

## Hypnosis as a Modulator of Cellular Immune Dysregulation During Acute Stress

Janice K. Kiecolt-Glaser, Phillip T. Marucha, Cathie Atkinson, and Ronald Glaser  
Ohio State University

To assess the influence of a hypnotic intervention on cellular immune function during a commonplace stressful event, the authors selected 33 medical and dental students on the basis of hypnotic susceptibility. Initial blood samples were obtained during a lower stress period, and a second sample was drawn 3 days before the first major exam of the term. Half of the participants were randomly assigned to hypnotic–relaxation training in the interval between samples. Participants in the hypnotic group were, on average, protected from the stress-related decrements that were observed in control participants' proliferative responses to 2 mitogens, percentages of CD3<sup>+</sup> and CD4<sup>+</sup> T-lymphocytes, and interleukin 1 production by peripheral blood leukocytes. More frequent hypnotic–relaxation practice was associated with higher percentages of CD3<sup>+</sup> and CD4<sup>+</sup> T-lymphocytes. These data provide encouraging evidence that interventions may reduce the immunological dysregulation associated with acute stressors.

Stressful events can alter a wide range of immunological activities. A series of prospective studies of medical students' responses to examinations showed transient changes in multiple facets of the cellular immune response and its mediators, including decreased natural killer (NK) cell activity, decreased gamma interferon production by lymphocytes stimulated with concanavalin A (Con A), increased plasma and intracellular levels of cyclic AMP, and decreased proliferative responses to mitogens (Dobbin, Harth, McCain, Martin, & Cousin, 1991; Glaser et al., 1987; Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986; Kiecolt-Glaser, Garner, Speicher, Penn, & Glaser, 1984; Kiecolt-Glaser et al., 1986; Marshall et al., 1998; Segerstrom, Taylor, Kemeny, & Fahey, 1998); indeed, stress-associated decrements in immunity have also been observed at the level of gene expression (Glaser et al., 1990). The importance of these immunological alterations for health is suggested by several studies. For example, stress influenced medical students' response to a series of three hepatitis B vaccinations (Glaser, Kiecolt-Glaser, Bonneau, Malarkey, & Hughes, 1992); the

students who seroconverted (produced an antibody response to the vaccine) after the first vaccination were significantly less stressed and less anxious than those who did not seroconvert until after the second inoculation. These data suggested that the immune response to a vaccine (and, by implication, to pathogens) could be modulated by a relatively mild stressful event in young, healthy adults.

Additionally, exam stress also substantially delayed wound repair. Wounds placed on the hard palate 3 days before a major test healed an average of 40% more slowly than those made on the same individuals during summer vacation, and interleukin-1 (IL-1), an important immunological mediator, was also substantially lower during exams (Marucha, Kiecolt-Glaser, & Favagehi, 1998).

Researchers have also explored the possibility that behavioral interventions could have positive consequences for immune function (Kiecolt-Glaser & Glaser, 1992). An early study from our lab assessed the impact of relaxation and social contact with 45 older adults (Kiecolt-Glaser et al., 1985). Participants were randomly assigned to one of three protocols: progressive relaxation training, social contact, or no intervention. Participants in the relaxation and social contact conditions were seen individually three times a week for 1 month. Blood samples and self-report data were obtained at baseline, at the end of the 1-month intervention, and at a 1-month follow-up. Only participants in the relaxation condition displayed significant increases in NK cell activity and decreases in antibody titers to latent herpes simplex virus Type 1, both consistent with improved immune function.

A further study explored the possibility that a hypnotic–relaxation intervention might have prophylactic value for some aspects of cellular immunity if used before a stressor (Kiecolt-Glaser et al., 1986). Half of a group of 34 medical students were randomly assigned to a hypnotic–relaxation group that met in the interval between baseline and examination blood draws. NK cell activity and percentages of CD4<sup>+</sup> T-lymphocytes declined in both groups during examinations. However, participants in the hypnotic–relaxation group showed wide variability in their frequency of practice, ranging from 5 to 50 times. Regression anal-

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Janice K. Kiecolt-Glaser, Department of Psychiatry, Ohio State University College of Medicine, and the Ohio State Institute for Behavioral Medicine Research, Ohio State University; Phillip T. Marucha, Section of Periodontology, College of Dentistry, Ohio State University, and the Ohio State Institute for Behavioral Medicine Research, Ohio State University; Cathie Atkinson, Department of Psychiatry, Ohio State University College of Medicine; Ronald Glaser, Department of Molecular Virology, Immunology, and Human Genetics, Ohio State University College of Medicine, and the Ohio State Institute for Behavioral Medicine Research, Ohio State University.

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Correspondence concerning this article should be addressed to Janice K. Kiecolt-Glaser, Department of Psychiatry, Ohio State University College of Medicine, 1670 Upham Drive, Columbus, Ohio 43210. Electronic mail may be sent to kiecolt-glaser.1@osu.edu.

yses showed that more frequent practice was associated with higher percentages of CD4<sup>+</sup> T-lymphocyte during exams after controlling for baseline levels.

A similar study from Whitehouse et al. (1996) examined the immunological consequences of self-hypnosis training for stress management throughout the first semester of medical school. Samples were obtained from 35 students at four time points: orientation, late semester, final exams, and postsemester recovery period. In contrast to most of the academic stress literature, the authors found increases in cell numbers and cellular immune function (blastogenic responses to two mitogens and NK cell activity) during exams. Although the self-hypnosis group reported less distress than did controls, the two groups did not differ with respect to immune function; however, greater increases in relaxation in response to the intervention were associated with higher NK cell numbers and activity.

Other psychoneuroimmunology (PNI) intervention studies have used a number of diverse strategies to modulate immune function including hypnosis, relaxation, exercise, classical conditioning, self-disclosure, exposure to a phobic stressor to enhance perceived coping self-efficacy, and cognitive-behavioral therapies, and these interventions have generally produced positive changes (Kiecolt-Glaser & Glaser, 1992). One excellent series of studies demonstrated that 10-week cognitive-behavioral stress management (CBSM) and aerobic exercise training programs buffered distress responses and immune alterations following notification of HIV seropositivity in asymptomatic men (Antoni, 1997; Ironson et al., 1990; LaPerriere et al., 1990; Schneiderman et al., 1994). The efficacy of the CBSM intervention also had positive consequences for mood and immune function in further studies with gay men whose disease had progressed to a symptomatic stage (Lutgendorf et al., 1997, 1998).

In this study, we assessed the impact of a hypnotic-relaxation intervention on immune function during examinations. Extending previous work, we were particularly interested in testing the hypothesis that the magnitude of the relationship would be related to both the frequency with which an individual practiced or used the intervention, and to the individual's hypnotic susceptibility.

## Method

### Participant Selection

We initially assessed hypnotic susceptibility in groups of 2 to 10 students by using the Harvard Group Scale of Hypnotic Susceptibility (HGSHS), Form A (Shor & Orne, 1962). Students who obtained a score of 7 or higher and who had no disqualifying chronic health problems, medications, or health behaviors (Kiecolt-Glaser & Glaser, 1988) were invited to return for individual assessments with the Stanford Hypnotic Susceptibility Scale, Form C (Weitzenhoffer & Hilgard, 1962). Disqualifying health problems included smoking, drinking more than 10 alcoholic drinks per week, excessive caffeine use, reporting any needle or blood phobias, and illnesses with immunological or endocrinological components or illnesses or medications with obvious consequences for these systems or for wound healing (e.g., excluding those individuals with cancer, recent surgeries, diabetes, peripheral vascular disease, wound-healing problems, and conditions such as asthma severe enough to require regular use of anti-inflammatories).

The study was designed to assess the influence of a hypnotic intervention on both immune function and wound repair, using an oral wound procedure described previously (Marucha et al., 1998). The oral biopsies

were scheduled later in the same day after the morning blood draws at both sample points. Unfortunately, because of equipment failure, the quality of the oral videographs proved to be too poor to allow independent raters to reliably assess wound closure.

Announcements describing the study were placed in the mailboxes of dental, medical, and dental hygiene students. In the memorandum that solicited volunteers, the students were told that half of them would be assigned to a hypnotic-relaxation group that would meet during lunch hours; volunteers were asked to be willing, in principle, to attend at least five sessions that would begin 8 days before the second blood draw, with the option of discontinuing any time they wished. They were also told that those participants who were not assigned to the hypnotic group would have the opportunity for training following their exams.

The first sample (baseline) for each of the cohorts was obtained either within the first few days of the quarter or immediately following spring vacation. The second sample occurred 3 days before the first major academic examination of the term. Students were paid \$5 for each of the two hypnotic assessment sessions and \$100 for each of the two sample points and associated follow-up wound videographs; in addition, students assigned to the hypnotic intervention received \$5 for each group session they attended.

A total of 130 students volunteered for the initial screening session. Among the final sample of 42 students who obtained a score of 7 or higher on both scales and came for the first sample point, 4 students did not return reliably for the daily wound videographs following the first sample and thus were not randomized or scheduled for the second sample point; 3 students changed their schedules related to the targeted exam (1 took a leave of absence and 2 medical students changed their preclinical track); and 1 student reported 18 drinks in the 3 days preceding baseline. A total of five separate cohorts were run over a 15-month period, with a final sample that included 19 women and 14 men with a mean age of 23.48 years ( $SD \pm 1.97$ ). The hypnotic group had 10 women and 7 men, whereas the control group included 9 women and 7 men.

### Hypnotic Intervention

The first hypnotic session, attended by all assigned participants for that cohort, provided an overview of hypnosis and its similarities to other forms of relaxation, as well as a group induction. Depending on scheduling, each group included 2-6 students. Each subsequent session began with the same series of deepening exercises used in the initial session; the middle portion of the session was varied and included various imagery exercises, with scenes drawn from several sources (Kroger & Fezler, 1976; Soskis, 1986); suggestions made each time included greater relaxation throughout the day and enhanced comprehension and retention of academic material. Daily independent practice of relaxation-self-hypnosis was emphasized in each session (Kroger & Fezler, 1976; Soskis, 1986). To standardize treatment across the cohorts, we used a written manual (available from the first author) that specified the content and order of components within each of the sessions, including deepening exercises, imagery, suggestions, and so forth, with scripts for each component. The group was designed to introduce the participants to a number of different kinds of hypnotic relaxation exercises so that participants might find the method or methods best suited to their needs. Sessions lasted 25-40 min, on the basis of the protocol for that particular session; the initial session was the longest, with the remainder lasting between 25 and 30 min. The group sessions were led by experienced clinical psychologists.

Prior to each of the daily group inductions, participants were asked to rate how they felt, from 0 (*extremely tense and anxious*) to 10 (*extremely calm and relaxed*). A second question asked the number of times the students had practiced on their own since the last time they had filled out the rating form and solicited comments on their experiences in their own practice or group sessions. At the completion of each group induction, the degree of current relaxation was evaluated a second time. Thus, these

assessments provided a way to regularly monitor individual practice and to assess responsiveness to the group exercises.

### Psychological Data and Health-Related Behaviors

The HGSHS, Form A (Shor & Orne, 1962), used for the initial screening of potential participants, has scores that range from 0 to 12; the amnesia item was scored as recommended (Kihlstrom & Register, 1984). Students who obtained an HGSHS score of 7 or higher were invited to return for individual assessments that included the Stanford Hypnotic Susceptibility Scale, Form C (Weitzenhoffer & Hilgard, 1962). This two-stage screening process using both the HGSHS and the Stanford Hypnotic Susceptibility Scale is a staple of the hypnotic literature and is designed to assure greater uniformity in hypnotic abilities among participants selected for research (Spiegel, Bierle, & Rootenberg, 1989). Both screening instruments involve inductions accompanied by suggestions for 12 representative hypnotic experiences (Kihlstrom & Register, 1984); for the HGSHS, the individual recalls and rates his or her responses after the induction, whereas responses on the Stanford Hypnotic Susceptibility Scale are assessed as they occur by the hypnotist. Among those selected for participation, the mean (*SEM*) scores for the HGSHS and Stanford Hypnotic Susceptibility Scale were 9.12 (0.22) and 8.82 (0.25), respectively.

The 10-item Perceived Stress Scale (PSS; Cohen & Williamson, 1988), administered at the time of each blood draw, measured the degree to which participants perceived their daily life during the prior week as unpredictable, uncontrollable, and overloading. Participants rated each item from 0 (*never*) to 4 (*very often*).

Administered at both sample points, the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) includes two 10-item mood scales. The two scales are largely uncorrelated and show good convergent and discriminant validity when related to state mood scales and other variables (Watson et al., 1988). Health complaints, perceived stress, social activity, and exercise have been related to these two affective dimensions (Watson, 1988).

To evaluate the possibility that the enhanced interpersonal contact provided by the intervention might be a primary mechanism facilitating immunological changes, at both points in time we used the shortened version of the New York University (NYU) Loneliness Scale, which contains three items assessing the frequency and extent of current perceptions of loneliness (Rubenstein & Shaver, 1982; e.g., "When I am completely alone, I feel lonely") Excluded items from the full scale had a trait orientation (e.g., "I am a lonely person" and "I always was a lonely person"). Possible scores range from 0 to 18, with higher scores indicating greater current loneliness.

Health-related behaviors assessed at each time point included recent medication use and caffeine and alcohol intake (Kiecolt-Glaser & Glaser, 1988). We also asked participants how many hours they had slept in the previous 3 days, as well as in the past 24 hr. At the baseline sample point, participants were asked to describe any chronic health problems. They were also asked to indicate the type and frequency of any regular relaxation practice (meditation, self-hypnosis, yoga, etc.) they used. On both occasions when blood was drawn, participants were asked to describe any recent acute health problems and medication use, as well as recent weight change.

### Immunological Assays

The *in vitro* use of mitogens (substances used in the laboratory that have the ability to stimulate lymphocyte proliferation or replication for large subsets of lymphocytes, analogous to a master key) can provide information on the immune system's ability to respond to certain foreign substances (Reinherz & Schlossman, 1980). The proliferative response of lymphocytes to stimulation by mitogens such as phytohemagglutinin (PHA) or Con A is termed *blastogenesis*.

A number of PNI studies have assessed the ability of NK cells to lyse or destroy "target" cells (usually cells from a tumor cell line), a process sometimes referred to as NK cell lysis (Kiecolt-Glaser et al., 1984, 1986; Whitehouse et al., 1996). The function and numbers of NK cells (particularly their function) appear relevant to a number of cancers, particularly the spread of metastatic cancer (Whiteside, Bryant, Day, & Herberman, 1990). The assay used was described previously (Kiecolt-Glaser et al., 1984, 1986).

Mitogen-stimulated peripheral blood leukocyte (PBL) activity was assessed by means of the Cell Titer 96 aqueous nonradioactive cell proliferation assay (Promega; Madison, WI), which determines the number of viable proliferating cells by colorimetry and results in data comparable with those obtained through radioactive isotope incorporation procedures (Gieni, Li, & HayGlass, 1996; Shobitz, 1994). The assay is based on the conversion of the tetrazolium salt 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) into a formazan that is soluble in tissue culture medium. MTS is converted into the aqueous soluble formazan by dehydrogenase enzymes found in metabolically active cells. The quantity of formazan product—and thus the amount of 490 nm absorbance—is directly proportional to the number of living cells in culture. Optical density (OD) is measured at 490 nm directly from a 96-well plate without additional processing. We used 96-well plates to set up samples in triplicate, with Con A (Sigma) and phytohemagglutinin (PHA; Sigma) at final concentrations of 10.0  $\mu\text{g/ml}$ , 5.0  $\mu\text{g/ml}$ , and 2.5  $\mu\text{g/ml}$ . Fifty microliters of sample cells from a stock solution of a concentration of  $1 \times 10^6$  cells per milliliter, in RPMI-1640 medium supplemented with 5% fetal bovine serum, were added to 50  $\mu\text{l}$  of each mitogen dilution and a media control. The plates were incubated in an atmosphere of 5%  $\text{CO}_2$  at 37  $^\circ\text{C}$ , with humidity, for approximately 68 hr. After incubation, 20  $\mu\text{l}$  of a 20:1 solution of MTS-phenazine methosulfate were added to the plates. The plates were then incubated for an additional 4 hr, after which OD was recorded by means of a Titertek Multiscan MCC (Bio Rad; Helsinki, Finland) plate reader. The background absorbance of the plate was removed by using a reference wavelength of 650 nm, per the manufacturer's suggestion. Analyses were performed on values averaged across concentration levels after subtracting the average unstimulated control value.

Monoclonal antibodies (Coulter) and flow cytometry were used to obtain percentages of T-lymphocyte, NK cells, and monocyte populations as previously described (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991).  $\text{CD3}^+$  (total T-lymphocytes), T4-RD1/T8 (helper/suppressor cells), NKH-1 (NK cells), and MO2-RD1/KC56 (macrophage/monocytes) were measured because of their inclusion in previous related work, in addition to their importance for wound repair (Kiecolt-Glaser et al., 1986; Martin & Muir, 1990). The monoclonal antibodies were conjugated to fluorescein isothiocyanate (FITC). The isotype control used was MS IgG1-FITC. Percentages of lymphocyte populations were obtained by gating on lymphocytes; the percentage of macrophage/monocytes was obtained by gating on leukocytes. Flow cytometry was performed using a Coulter Epics Profile II flow cytometer (Coulter; Hialeah, FL).

IL-1 plays a critical role in wound healing by regulating inflammatory cell recruitment and activation, metabolism of matrix components, and production of growth factors early in the wound-healing process. Thus, lowered IL-1 responses may be an important mechanism for delayed healing (Hübner et al., 1996; Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998) associated with the stress-related delays in wound recovery observed in previous studies (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995; Kiecolt-Glaser et al., 1998); for example, consistent with the large differences in wound-healing times observed in a previous study with students, IL-1 $\beta$  declined dramatically during examinations (Marucha et al., 1998).

To assess IL-1 $\beta$ , we diluted heparinized blood with an equal volume of saline and treated it with 1  $\mu\text{g/ml}$  of *Salmonella typhimurium* lipopolysaccharide (Sigma, St. Louis, MO) for 4 hr at 37  $^\circ\text{C}$  5% carbon dioxide. The

plasma was then isolated by centrifugation. Monoclonal antibodies for IL-1 for both coating (M-421B) and detecting (M420B-B) were obtained from Endogen (Woburn, MA). Antibody was bound to enhanced protein-binding 96 well plates (Corning #25805-96; Acton, MA) at a concentration of 1 mg/mL. After overnight incubation at 4 °C, excess antibody was removed and wells were blocked with 10% FBS/PBS at room temperature for 2 hr. Dilutions of a recombinant standard from Biosource (PHC0815, Camarillo, CA) or samples were added, and the plates were incubated overnight at 4 °C. Biotinylated anticytokine monoclonal antibody diluted to 1 mg/mL was added and the plates were incubated at room temperature for 45 min. After washing, avidin-horseradish peroxidase (Vector Laboratories #A-2004) diluted 1:500 was added and the plates were incubated for 30 min. Plates were washed and an ABTS substrate was added. Color was allowed to develop at room temperature. Color reaction was stopped with SDS/DMF stop solution. Optical density was read at 405 nm on a Bio-Tek model EL-310 (Winooski, VT).

**Data Analyses**

We analyzed data for NK cell lysis, Con A, and PHA using multivariate analysis of variance with two within-subject variables (change between baseline and exams and change across the three effector-to-target cell ratios for NK cell lysis, or concentrations, for mitogens), as well as two between-subjects variables (group assignment and gender). Analyses for the remaining immunological measures and self-report data used a single within-subject variable, change between baseline and exams. Multiple regression analyses within the hypnotic-relaxation group were used to evaluate the hypothesis that the frequency of practice and hypnotic susceptibility were significant predictors of immune function, after controlling for baseline levels. All tests are two-tailed unless otherwise indicated.

Throughout our data, we found no significant gender differences related to group assignment, change over time, or their interaction. Thus, although gender was included as a between-subjects variable in earlier analyses, sex differences are not reported.

**Results**

**Psychological Data and Health-Related Behaviors**

Baseline comparisons revealed no significant pretreatment differences between the hypnotic and control groups on age, immune

function, or health behaviors (see Table 1). Similarly, the groups did not differ significantly on the PSS, the PANAS, or current loneliness. No participant reported any relaxation practice at baseline.

Students reported significantly more stress on the PSS prior to examinations than at baseline,  $F(1, 30) = 32.54, p < .001$ ; although it was in the expected direction (see means in Table 1), the Group  $\times$  Time interaction was not significant,  $F(1, 30) = 1.28$ . The pattern for PANAS negative affect was similar, with a significant increase in negative affect prior to exams,  $F(1, 31) = 21.50, p < .001$ , and a nonsignificant Group  $\times$  Time interaction,  $F(1, 31) = 1.59$ .

Data from the short NYU Loneliness Scale showed a marginal decrease over time,  $F(1, 31) = 3.98, p < .06$ , without either a significant effect for group,  $F(1, 31) = 1.53$ , or, of most importance, a Group  $\times$  Time interaction, ( $F < 1$ ; see means in Table 1). Thus, there was no differential change in loneliness related to group membership.

Prescription medications taken by participants at both time points included birth control pills (3 hypnotic and 2 control participants) and thyroid supplements (1 control). Two hypnotic and 2 control participants reported use of over-the-counter antihistamines within the past 3 days at both sample points, whereas 1 hypnotic participant reported use at baseline and 1 control reported use only prior to exams. Three hypnotic and 2 control participants reported use of nonprescription Tylenol, Advil, or Ibuprofen within the past 3 days at both sample points, whereas 2 hypnotic participants and 2 controls reported use only at baseline and 1 control reported use only prior to exams. Thus, there were no systematic differences in medication use between the groups.

Health-related behaviors changed between the two sample points, similar to changes observed in other academic stress studies (see Table 1). Alcohol intake declined from baseline to exams,  $F(1, 31) = 12.00, p < .01$ . Students reported an average of  $2.88 \pm 0.61$  drinks over the prior 3 days at baseline, compared with  $1.33 \pm 0.43$  drinks in the 3 days prior to the exam sample. Caffeine intake increased from an average of  $1.09 \pm 0.25$  cups per

Table 1  
Changes in Mean and Standard Error of the Mean Psychological Data and Health-Related Behaviors

Questionnaire and health related behavior	Baseline				3 days before exam			
	Hypnosis		Control		Hypnosis		Control	
	M	SEM	M	SEM	M	SEM	M	SEM
Perceived stress scale*** <sup>a</sup>	7.59	1.23	9.86	1.34	13.53	1.71	15.69	1.89
PANAS, negative affect*** <sup>a</sup>	14.38	0.72	15.38	0.72	18.00	1.52	21.75	2.06
PANAS, positive affect	36.00	1.48	36.69	1.32	34.65	1.36	35.50	1.28
NYU Loneliness (short form)	10.88	0.38	11.63	0.40	10.53	0.40	11.06	0.41
Caffeine, past 24 hr** <sup>a</sup>	1.06	0.28	1.13	0.44	2.12	0.60	2.13	0.52
Alcohol, past 3 days** <sup>a</sup>	3.53	0.97	2.19	0.70	1.41	0.59	1.25	0.63
Sleep (hours), past 3 days* <sup>b</sup>	22.82	0.48	22.06	0.69	21.00	0.67	22.12	0.57
Sleep (hours), past 24 hr* <sup>a</sup>	6.59	0.36	6.75	0.18	5.82	0.33	6.13	0.29
Exercise (hours), past week	3.59	0.75	4.19	0.70	3.41	0.72	3.94	0.44

Note. PANAS = Positive and Negative Affect Schedule; NYU = New York University.

<sup>a</sup> Change from baseline to exams. <sup>b</sup> Significant interaction between group and time.

\*  $p < .05$ . \*\*  $p < .01$ . \*\*\*  $p < .001$ .

day at baseline to  $2.12 \pm 0.50$  cups prior to exams,  $F(1, 31) = 10.52, p < .01$ . There were no significant group differences for either alcohol or caffeine intake ( $F < 1$ ) and no significant interaction between group and time for either behavior ( $F_s < 1.80$ ).

Students slept less in the 24 hr prior to exams than at baseline,  $F(1, 31) = 6.11, p < .02$ , with no significant group or Group  $\times$  Time effects,  $F_s < 1$  (Table 1). A second question assessed hours of sleep in the preceding 3 nights at both sample points; in this case, change over time approached significance,  $F(1, 31) = 3.90, p < .06$ , and the significant Group  $\times$  Time interaction reflected the fact that control participants reported essentially the same number of hours at both points in time, whereas hypnotic participants showed a modest decrease in sleep as exams approached,  $F(1, 31) = 4.47, p < .05$ . Both measures of sleep, the past 24 hr and the past 3 days, were negatively correlated with perceived stress scores,  $r = -.26$  and  $-.27$ , respectively,  $p = .14$ . Correlations between sleep data and immune data were small and nonsignificant, ranging from  $r = -.01$  to  $r = -.13$ . Thus, we found no health-related behaviors that appeared to account for the alterations observed in immune function.

### Immunological Data

Although the hypnotic and control groups started at comparable levels at the lower stress baseline, control participants' lymphocyte proliferation decreased prior to exams (see Figure 1 and Figure 2); in contrast, the proliferative responses of hypnotic participants remained relatively stable or increased slightly, producing significant Group  $\times$  Time interactions for both PHA,  $F(1, 31) = 4.94, p < .04$ , and Con A,  $F(1, 31) = 4.26, p < .05$ . The three Con A concentrations produced the expected differences in response,  $F(2, 30) = 16.33, p < .001$ , and there were greater group differences at lower concentrations, resulting in a Time  $\times$  Concentration interaction,  $F(2, 30) = 3.28, p < .05$ . There was also a significant group effect for PHA stimulation,  $F(1, 31) = 4.58, p < .05$ , largely reflecting the Group  $\times$  Time interaction. In addition, differences between hypnotic and control groups were greater at lower PHA concentrations,  $F(2, 62) = 3.31, p < .04$ , producing a Group  $\times$  Concentration interaction.

Changes in the percentages of CD3<sup>+</sup> T-lymphocytes and CD4<sup>+</sup> (helper/inducer) T-lymphocytes followed very similar patterns to

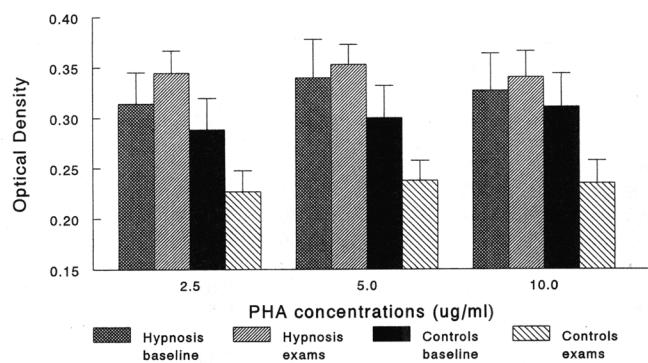


Figure 1. Changes in the blastogenic response to phytohemagglutinin (PHA) between baseline and exams in hypnotic and control group participants.

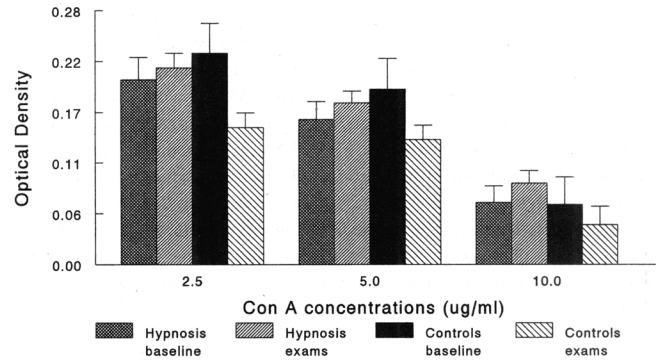


Figure 2. Changes in the blastogenic response to concanavalin A (Con A) between baseline and exams in hypnotic and control group participants.

those for the two T-cell mitogens; although the two groups did not differ significantly at baseline, values for hypnotic-relaxation participants remained relatively stable in the exam sample but those of control participants declined (Table 2). Thus, for CD3<sup>+</sup> T-lymphocytes, the Group  $\times$  Time interaction was  $F(1, 31) = 5.76, p < .03$ ; for CD4<sup>+</sup> cells, the interaction was  $F(1, 31) = 6.05, p < .03$ . In neither case were there significant main effects for group ( $F_s < 1$ ) or for time,  $F(1, 31) = 2.29$  for total T-lymphocytes and  $F < 1$  for CD4<sup>+</sup> T-cells.

In contrast to the significant impact of interventions observed for CD3<sup>+</sup> and CD4<sup>+</sup> T-lymphocytes, percentages of CD8<sup>+</sup> (suppressor/cytotoxic) T-cells did not reflect any significant changes in group, time, or their interaction ( $F_s < 1.57$ ). Thus, these data suggest that the intervention's impact on CD3<sup>+</sup> T-cells was greatest for the CD4<sup>+</sup> (helper/inducer) subset.

Production of IL-1 $\beta$  declined during examinations,  $F(1, 31) = 19.52, p < .001$ , with a mean of  $7.41 \pm 0.24$  ng/ml for the first sample compared with  $6.88 \pm 0.20$  ng/ml 3 days prior to examinations; the skewed distribution of these data necessitated a log transformation prior to analysis (after multiplying all values by 1,000). Although there were no significant group or Group  $\times$  Time effects,  $F_s < 1$ , the uniformity of change within each of the groups was also of interest, particularly in view of the highly skewed distribution; before the log transformation, values ranged from 0.12 to 40 ng/ml, or more than a 300-fold difference. In a prior academic stress study, 9 out of 9 dental students showed declines in the production of IL-1 $\beta$  by PBLs obtained during exams compared to cells taken at the end of summer vacation (Marucha et al., 1998); in the current cohort, 13 out of 16 (81%) of the control participants had lower values during exams compared with only 9 out of 17 (53%) of the hypnotic group,  $\chi^2(1, N = 33) = 2.97, p < .05$  (one-tailed).

IL-1 $\beta$  is produced by monocytes, and the pattern of change for percentages of MO2<sup>+</sup> macrophage/monocytes paralleled those observed in T-lymphocytes. The Group  $\times$  Time interaction reflected the fact that control participants exhibited a trend toward greater downward change than did hypnotic participants,  $F(1, 31) = 3.16, p < .08$ . Neither the main effect for group nor that for time was significant in either case ( $F_s < 1$ ).

Analysis of NK cell lysis data showed that the three effector-to-target cell ratios produced the expected differences in lysis,  $F(2, 28) = 4.94, p < .02$ , without significant effects for time, group, or

Table 2  
Changes in Mean and Standard Error of the Mean Leukocyte Percentages

Leukocyte %	Baseline				3 days before exam			
	Hypnosis		Control		Hypnosis		Control	
	<i>M</i>	<i>SEM</i>	<i>M</i>	<i>SEM</i>	<i>M</i>	<i>SEM</i>	<i>M</i>	<i>SEM</i>
CD3 <sup>+</sup> T cells*	76.97	1.77	77.69	1.87	77.48	1.63	75.41	2.10
CD4 <sup>+</sup> T cells*	45.01	2.06	46.93	1.91	46.25	2.13	45.10	2.01
CD8 <sup>+</sup> T cells	28.19	1.74	27.85	1.34	27.32	1.49	27.79	1.29
NK cells	10.68	1.62	9.59	0.94	9.23	1.01	9.74	1.06
MO2 (macrophage/monocytes)	13.72	0.78	16.06	1.58	15.33	0.91	15.07	1.08

Note. NK = natural killer.

\*  $p < .05$ , significant interaction between group and time.

the Group  $\times$  Time interaction,  $F_s < 1$ . Similarly, the percentages of NK cells did not show significant differences related to time, group, or the interaction of these variables,  $F_s < 1.93$ .

### Intervention Group Participation

The ratings taken before and after each of the group hypnotic sessions were averaged across sessions to provide a composite measure of responsiveness. The mean rating prior to the induction was  $5.04 \pm 0.31$ , increasing to  $8.67 \pm 0.21$  postsession, reflecting a highly reliable increase in feelings of calmness or relaxation,  $F(1, 16) = 177.60, p < .0001$ , and participants' written comments on the group sessions were similarly positive. Students attended from 4 to 8 group sessions ( $M = 6.24 \pm .30$ ) prior to the second blood draw and practiced individually from 0 to 7 times.

Multiple regression analyses that used residualized change scores from each of the immunological assays as the dependent measure were used to evaluate the hypothesis that frequency of practice and hypnotic susceptibility were significant moderators of immune change within the hypnotic-relaxation group. As the length of individual practice sessions varied greatly, ranging from less than 5 min to 30 min, we used the number of group sessions in these analyses. More frequent group attendance was associated with significantly higher percentages of both CD3<sup>+</sup> and CD4<sup>+</sup> cells; for CD3<sup>+</sup>,  $\beta = .579, p < .02, R^2 = .36$ ; and for CD4<sup>+</sup>,  $\beta = .60, p < .01, R^2 = .34$ . No significant relationships were found for other immunological measures, and in no case was hypnotic susceptibility as assessed by either the HGSHS or the Stanford Hypnotic Susceptibility Scale significantly associated with immune change for any of the assays.

### Discussion

The data from this study provide encouraging evidence that interventions may reduce the immunological dysregulation associated with acute stressors; hypnotic participants were, on average, protected from the stress-related decrements that were observed in control participants in the proliferative responses of their PBLs to Con A and PHA and participants' percentages of CD3<sup>+</sup> and CD4<sup>+</sup> T-lymphocytes. Furthermore, a greater proportion of hypnotic participants were able to maintain their baseline levels of IL-1 $\beta$  during exams compared with control participants. Additionally, more frequent practice was associated with higher percentages of

CD3<sup>+</sup> and CD4<sup>+</sup> T-lymphocytes, a finding consistent with our previous study (Kiecolt-Glaser et al., 1986).

The proliferative response of lymphocytes to stimulation by mitogens is thought to provide a model of the body's response to challenge by infectious agents, such as bacteria or viruses (Reinherz & Schlossman, 1980). Decreased lymphocyte proliferation reflects the down regulation of normal immune responses in a variety of immunodeficiency conditions, including recovery from surgery (Linn & Jensen, 1983; Linn, Linn, & Jensen, 1983), AIDS (Fletcher, Baron, Asman, Fischl, & Klimas, 1987), and less severe illnesses, such as trenchmouth and infectious mononucleosis (Cogen, Stevens, Cohen-Cole, Kirk, & Freeman, 1982; Lumino, Welin, Hirvonen, & Weber, 1983). Thus, alterations in blastogenesis have been associated with a number of health outcomes. Similarly, IL-1 is a cytokine that is involved in many immunological, inflammatory, and developmental processes. IL-1 expression has been associated with delayed healing, as well as with altered immune responses to vaccines in caregivers (Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996; Kiecolt-Glaser et al., 1995; Marucha et al., 1998). Accordingly, even in the absence of wound-healing outcomes, the immunological changes observed have relevance for health.

Neither NK cell lysis nor NK cell percentages were responsive to the hypnotic intervention; however, perhaps the absence of an intervention effect is not surprising in light of the fact that neither variable reflected changes in response to the approaching exams, in contrast to prior academic stress studies that have revealed decrements in both (Glaser et al., 1986; Kiecolt-Glaser et al., 1984; 1986). It may not be possible to enhance immune function in young and healthy individuals such that it would rise above normal (nonstressed) levels, and it is possible that it would be undesirable to do so (Kiecolt-Glaser & Glaser, 1992).

In two prior studies with medical students, membership in the hypnotic group appeared to offer no direct protection or benefit for immune function during exams, although frequency and success of practice were associated with better outcomes in secondary analyses. In both of those studies, intervention participants reported less distress during exams than did their counterparts in the control condition. Why might the data from this study differ from related work? Importantly, the timing of the blood samples differed. In the current study, data were collected 3 days prior to examinations. In contrast, Whitehouse et al. (1996) obtained their examination

blood samples during final exams, in conjunction with the highly stressful National Board Examinations in physiology and biochemistry, and Kiecolt-Glaser et al. (1986) acquired blood samples on the 3rd day of a 3-day exam block.

In this context, sleep may have been an important mediator and may be related to the absence of stress-related NK cell changes in our data because even partial sleep deprivation can reduce NK cell activity significantly (Irwin et al., 1994). In comparison with prior academic stress studies, the sleep deficits reported by our students were quite modest. Thus, variance related to the pervasive sleep deficits may have obscured group differences in the two related studies. Moreover, another report from the same cohort of medical students studied by Whitehouse et al. (1996) showed that periods of reduced sleep were associated with significantly heightened perceptions of increased daily stress across the semester (Dinges et al., 1991). In our data, although control participants reported essentially the same number of hours of sleep at both points in time, our hypnotic participants showed a modest but significant decrease in sleep as exams approached. Accordingly, the association between perceived stress and sleep may provide one explanation for the fact that our intervention participants did not report significantly less distress during exams than controls.

In addition to differences in the timing of the blood samples, the timing and intensity of the intervention in this study differed from related studies. Whitehouse et al. (1996) began their intervention during orientation and continued with weekly group sessions that were spread across the academic term, whereas Kiecolt-Glaser et al. (1986) began their intervention 2 and a half weeks prior to exams. We timed the intervention for this study so that it began 8 days prior to the final blood draw, with the goal of maximizing practice before the second sample. (In this context it should be noted that one limitation of the study is the fact that the number of home practice sessions might have been subject to social desirability and recall biases.)

Participant selection criteria provide another possible explanation for the greater efficacy of the intervention in this study versus the two prior related studies; by using hypnotic susceptibility as a criterion, we specifically recruited individuals who were theoretically more likely to benefit from the intervention. If the results were simply a function of participants' hypnotic susceptibility, however, we should have found a relationship between our measures of hypnotizability and the immunological or psychological data, and we did not. It is possible that the relatively limited range of hypnotic ability may have been a factor. Moreover, although we used a hypnotic intervention and participants were selected on the basis of hypnotic susceptibility, it is certainly possible that techniques using other forms of relaxation might have produced similar results (Kiecolt-Glaser & Glaser, 1992; Lichstein, 1988).

Because the students in this study were not, as a group, significantly distressed or otherwise symptomatic before the intervention, their level of involvement and incentive for intensive individual practice may have been lower than that found in many clinical populations. Moreover, brief training in progressive relaxation is frequently not associated with significant autonomic changes among less anxious participants (Lehrer, Schoickett, Carington, & Woolfolk, 1980). Thus, these data may underestimate the magnitude of immune change possible in more distressed samples.

Indeed, some of the strongest evidence for the beneficial effects of hypnotic-relaxation interventions comes from the surgical literature (Blankfield, 1991; Lang et al., 2000). A variety of hypnotic-relaxation interventions appear to shorten hospital stays, decrease pain, and promote more rapid recovery following surgery (Blankfield, 1991); most are brief, often single session, and many involve taped suggestions. Although the absence of participants low on hypnotizability in this study makes it difficult to directly translate these findings to surgical settings where individuals would represent the full range of hypnotic abilities, only a minority of medical studies have actually assessed hypnotizability or made it a selection criteria. For example, 241 patients undergoing a stressful medical procedure were randomized to receive intraoperative standard care, structured attention, or self-hypnotic relaxation; self-hypnotic relaxation patients showed lower pain and anxiety, lower use of self-administered pain medication, shorter procedure times, and less hemodynamic instability than the other two groups (Lang et al., 2000). These group differences were particularly impressive in view of the brevity of the intervention and the presumed heterogeneity of the patients' hypnotic abilities. Thus, we might expect more dramatic results from an extended intervention with patients who were highly hypnotizable.

These and other biobehavioral studies are providing notable evidence relating physiological changes to psychological states and providing mechanistic explanations for clinically significant health changes. For example, psychological stress, even within a normal range, has measurable consequences for proinflammatory cytokine production in the local wound environment (Glaser et al., 1999). Much larger effects are likely among clinically depressed individuals, on the basis of the well-documented links between depression and immune dysregulation, as well as depression and cortisol (Keller, Shiflett, Schleifer, & Bartlett, 1994; Miller, 1998). Given the substantial consequences of stress for wound repair (Kiecolt-Glaser et al., 1998), even small diminutions in stress or anxiety among surgery patients could have substantial clinical consequences, both directly and indirectly.

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### New Editors Appointed, 2003–2008

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Manuscript submission patterns make the precise date of completion of the 2002 volumes uncertain. Current editors, Kevin R. Murphy, PhD, Michael Pressley, PhD, Philip C. Kendall, PhD, Chester A. Insko, PhD, and Nancy Eisenberg, PhD, respectively, will receive and consider manuscripts through December 31, 2001. Should 2002 volumes be completed before that date, manuscripts will be redirected to the new editors for consideration in 2003 volumes.