, Regelson W, Fabris N. New York, The New York Academy of Sciences, 1994, pp 146-158
- Kabat-Zinn J: An out-patient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *Gen Hosp Psychiatry* 4:33-47, 1982
- Kabat-Zinn J: *Full Catastrophe Living*. New York, Delacorte, 1990
- Kabat-Zinn J: *Wherever You Go, There You Are*. New York, Hyperion, 1994
- Kabat-Zinn J, Lipworth L, Burney R: The clinical use of mindfulness meditation for the self-regulation of chronic pain. *J Behav Med* 8:163-190, 1985
- Kabat-Zinn J, Lipworth L, Burney R, et al: Four-year follow-up of a meditation-based program for the self-regulation of chronic pain: treatment outcomes and compliance. *Clin J Pain* 2:159-173, 1986
- Kabat-Zinn J, Skillings A, Santorelli SF: Sense of coherence and stress hardiness as predictors and measures of outcome of a stress reduction program. Poster presented at the annual meeting of the Society of Behavioral Medicine, San Francisco, CA, March 31, 1989
- Kabat-Zinn J, Massion AO, Kristeller J, et al: Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. *Am J Psychiatry* 149:936-943, 1992
- Kabat-Zinn J, Massion AO, Hebert JR, et al: Meditation, in *Textbook of Psycho-oncology*. Edited by Holland J. London, Oxford University Press, in press
- Katz VL, Ekstrom RD, Mason GA, et al: 6-sulphatoxymelatonin levels in pregnant women during workplace and nonworkplace stresses: a potential biologic marker of sympathetic activity. *Am J Perinatol* 12:299-302, 1995

- Khan R, Daya S, Potgieter B: Evidence for a modulation of the stress response by the pineal gland. *Experientia* 46:860-862, 1990
- Kornfield J: *A Path With Heart*. New York, Bantam, 1993
- Levine S: *A Gradual Awakening*. New York, Doubleday, 1979
- Lewy AJ, Wehr TA, Goodwin FK, et al: Light suppresses melatonin secretion in humans. *Science* 210:1267-1269, 1980
- Lissoni P, Tancini G, Barni S: Melatonin increase as predictor for tumor objective response to chemotherapy in advanced cancer patients. *Tumori* 74:339-345, 1988
- Lissoni P, Barni S, Crispino S, et al: Endocrine and immune effects of melatonin therapy in metastatic cancer patients. *European Journal of Cancer and Clinical Oncology* 25:789-795, 1989
- Lissoni P, Barni S, Cattaneo G, et al: Clinical results with the pineal hormone melatonin in advanced cancer resistant to standard antitumor therapies. *Oncology* 48:448-450, 1991
- Lissoni P, Tisi E, Barni S, et al: Biological and clinical results of a neuroimmunotherapy with interleukin-2 and the pineal hormone melatonin as a first line treatment in advanced nonsmall cell lung cancer. *Br J Cancer* 66:155-158, 1992a
- Lissoni P, Barni S, Ardizzoia A, et al: Immunological effects of a single evening subcutaneous injection of low-dose interleukin-2 in association with the pineal hormone melatonin in advanced cancer patients. *J Biol Regul Homeost Agents* 6(4):132-136, 1992b
- Lissoni P, Barni S, Ardizzoia A, et al: Randomized study with the pineal hormone melatonin versus supportive care alone in advanced nonsmall cell lung cancer resistant to a first-line chemotherapy containing cisplatin. *Oncology* 49:336-339, 1992c
- Lissoni P, Barni S, Tancini G, et al: Immunotherapy with subcutaneous low-dose interleukin-2 and the pineal indole melatonin as a new effective therapy in advanced cancers of the digestive tract. *Br J Cancer* 67:1404-1407, 1993
- Lissoni P, Barni S, Tancini G, et al: A randomised study with subcutaneous low-dose interleukin-2 alone versus interleukin-2 plus the pineal neurohormone melatonin in advanced solid neoplasms other than renal cancer and melanoma. *Br J Cancer* 69:196-199, 1994a
- Lissoni P, Barni S, Ardizzoia A, et al: A randomized study with the pineal hormone melatonin versus supportive care alone in patients with brain metastases due to solid neoplasms. *Cancer* 73:699-701, 1994b

- Maestroni GJM, Conti A: Melatonin in relation to the immune system, in *Melatonin: Biosynthesis, Physiological Effects, and Clinical Applications*. Edited by Yu H-S, Reiter R. Boca Raton, FL, CRC Press, 1993, pp 289-309
- Maharishi: Maharishi Mahesh Yogi on the Bhagavad-Gita. London, Arkana, 1990
- Massion AO, Teas J, Hebert JR, et al: Meditation, melatonin and breast/prostate cancer: hypothesis and preliminary data. *Med Hypotheses* 44:39-46, 1995
- McIntyre IM, Norman TR, Burrows GD, et al: Melatonin rhythm in human plasma and saliva. *J Pineal Res* 4:177-183, 1987
- McIntyre IM, Norman TR, Burrows GD, et al: Human melatonin suppression by light is intensity dependent. *J Pineal Res* 6:149-156, 1988
- McNair D, Lorr M, Droppleman L: *Manual for the Profile of Mood States*. San Diego, CA, Educational and Industrial Testing Service, 1971
- Miller JJ, Fletcher K, Kabat-Zinn J: Three-year follow-up and clinical implications of a mindfulness meditation-based stress reduction intervention in the treatment of anxiety disorders. *Gen Hosp Psychiatry* 17:192-200, 1995
- Monteleone P, Maj M, Fuschino A, et al: Physical stress in the middle of the dark phase does not affect light-depressed plasma melatonin levels in humans. *Neuroendocrinology* 55:367-371, 1992
- Monteleone P, Maj M, Franza F, et al: The human pineal gland responds to stress-induced sympathetic activation in the second half of the dark phase: preliminary evidence. *J Neural Transm* 92:25-32, 1993
- Moorey S, Greer S: *Psychological Therapy for Patients With Cancer: A New Approach*. Washington, DC, American Psychiatric Press, 1989
- Moorey S, Greer S, Watson M, et al: Adjuvant psychological therapy for patients with cancer: outcome at one year. *Psycho-oncology* 3:39-46, 1994
- Moras K, Craske MG, Barlow DH: Behavioral and cognitive therapies for panic disorder, in *Handbook of Anxiety, Vol 4: The Treatment of Anxiety*. Edited by Noyes RJ, Roth M, Burrows G. Amsterdam, Elsevier Science, 1990, pp 311-325
- Reiter RJ: Pineal melatonin: cell biology of its synthesis and of its physiological interactions. *Endocr Rev* 12:151-180, 1991
- Romijn HJ: Minireview: the pineal, a tranquilizing organ? *Life Sci* 23:2257-2274, 1978

- Roth R: Maharishi Mahesh Yogi's Transcendental Meditation. New York, Primus, Donald I Fine, 1994
- Schneider RH, Staggers F, Alexander CN, et al: A randomized controlled trial of stress reduction for hypertension in older African Americans. *Hypertension* 26:820-827, 1995
- Spiegel D, Spira J: Supportive-Expressive Group Therapy: A Treatment Manual of Psychosocial Intervention for Women With Recurrent Breast Cancer. Stanford, CA, Psychosocial Treatment Laboratory, Stanford University School of Medicine, 1991
- Spiegel D, Bloom J, Kraemer H, et al: Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet* 2:888-891, 1989
- Spielberger CD, Sydeman ST: State-Trait Anxiety Inventory and State-Trait Anger Expression Inventory, in *The Use of Psychological Testing for Treatment Planning and Outcome Assessment*. Edited by Marvish ME. Hillsdale, NJ, Lawrence Earlbaum Associates, 1994, pp 292-321
- Stankov B, Fraschini F, Reiter RJ: The melatonin receptor: distribution, biochemistry, and pharmacology, in *Melatonin: Biosynthesis, Physiological Effects, and Clinical Applications*. Edited by Yu H-S, Reiter R. Boca Raton, FL, CRC Press, 1993, pp 156-186
- Statistical Analysis System (SAS) Users Guide. Cary, NC, SAS Institute, 1993
- Suzuki S: *Zen Mind, Beginner's Mind*. New York, Weatherall, 1970
- Thera N: *The Heart of Buddhist Meditation*. New York, Weiser, 1962
- Walton KG, Brown GM, Pugh N, et al: Indole-mediated adaptation: does melatonin mediate resistance to stress in humans? (abstract). *Society of Neuroscience Abstracts* 16:273, 1990
- Weekes C: *Hope and Help for Your Nerves*. New York, Signet, 1969
- Woolfolk RL, Carr-Kaffashan L, McNulty TF, et al: Meditation training as a treatment for insomnia. *Behavior Therapy* 7:359-365, 1976
- Yeshe LT: *Wisdom Energy 2*. Ulverston, Cumbria, England, Wisdom Culture, 1979