Available online at www.sciencedirect.com
SCIENCE DIRECT®
Brain, Behavior, and Immunity 17 (2003) S51–S57
BRAIN, BEHAVIOR, and IMMUNITY
www.elsevier.com/locate/ybrbi

Conditioned immunomodulation: Research needs and directions

Robert Ader*

Center for Psychoneuroimmunology Research, Department of Psychiatry, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, USA

Received 1 April 2002; received in revised form 15 August 2002; accepted 15 August 2002

Abstract

Considering the brief time that psychoneuroimmunology has existed as a bona fide field of research, a great deal of data has been collected in support of the proposition that homeostatic mechanisms are the product of an integrated system of defenses of which the immune system is a critical component. It is now clear that immune function is influenced by autonomic nervous systems activity and by the release of neuroendocrine substances from the pituitary. Conversely, cytokines and hormones released by an activated immune system influence neural and endocrine processes. Regulatory peptides and receptors, once confined to the brain, are expressed by both the nervous and immune systems enabling each system to monitor and modulate the activities of the other. It is hardly surprising, then, that immunologic reactivity can be influenced by stressful life experiences or by Pavlovian conditioning.

1. Introduction

The oldest experimental studies of a relationship between the brain and the immune system were studies of conditioning conducted by Soviet investigators in the 1920s (e.g., Metal'nikov & Chorine, 1926). The earliest modern studies on conditioned change in immunologic reactivity were confined to immunosuppressive responses and the conditioned taste aversion paradigm (Ader & Cohen, 1975; Rogers, Reich, Strom, & Carpenter, 1976; Wayner, Flannery, & Singer, 1978). Research in this area now includes a variety of experimental circumstances under which conditioning can modulate immune responses. The experimental design requirements for studies of conditioning, however, are basically the same (Table 1). The critical experimental group (Group CS) consists of animals that are conditioned by the pairing of a conditioned stimulus (CS, e.g., the novel taste of saccharin) and an unconditioned stimulus (UCS, e.g., the immunomodulating effects of a drug or an antigen). Some time after conditioning, these animals may or may not be injected with an antigen and are reexposed to the CS. Measures of immunologic reactivity are obtained periodically thereafter. The most critical of the control groups (Group CSo) are similarly conditioned animals that are *not* subsequently reexposed to the CS. A conditioned group that is again exposed to the UCS is included to define the unconditioned effects of the immunomodulating agent. Still another conditioned group that is reexposed to the CS (Group CSp) consists of animals exposed to the conditioned stimulus *before* conditioning. This preexposed group, which should show an attenuated conditioned response, adds further to the argument that associative processes are involved in the alteration of immune function. There are, in addition to the conditioned groups, nonconditioned animals. Group NC receives both the CS solution and the UCS, but in an unpaired or noncontingent fashion. Subsequently, these

* Fax: 585-273-1384.
E-mail address: Robert_Ader@urmc.rochester.edu.

0889-1591/03/$ - see front matter © 2003 Elsevier Science (USA). All rights reserved.
PII: S0889-1591(02)00067-3

Table 1
Treatment conditions[a]

Group	Pre-trtmnt.	Treatment	Sub-group	Test trial(s)	Rationale
Cond.	None	CS + UCS	CS	CS + Sal	Experimental group: Conditioning effects
	None		CSo	H_2O	Control: Effects of conditioning, per se; Residual effects of CS + UCS
	CS		CSp	CS + Sal	Control: Effects of CS pre-exposure (attenuation of CR)
	None		UCS	H_2O + UCS	Unconditioned effects
Noncond.	None	CS ≠ UCS	NC	CS	Control: Noncontingent CS – UCS pairing; Nonassociative factors; Residual effects of UCS
Placebo	None	CS + Sal	P	CS + Sal	Control: Residual effects of CS and handling, injections, etc.

CS = conditioned stimulus; CSo = no conditioned stimulus; UCS = unconditioned stimulus; + = paired; ≠ = unpaired; Sal = saline.
[a] Adapted from Ader and Cohen (2001), with permission.

nonconditioned animals are reexposed to the CS which, presumably, has no associative value. Finally, a control group that defines the residual effects of the conditioned stimulus and other procedural manipulations (Group P) is exposed to the CS but not to any immunomodulating UCS and, like the other groups, is subsequently reexposed to the CS.

There are no shortcuts—especially if there is a change from previous studies in the CS, the UCS, or the components of immune function being assessed. We cannot be certain that all immune responses are subject to conditioning or that they can be conditioned under the same experimental circumstances.

As described elsewhere (Ader & Cohen, 2001), conditioning effects have been independently verified under a variety of experimental conditions. In contrast to the initial studies, the major thrust of current research has been on the conditioned *enhancement* of antibody production using antigen as the unconditioned stimulus. Antigen is, by definition, the most salient stimulus for activation of the immune system. In the first of these studies, Gorczynski, Macrae, and Kennedy (1982) repeatedly grafted skin tissue from C57BL/6J mice onto CBA mice. The recipient mice were subsequently reexposed to the grafting procedures but did not actually receive the allogeneic tissue. There was, nevertheless, an increase in the number of cytotoxic lymphocyte precursor cells in response to the CS. Interestingly, in several replications of the same experiment only approximately half the animals in each experiment displayed the conditioned response. "Responder" mice were then subdivided into those that received additional conditioning trials and those that received unreinforced exposures to the complex of stimuli that defined the CS. When subsequently tested, all the "responder" mice that received additional conditioning trials showed the conditioned response; none of the "responder" mice that had received extinction trials showed the conditioned response.

In our first study of conditioned immunoenhancement (Ader, Kelly, Moynihan, Grota, & Cohen, 1993), the antigen keyhole limpet hemocyanin (KLH) was paired repeatedly with the consumption of chocolate milk. Conditioned animals reexposed to the CS solution alone did not show an elevation in antibody titers, but conditioned animals that were reexposed to the CS in the context of a low-dose booster injection of KLH did show a conditioned increase in IgG.

Using hen egg lysosome, Alvarez-Borda, Ramírez-Amaya, Pérez-Montfort, and Bermúdez-Rattoni (1995) found an increase in both IgG and IgM among animals reexposed to a conditioned stimulus previously paired with HEL; a booster injection of antigen was not required. Although our effects were of a lesser magnitude, we (Madden et al., 2001) were able to replicate the increased production of IgG in animals reexposed to a CS previously paired with HEL in a study that very closely reproduced the procedures described by Alverez-Borda and his colleagues. The magnitude of our differences were subsequently affirmed in an even more recent study from Bermúdez-Rattoni's laboratory (unpublished observations).

Studies of conditioned enhancement in human subjects are more difficult to implement than studies in animals and have yielded inconsistent results. For example, Smith and McDaniels (1983) observed a conditionally reduced delayed type hypersensitivity (DTH) response but were unable to elicit a DTH reaction in response to a stimulus previously paired with tuberculin injections. Booth, Petrie, and Brook (1995), however, were unable to repeat these observations. In a jointly published paper by German and Dutch investigators (Kirschbaum et al., 1992) it was reported (and confirmed in subsequent studies) that, in Germany, the repeated pairing of a gustatory stimulus and epinephrine resulted in a conditioned increase in natural killer (NK) cell activity when subjects were reexposed to the

CS; in The Netherlands, however, no significant effects were observed. Presumptive evidence of conditioning was obtained by Gauci, Husband, Saxarra, and King (1994) who studied allergic rhinitis patients and used an allergen as the UCS and by Longo and his associates (1999) who used recombinant interferon-γ as the UCS, but the design of these studies precluded definitive conclusions.

2. Future studies

2.1. Methodological considerations

Before discussing the mediation or biologic significance of conditioned effects, it is necessary to address issues of methodology and definition that are critical for identifying some of the questions that need to be asked as well as the design of subsequent research.

Many, perhaps most, in vivo studies in immunology immunize with what are probably suprathreshold levels of antigenic stimulation in an attempt to induce an "optimal" response. That "optimal" (frequently maximal) response, however, may provide no latitude for the observation of the effects of behavioral interventions. Thus, we are in need of studies that include systematic variation of the immunogenic stimulation in order to better assess the magnitude and extent of the effects of conditioning or, for that matter, stressful life experiences or other behavioral interventions.

In designing a conditioning study, it is not known when, optimally, the CS "should" be presented in relation to immunization. Such information is critical for determining what temporal relationship would be appropriate to define a "noncontingent" control group. At the same time, it addresses the question of what component of the immune response to an immunomodulating agent (or pathogenic, e.g., carcinogenic, stimulus) is being associated with what sensory stimulation. Methodologically, then, it is important to increase the duration of exposure to the CS during conditioning and/or systematically vary when, in relation to immunogenic stimulation, the CS is presented. Such information would allow the CS to be introduced at times that correlate with empirically established antigen specific and antigen nonspecific events. If the effects of conditioning are thereby magnified, we would be better able to study the generalization or extinction or retention of conditioned alterations of immunity. It would, at the same time, provide clues to the identity of mediating pathways for conditioned changes in immunity which are, presumably, related to the quality and quantity of immunogenic stimulation.

In addition to procedural differences, another factor that may contribute to some of the small or inconsistent effects in studies of conditioning—and stress, for that matter—is the variation in experimental subjects. However, differences in host characteristics should be viewed, not as complications, but as opportunities. Age differences, gender differences, strain differences, and species differences in behavioral and physiologic (including immunologic) function permit one to identify and focus on empirically derived candidates for the mediation of behaviorally induced changes in immune function that could contribute to alterations in the susceptibility to or progression of disease. Thus, rather than a discrete but intrusive intervention that induces a multitude of physiological changes, one could take advantage of the neuroendocrine and immunologic differences between young and old animals or the difference in the pattern of cytokine responses that characterize different strains of animals to identify processes that could be involved in mediating conditioned and other behaviorally induced immunologic changes.

Another critical issue for defining the nature of conditioned alterations in immune function—and, thus, the search for underlying mechanisms—is the specificity of conditioned immune responses. Are the conditioned changes responsible for the enhanced production of antibody, a consequence of immunologic reactions specific to the antigen used as the UCS or is antibody production mediated entirely by neuroendocrinologically induced, nonspecific immunologic reactions? One approach to this question would use a discriminative conditioning paradigm in which animals would be conditioned by the pairing of CS-1 with antigen-1 and CS-2 with antigen-2. On the test trial, the animals would be reexposed to CS-1 or CS-2. An elevation in the antibody titers previously elicited by both antigen-1 and antigen-2 (Ab-1 and Ab-2) in response to reexposure to either CS-1 or CS-2 would indicate a nonspecific enhancement of antibody production. An enhancement of antibody production confined to the antigen previously paired with CS-1 would indicate the conditioning of a specific response—assuming confirmation by the elevation of only Ab-2 in response to CS-2. In short, parametric studies of the behavioral, neuroendocrine, and immunologic circumstances that give rise to the conditioned enhancement of immune responses are critical for developing strategies to address the mechanisms underlying these conditioned alterations of immunity.

2.2. Biological significance of conditioned alterations of immunity

At present, little is known about the mediation of conditioned immune responses (Ader & Cohen, 2001). Presumably, the mechanisms involve autonomic nervous system and/or neuroendocrine processes plus feedback regulation by the immune system. Furthermore, it is likely that different pathways support the development and/or expression of different alterations of different

immune responses, i.e., there's probably no single pathway that can account for the observed effects. Before seeking mechanisms, then, it behaves one to define the nature of the phenomena one is trying to explain. Thus, psychoneuroimmunology is faced with the issue and the challenge of demonstrating the biological importance or clinical significance of behaviorally induced changes in immune function. The effects of conditioning in suppressing or enhancing immunity have not been large. Therefore, the question arises: do behaviorally induced alterations of immunity have any biological significance in relation to disease? There are, in fact, several illustrations of the potential clinical significance of such processes.

Ader and Cohen (1982) hypothesized that the substitution of CSs for active immunosuppressive drug would have a salutary effect on the course of autoimmune disease in lupus-prone mice and, as predicted, the onset of proteinuria and mortality was significantly delayed in conditioned animals compared to nonconditioned animals treated with the same amount of drug. That is, the onset of autoimmune disease in these genetically susceptible mice was delayed using a cumulative dose of active drug that was not, by itself, sufficient to alter progression of the autoimmune disorder. In addition, previously conditioned lupus-prone mice that were reexposed to the gustatory CS after active drug treatment was discontinued survived longer than similarly conditioned animals that received neither active drug nor CS (Ader, 1985). Using different conditioning situations, reexposure to a CS previously associated with different immunosuppressive stimuli has also been reported to reduce the severity of adjuvant-induced arthritis in rats (Klosterhalfen & Klosterhalfen, 1983, 1990; Lysle, Luecken, & Maslonek, 1992).

Transplantation models offer still another dramatic illustration of the impact of conditioning. Normally, A/J mice reject skin grafts from BALB/c or C57BL/6 donors within two weeks. A low dose of CY administered on the day of grafting, however, promotes survival of the allograft. Based on such data, Gorczynski (1990) paired saccharin consumption with an injection of CY and then reexposed conditioned A/J mice to the CS alone on the day of allografting and at 5-day intervals thereafter. Survival of the skin allograft was prolonged in conditioned mice reexposed to the CS compared to the several control groups. Comparable results were obtained by Grochowicz and his colleagues (1991) and by Exton and his associates (1998).

Finally, following from the animal research on conditioning in lupus-prone mice, a regimen of chemotherapy that capitalized on conditioning processes was prescribed for a child with systemic lupus erythematosus (Olness & Ader, 1992). A combined gustatory and olfactory CS was administered with the infusion of cytoxan. During the course of a year of monthly treatments, the child received only half the amount of cytoxan she would normally have received; half the treatments consisted only of CS exposures and vehicle infusions. Few definitive conclusions can be drawn from a single case study, but the patient improved clinically and continued to do well for several years.

In a study of asthmatic children (Castes, Palenque, Canelones, Hagel, & Lynch, 1998), a β_2 agonist bronchodilator inhalation (salbutamol) was paired with a vanilla odor twice a day for 15 days. Control subjects received only the bronchodilator or unpaired exposures to the odor. In conditioned children, reexposure to the odor alone increased pulmonary function. It was also reported that children accustomed to inhaler therapy showed a significant increase in pulmonary function in response to a placebo inhaler.

In addition to addressing the potential clinical significance of conditioned alterations in immune function, studies such as these suggest that conditioning principles would be relevant in the design of pharmacotherapeutic regimens prescribed to maintain a variety of other physiologic states within homeostatic bounds. An analysis of the role of conditioning in pharmacotherapies and its implications for an understanding of placebo effects is elaborated elsewhere (Ader, 1997).

In the case of cancer, the clinical role of conditioning first emerged in relation to the anticipatory nausea and vomiting associated with chemotherapy (e.g., Andrykowski, Redd, & Hatfield, 1985; Carey & Burish, 1988). Bovbjerg and his associates (1990) examined the possibility that chemotherapy patients might show conditioned immunosuppression as well as conditioned nausea and vomiting. Women receiving chemotherapy for ovarian cancer were sampled at home (before a scheduled chemotherapy session) and in the hospital on the day of their chemotherapy. No differences were found in NK cell activity or in lymphocyte counts or subset numbers, but the lymphoproliferative response to the T-cell mitogens, Con A and PHA, were lower in the hospital just before chemotherapy than they were at home. Also, there was a significant relationship between anticipatory nausea and the "anticipatory" effect on mitogen responsiveness. Fredrikson, Fürst, Lekander, Rotstein, and Blomgren (1993), however, were unable to confirm these observations, but there were major differences between the populations studied and the experimental conditions. Studies involving conditioned changes in immune function using patients subjected to immunomodulating medications are difficult to implement because, among other things, one cannot create conditions for a noncontingent presentation of the cues associated with chemotherapy and the chemotherapy, itself.

The literature on conditioned changes in immune function in relation to cancer in animals is also inconsistent. In contrast to the conditioned increase in NK

cell activity reported by others (in other experimental conditions) (e.g., Solvason, Ghanta, & Hiramoto, 1988), Gorczynski and Kennedy (1984) found a decrease in NK cell activity when animals were exposed to a CS previously paired with poly I:C. Mice that showed the immunosuppression also showed decreased survival to an adoptively transferred, NK sensitive tumor (the YAC-1 lymphoma). No such effects were seen using an NK resistant tumor. In another study (Gorczynski, Kennedy, & Ciampi, 1985), mice conditioned with CY were subsequently challenged with a syngeneic plasmacytoma. Conditioned mice reexposed to the CS showed an accelerated mortality rate compared to conditioned animals that were not reexposed to the CS as well as nonconditioned and placebo treated groups. These results provide consensual validity for the studies on spontaneous lupus and adjuvant-induced arthritis discussed above.

Using an NK *resistant*, transplanted MOPC 104E myeloma, Ghanta, Hiramoto, Solvason, and Spector (1987) reported that reexposure to a CS previously paired with poly I:C which elevates NK cell activity can reverse the growth of the tumor and enhance survival in BALB/c mice. Conditioned mice received 10 trials on which a 4-h exposure to the odor of camphor was paired with an injection of poly I:C. After inoculation with tumor cells, the animals were reexposed to the camphor for 4 h every three days. A control group of conditioned animals was not reexposed to the CS following the tumor transplant. A third group received only poly I:C before transplantation and was subsequently exposed to camphor plus additional injections of poly I:C. A final group received no treatment. There were no overall differences among the several groups. Two "outlier" mice in the conditioned group reexposed to the CS did not die, but the median survival time for the remaining animals in the CS group was no different from that of the other groups—including the group that received poly I:C throughout the study.

In a subsequent meeting report, additional data on the susceptibility to the NK resistant, MOPC 104E plasmacytoma were presented (Ghanta, Miura, Hiramoto, & Hiramoto, 1988). Again, the results suggested a slower mortality rate among animals reexposed to the CS. However, there were no nonconditioned groups or a control group to define the unconditioned effects of poly I:C on tumor growth and mortality. However provocative, problems with design and data analyses in these and other studies attempting to use conditioning to influence the response to tumors (e.g., Ghanta, Hiramoto, Solvason, Soong, & Hiramoto, 1990), preclude any conclusions about the biologic impact or clinical significance of conditioned alterations of immune function.

In a study by Blom, Tamarkin, Shiber, and Nelson (1995), saccharin consumption was paired with CY on a single trial and conditioned mice were reexposed to the CS on one or two occasions after being injected with the chemical carcinogen, 9,10-dimethylbenanthracene (DMBA). There was no CSo group, but there was an NC group exposed to the CS and UCS in a noncontingent manner and later reexposed to saccharin and a placebo-treated group that was also reexposed to saccharin when they were injected with DMBA (and again three days later). In the first experiment, a greater percentage of the twice-reexposed CS group had verified tumors than the nonconditioned (noncontingent) animals that were also reexposed to the CS on two occasions. In a second experiment, the CS group did not differ from an NC group that experienced the noncontingent CS–UCS presentation. The results, then, are less than definitive, but consistent with some previous findings (Gorczynski et al., 1985).

To the extent that immune function is implicated in the response to carcinogens or some neoplastic processes, conditioning could be expected to influence CNS-immune system interactions that influence the precipitation or progression of the disease. While the available data are better for some pathophysiological processes than others, reexposure to an immunologically neutral stimulus previously associated with an immunomodulating agent or the immunologic effects of a stressful experience can evoke responses that influence immunocompetence, the progression of pathophysiologic processes and, ultimately, survival. To the extent that the effects of some immunomodulating agents on neoplastic processes are not direct target organ effects, conditioning could also have a role in the design of chemotherapeutic regimens in much the same manner as it appears to act on other disease processes—at least in animals. No research has yet attempted to extrapolate from the animal or human studies on the role of conditioning in the pharmacotherapy of lupus or on the animal studies of arthritis or transplant phenomena to modify a combined drug regimen of chemotherapy for cancer. The data thus far available and extrapolations from these observations hint at the clinical significance and therapeutic potential of conditioned alterations in immune function in autoimmune and infectious diseases and in cancer.

3. Concluding remarks

Let me conclude this brief review by mentioning some broader issues related to the biologic significance of behaviorally induced alterations of immune function. Are the changes in immune function induced by conditioning relevant to and of sufficient magnitude to influence the development (or recovery) from autoimmune, infectious or neoplastic diseases under conditions that exist in the real world? Can reexposure to a symbolic stimulus previously associated with an immunomodu-

lating agent or stressful life experiences precipitate manifest disease? Probably, not. If, however, the question is restated as: "Can reexposure to a symbolic stimulus previously associated with an immunomodulating agent or stressful life experiences—in biologically vulnerable individuals, immunocompromised hosts, or in the presence of a pathogen or a latent infection—precipitate or reactivate manifest disease?" then the answer is, probably, yes. Conversely, can reexposure to a symbolic stimulus previously associated with immunomodulating circumstances contribute to the resistance to or recovery from disease? Again, in consideration of relevant host factors, the answer is probably, yes.

Admittedly, the magnitude of the effects of conditioning have not been "large" (although there is no necessary relationship between the size of an effect and the biological importance of the effect). Nevertheless, the significance of much past research has been questioned on grounds that the effects are not large enough to be of clinical importance. That is, the effects are within homeostatic limits. I am under no illusion that data will alter the belief systems of those who seek main effects in a world made up of interactions, but there are dramatic data on the biologic effects of conditioning that were referred to, above. Unfortunately, the argument that the effects are not large enough to be of clinical importance has been accepted without question by many people, including some within the field of psychoneuroimmunology. The notion that a conditioned stimulus or psychosocial circumstances could perturb the immune system to an extent that exceeded homeostatic limits seems somewhat simplistic from a behavioral as well as an immunologic point of view. Except, perhaps, for rare and extreme circumstances, I cannot imagine why a conditioned stimulus (or a stressful experience, for that matter) could be expected to cause a major deviation from homeostasis within a normal immune system—or any other normally functional homeostatic system—unless one accepts the very questionable assumption that psychological factors, by themselves, are sufficient for the development of physical pathology.

Given the complexity of the cellular interactions and feedback and feedforward mechanisms within and between the immune and nervous systems, behaviorally induced deviations of immune function that did not exceed homeostatic limits would seem to be the only response that could reasonably be expected. One could hardly refer to the immune system as an agency of defense if, in response to even severe environmental circumstances, it could be caused to exceed its homeostatic bounds. It is not unreasonable, however, to hypothesize that behaviorally conditioned neuroendocrine changes are capable of altering immune responses that could have clinical consequences—in interaction with specific environmental pathogens or when superimposed upon existing pathology or an immune system compromised by endogenous or exogenously introduced circumstances. These are reasonable enough hypotheses to justify the continued study of conditioned alterations of immunity.

References

Ader, R. (1985). Psychoneuroimmunologic contributions to the study of rheumatic diseases. In S. Gupta & N. Jalal (Eds.), *Immunology of rheumatic diseases* (pp. 669–696). New York: Plenum Press.

Ader, R. (1997). The role of conditioning in pharmacotherapy. In A. Harrington (Ed.), *The Placebo: An interdisciplinary exploration* (pp. 138–165). Cambridge, MA: Harvard University Press.

Ader, R., & Cohen, N. (1975). Behaviorally conditioned immunosuppression. *Psychosom. Med., 37*, 333–340.

Ader, R., & Cohen, N. (1982). Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. *Science, 215*, 1534–1536.

Ader, R., & Cohen, N. (2001). Conditioning and immunity. In R. Ader, D. L. Felten, & N. Cohen (Eds.), *Psychoneuroimmunology* (vol. 2, (third ed., pp. 3–34). New York: Academic Press.

Ader, R., Kelly, K., Moynihan, J. A., Grota, L. J., & Cohen, N. (1993). Conditioned enhancement of antibody production using antigen as the unconditioned stimulus. *Brain Behav. Immun., 7*, 334–343.

Alvarez-Borda, B., Ramírez-Amaya, V., Pérez-Montfort, R., & Bermúdez-Rattoni, F. (1995). Enhancement of antibody production by a learning paradigm. *Neurobiol. Learn. Mem., 64*, 103–105.

Andrykowski, M., Redd, W. H., & Hatfield, A. (1985). The development of anticipatory nausea: A prospective analysis. *J. Consult. Clin. Psychol., 53*, 447–454.

Blom, J. M. C., Tamarkin, L., Shiber, J. R., & Nelson, R. J. (1995). Learned immunosuppression is associated with an increased risk of chemically-induced tumors. *Neuroimmunomodulation, 2*, 92–99.

Booth, R. J., Petrie, K. J., & Brook, R. J. (1995). Conditioning allergic skin responses in humans: A controlled study. *Psychosom. Med., 57*, 492–495.

Bovbjerg, D. H., Redd, W. H., Maier, L. A., Holland, J. C., Lesko, L. M., & Niedzwiecki, D., et al. (1990). Anticipatory immune suppression and nausea in women receiving cyclic chemotherapy for ovarian cancer. *J. Consult. Clin. Psychol., 58*, 153–157.

Carey, M. P., & Burish, T. G. (1988). Etiology and treatment of the psychological side effects associated with cancer chemotherapy: A critical review and discussion. *Psychol. Bull., 104*, 307–325.

Castes, M., Palenque, M., Canelones, P., Hagel, I., & Lynch, N. (1998). Classic conditioning and placebo effects in the bronchodilator response of asthmatic children. *Neuroimmunomodulation, 5*, 70.

Exton, M. S., von Hörsten, S. B., Schult, M., Vöge, J., Strubel, T., & Donath, S., et al. (1998). Behaviourally conditioned immunosuppression using cyclosporin A: Central nervous system reduces IL-2 production via splenic innervation. *J. Neuroimmunol., 88*, 182–191.

Fredrikson, M., Fürst, C. J., Lekander, M., Rotstein, S., & Blomgren, H. (1993). Trait anxiety and anticipatory immune reactions in women receiving adjuvant chemotherapy for breast cancer. *Brain Behav. Immun., 7*, 79–90.

Gauci, M., Husband, A. J., Saxarra, H., & King, M. G. (1994). Pavlovian conditioning of nasal tryptase release in human subjects with allergic rhinitis. *Physiol. Behav., 55*, 823–825.

Ghanta, V. K., Hiramoto, N. S., Solvason, H. B., Soong, S.-J., & Hiramoto, R. N. (1990). Conditioning: A new approach to immunotherapy. *Cancer Res., 50*, 4295–4299.

Ghanta, V., Hiramoto, R. N., Solvason, B., & Spector, N. H. (1987). Influence of conditioned natural immunity on tumor growth. *Ann. N. Y. Acad. Sci., 496*, 637–646.

Ghanta, V. K., Miura, T., Hiramoto, N. S., & Hiramoto, R. N. (1988). Augmentation of natural immunity and regulation of tumor growth by conditioning. *Ann. N. Y. Acad. Sci., 521*, 29–42.

Gorczynski, R. M. (1990). Conditioned enhancement of skin allografts in mice. *Brain Behav. Immun., 4*, 85–92.

Gorczynski, R. M., & Kennedy, M. (1984). Associative learning and regulation of immune responses. *Progr. Neuropsychopharmacol. Biol. Psych., 8*, 593–600.

Gorczynski, R. M., Kennedy, M., & Ciampi, A. (1985). Cimetidine reverses tumor growth enhancement of plasmacytoma tumors in mice demonstrating conditioned immunosuppression. *J. Immunol., 134*, 4261–4264.

Gorczynski, R. M., Macrae, S., & Kennedy, M. (1982). Conditioned immune response associated with allogeneic skin grafts in mice. *J. Immunol., 129*, 704–709.

Grochowicz, P., Schedlowski, M., Husband, A. J., King, M. G., Hibberd, A. D., & Bowen, K. M. (1991). Behavioral conditioning prolongs heart allograft survival in rats. *Brain Behav. Immun., 5*, 349–356.

Kirschbaum, C., Jabaij, L., Buske-Kirschbaum, A., Hennig, J., Blom, M., & Dorst, K., et al. (1992). Conditioning of drug-induced immunomodulation in human volunteers: A European collaborative study. *Br. J. Clin. Psychol., 31*, 459–472.

Klosterhalfen, S., & Klosterhalfen, W. (1990). Conditioned cyclosporine effects but not conditioned taste aversion in immunized rats. *Behav. Neurosci., 104*, 716–724.

Klosterhalfen, W., & Klosterhalfen, S. (1983). Pavlovian conditioning of immunosuppression modifies adjuvant arthritis in rats. *Behav. Neurosci., 97*, 663–666.

Longo, D. L., Duffey, P. L., Kopp, W. C., Heyes, M. P., Alvord, W. G., & Sharfman, W. H., et al. (1999). Conditioned immune response to interferon-γ in humans. *Clin. Immunol., 90*, 173–181.

Lysle, D. T., Luecken, L. J., & Maslonek, K. A. (1992). Suppression of the development of adjuvant arthritis by a conditioned aversive stimulus. *Brain Behav. Immun., 6*, 64–73.

Madden, K. S., Boehm, G. W., Lee, S. C., Grota, L. J., Cohen, N., & Ader, R. (2001). One-trial conditioning of the antibody response to hen egg lysozyme in rats. *J. Neuroimmunol., 113*, 236–239.

Metal'nikov, S., & Chorine, V. (1926). Rôle des réflèxes conditionnnels dans l'immunité. *Ann. Inst. Pasteur, 40*, 893–900.

Olness, K., & Ader, R. (1992). Conditioning as an adjunct in the pharmacotherapy of lupus erythematosus: A case report. *J. Dev. Behav. Pediat., 13*, 124–125.

Rogers, M. P., Reich, P., Strom, T. B., & Carpenter, C. B. (1976). Behaviorally conditioned immunosuppression: Replication of a recent study. *Psychosom. Med., 38*, 447–452.

Smith, G. R., & McDaniels, S. M. (1983). Psychologically mediated effect on the delayed hypersensitivity reaction to tuberculin in humans. *Psychosom. Med., 45*, 65–70.

Solvason, H. B., Ghanta, V. K., & Hiramoto, R. N. (1988). Conditioned augmentation of natural killer cell activity: Independence from nociceptive effects and dependence on interferon-β. *J. Immunol., 140*, 661–665.

Wayner, E. A., Flannery, G. R., & Singer, G. (1978). The effects of taste aversion conditioning on the primary antibody response to sheep red blood cells and Brucella abortus in the albino rat. *Physiol. Behav., 21*, 995–1000.