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STRESS COPING AND INFECTIOUS ILLNESS: PERSISTENTLY LOW  
NATURAL KILLER CELL (U) PITTSBURGH UNIV PA  
S M LEVY ET AL 14 MAR 88 N00014-87-K-0224

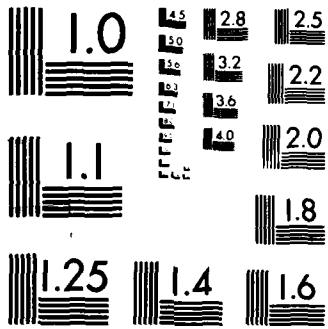
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19. ABSTRACT (Continue on reverse if necessary and identify by block number) Recent Japanese research, as well as pilot work preliminary to this current project, have pointed to a possible association between mood and lowered natural killer (NK) cell activity. In this previous work, a subgroup of individuals characterized by persistently low NK activity, and self-reported depression and fatigue, tended to report more serious illness on follow-up assessment. In this current study, we have accrued approximately, sixty-two normal individuals to this prospective project. Subjects are assessed both psychologically and physically at baseline, and are serially monitored over a six-month follow-up period in order to identify predictors of infectious illness over time. As in the preliminary work, we are finding that approximately 1/3 of the sample has persistently low NK activity, and this immunological pattern is strikingly associated with daily stress levels, as well as reports of depression and chronic anxiety. In a very preliminary fashion, we have also found a trend of association between this low NK activity pattern, and some categories of follow-up illness.	
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## ANNUAL REPORT

### Stress, Coping, and Infectious Illness: Persistently Low Natural Killer Cell Activity as a Host Risk Factor

ONR Contract #: N00014-87-K-0224

#### I. Introduction

The study of stress and coping responses linked with disease end-points in animal systems has revealed enhancement of disease risk under a variety of stress conditions (Riley, 1981; Visintainer, Volpicelli, and Seligman, 1982; Weiss, 1972; Laudenslager, Ryan, Drugan, et al., 1983). A number of such studies have also examined endocrinological and immunological mechanisms potentially mediating behavior and disease end-points (Shavit, Lewis, Terman, et al., 1983; Sklar and Anisman, 1979; Greenberg, Dyck, and Sandler, 1985; Schneiderman, 1986). However, there are scant clinical data demonstrating a link between distress response and disease end-points mediated by regulatory mechanisms such as immune function.

A number of studies have demonstrated a correlation between stressful life events of various kinds and increased incidence of acute, infectious illnesses, such as upper respiratory infections and infectious mononucleosis, as well as outbreaks of herpes simplex (Ishigami, 1919; Hinkle and Plummer, 1952; McClelland, Alexander, and Marks, 1982; Kemeny, et al., 1986). Several investigations have also indicated an association between stressful events and lymphocyte alteration (Palmlblad, Blomback, Egberg, et al., 1977; Bartrup, Luckhurst, Lazarus, et al., 1977; Crary, Borysenko, Sutherland, et al., 1983; Jemmott and Locke, 1984). However, with only a few exceptions (Kasl, et al., 1979 and Kemeny, et al., 1986), a major limitation of most human studies has been that they were not conducted in a prospective fashion, examining the association of life stress and coping ability with hormonal and immunological changes, with subjects then followed to assess the incidence of disease episodes. Since most studies have not made the final, longitudinal link with actual disease, the biologic significance of stress-related immune impairment remains unclear.

Preliminary work by our research team suggests that it may be possible to identify a subgroup of vulnerable individuals at particular risk of infectious illness. For example, research carried out by Aoki, Herberman and colleagues (1985) points to a possible association between mood and lowered NK activity. They identified a subgroup within a patient sample characterized by low NK activity, remittent fever, and self-reported depression and fatigue. The depressive and fatigue-like symptoms were sufficiently prominent that these individuals had frequently been seen by psychiatrists rather than by other health care specialists. These investigators concluded that these individuals may be suffering from a new immunological disorder termed Low Natural Killer Cell Syndrome (LNKS), and reported some success in treating them with an immunopotentiator, letinen.

The Principal Investigator and Co-Principal Investigator on this proposed project (S. Levy and R. Herberman) conducted preliminary work in the

Biological Response Modifiers Program at the NCI with resultant data consistent with Aoki, et al.'s. That study examined the predictive value of daily stressors, personality, and coping factors, as well as repeated baseline measures of natural immunity (NK activity) and hormonal distress markers (excreted epinephrine and norepinephrine) relevant to episodes of infectious illness in a sample of healthy laboratory volunteers. Results from that prospective study revealed a subgroup at risk for disease, identified as having "low natural killer cell syndrome" (LNKS). Such individuals, operationally defined as having persistently low functional levels of NK activity across all three times of measurement (three baseline measures separated by two-week intervals), tended to report more serious illness over a three-month follow-up period. When comparing the psychological and demographic profile of the LNKS versus "normal" NK group, the LNKS individuals tended to be younger, report more daily distress, and had higher levels of excreted urinary catecholamines than individuals with normal NK activity.

Taken together, these studies suggest that inadequate coping (reflected in reports of depression and/or fatigue, coupled with report of high levels of daily hassles), psychological distress (reflected in higher levels of norepinephrine and epinephrine excretion) and immune function (specifically NK activity) may interact to increase risk for infectious illness.

The direction of association is unclear at this time. It is plausible that psychological distress produced by inadequate problem solving of life's hassles may compromise immune function and lead to the development of illness. On the other hand, low levels of natural immunity may produce cognitive and behavioral effects such as dysphoria and inability to cope. This project is designed to assess the relevant variables over a sufficient length of time to begin to understand these complex relationships.

## II. Progress Report

During the first eleven months of this contract, we have trained a research associate who has served as a key project staff member for recruiting individuals from the community. We have also trained two lab technicians, and have begun carrying out endogenous opioid assays (plasma beta endorphin) in Dr. Fernstrom's laboratory, and have begun analyzing NK activity, and conducting flow cytometry analyses in Dr. Whiteside's laboratory.

We have accrued approximately sixty normal community volunteers to date for this prospective study. Initially, we intended to accrue both normal volunteers, and individuals who received a psychiatric diagnosis of dysthymia (chronic low level depression). However, it quickly became clear that the latter category of subjects was not available for study, as most wished to receive some sort of psychological treatment. We initially thought that we would randomize half of this sub-sample to a treatment and a wait-list control condition. However, after much consideration, we decided that the latter option would take us too far afield from the intention of this current project. Hence, in consultation with our project officer, we decided to focus on accruing a normal sample, from which the findings would be most generalizable to a military population. We have had very good response from the community, and our accrual of this sample to date has been excellent.



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Demographics. The mean age of the sample accrued so far is 30 (range, 18-44 years). The average educational level is 17.5 years, with approximately 60% of the sample as female. Fifty-three percent of the sample is single, with 33% married, and 13% divorced.

In terms of NK function, mean NK activity at the 50:1 E/T ratio = 44% (range, 18-80%), and the mean lytic unit value is 131.6. Approximately 24% of the sample shows persistently low NK activity, defined as NK function below the group mean at baseline, and also at three follow-up visits.

Follow-up illnesses reported. The following categories of illnesses, with numbers of individuals reporting having experienced these health end-points, are shown in Table 1.

TABLE I  
Illness reported on Follow-up

Illness Category	Numbers of Individuals
Cold	22
Influenza	4
Pneumonia	0
Cold sore	4
Gum infection	6
Mononucleosis	0
Strep throat	3
Gastrointestinal virus	9
Fever symptoms	7
Sore throat	7
Other	25

Preliminary Pearson correlations between NK activity and other study key variables. Table 2 displays selected correlations between study variables of major interest in this project. As can be seen, there are some interesting clusters of correlations in this Table. First, NK activity, at two E/T ratios, as well as measured in lytic units, was significantly negatively correlated with reported days ill with strep infection. (Please note that the N reporting strep infection is small, and this correlation should be viewed with caution.) NK function was also negatively correlated with frequency and severity of daily stressors or hassles. Hassles, or daily stressors, are also significantly positively correlated with other indices of distress, namely total Profile of Mood States scores, and specifically, with the report of fatigue-like symptoms. The latter is particularly interesting because of Aoki, et al's., (1985) findings that fatigue, or "uncomfortable general dullness" is associated with what he terms Low NK Syndrome. (Please note: We have not analyzed the largest illness category of "Other," so these data are quite preliminary in terms of simple associations with illness episodes.) Interestingly, NK function was positively correlated with age, and this is consistent with findings from other studies that we have carried out.

Persistently low NK activity. As indicated earlier, approximately 29% of the subjects had persistently low NK activity at baseline and at two follow-up periods, and 24% of subjects has persistently low NK activity at three repeat

assessment periods (baseline, and three follow-up measurements). Using the latter as the most stringent criterion for persistently low NK activity, we carried out a Chi-Square test, stratifying subjects into low NK activity versus other, and serious versus non-serious illness on follow-up (omitting the "Other" category, and the symptom category of fever). The "serious" category included: Influenza, pneumonia, mononucleosis, strep infection, and gastrointestinal virus. The "non-serious" illness category included: Cold, cold sore, gum infection, and minor sore throat. A non-significant trend was found for this preliminary analysis, with those falling into the persistently low NK category tending to report more serious illness on follow-up (Likelihood ratio Chi-Square = 1.5,  $p < .2$ ).

When comparing those with persistently low NK activity with others in the sample, many of our earlier pilot findings were confirmed here. Individuals with the low NK profile were also significantly more chronically anxious ( $t=2.1$ ,  $p < .05$ ), more depressed ( $t=1.7$ ,  $p < .04$ ), more confused ( $t=1.9$ ,  $p < .05$ ), with trends in the direction of more fatigue ( $t=1.5$ ,  $p < .1$ ) and acute anxiety ( $t=1.6$ ,  $p < .1$ ). Again, those with persistently low NK activity reported strikingly more frequent daily stressors ( $t=2.6$ ,  $p < .02$ ), more severe stressors ( $t=2.8$ ,  $p < .01$ ) and more intense daily stress levels ( $t=2.6$ ,  $p < .01$ ).

In sum, we are finding very similar trends and patterns in the current study to those we found in our pilot work for this project. It should be emphasized that these are preliminary data, and that when this prospective study is complete, we will be able to test by causal modeling procedures the direction and strength of associations between our predictor variables and illness endpoints.

## REFERENCES

- Aoki, T., Usuda, Y., Miyakoski, H., Tamura, K., Fujimoto, M., and Herberman, R., (1985). Low NK syndrome (LNKS). Proceedings of the Seventh Symposium on Host Defense Mechanisms Against Cancer, Hakone, November 8-10, 1985.
- Bartrup, R., Lazarus, L., Luckhurst, E., Kiloh, L., and Penny, R., (1977). Depressed lymphocyte function after bereavement. Lancet, 1, 834-836.
- Crary, B., Borysenko, M., Sutherland, D., Kutz, I., Borysenko, J., and Benson, H., (1983). Decrease in mitogen responsiveness of mononuclear cells from peripheral blood after epinephrine administration in humans. Journal of Immunology, 130, 604-607.
- Greenberg, A., Dyck, D., and Sandler, L., (1984). Opponent processes, neurohormones, and natural resistance. In B. Fox and B. Newberry (Eds.), Psychoneuroendocrine Systems in Cancer and Immunity. Toronto: Hogrefe.
- Hinkle, L., and Plummer, N., (1952). Life stress and industrial absenteeism. Industrial Medicine and Surgery, 21, 363-375.
- Ishigami, T., (1919). The influence of psychic acts on the progress of pulmonary tuberculosis. American Review of Tuberculosis, 2, 470-484.
- Jemmott, J., and Locke, S., (1984). Psychosocial factors, immunologic mediation, and human susceptibility to infectious diseases: How much do we know? Psychological Bulletin, 95, 78-108.
- Kasl, S., Evans, A., and Neiderman, J., (1979). Psychosocial risk factors in the development of infectious mononucleosis. Psychosomatic Medicine, 41, 445-466.
- Kemeny, M., Cohen, F., and Zegams, L., (1986). The relationship of coping strategies to immunity and genital herpes recurrence. Paper presented to the Society of Behavioral Medicine Meeting, San Francisco, March 3-5.
- Levy, S., (1987). Behavior, immunity, and breast cancer: The role of individual differences. Presented at the 95th Annual Convention of the American Psychological Association at New York City, August 28, 1987.
- McClelland, D., Alexander, C., and Marks, E., (1982). The need for power, stress, immune function, and illness among male prisoners. Journal of Abnormal Psychology, 91, 61-70.
- Palmblad, J., Blomback, M., Egberg, N., Froberg, J., Karlsson, C., and Levi, L., (1977). Experimentally induced stress in man: Effects on blood coagulation and fibrinolysis. Journal of Psychosomatic Research, 21, 87-92.
- Schneiderman, N., (1986). Issues on intervention in coronary prone behavior. Paper presented at the Banff International Conference on Behavioral Science, Banff, Alberta, Canada, March 16-20.

Shavit, Y., Lewis, J., Terman, G., Gale, R., and Liebeskind, J., (1984). Opioid peptides mediate the suppressive effect of stress on natural killer cell cytotoxicity. Science, 223, 188-190.

Sklar, L., and Anisman, H., (1979). Stress and coping factors influence tumor growth. Science, 205, 513-515.

TABLE 2  
Pearson Correlations Between Study Variables

	NK 50:1	25:1	LU	AGE	COLD	FLU	STREP	FEVER	FAT.	TOT POMS	Leu 19	H-FREQ.	H-SEV.	H-I
NK (50:1)		.94**	.92**	.46**	NS	NS	-.33*	NS	NS	NS	NS	-.36**	-.31**	NS
NK (25:1)			.96**	.55**	NS	NS	-.25	NS	-.18	NS	NS	-.41**	-.40**	NS
NK Lu				.45**	NS	NS	-.25	NS	NS	NS	NS	-.32**	-.31**	NS
Age					-.51**	NS	NS	NS	NS	NS	.20	NS	NS	NS
Cold						NS	NS	NS	NS	NS	-.40**	NS	NS	NS
Flu							NS	NS	NS	NS	NS	NS	NS	NS
Strep								.31*	NS	NS	NS	NS	NS	.28
Fever									NS	NS	NS	NS	NS	NS
Fatigue										.67**	NS	.28*	.34*	.44*
Tot POMS											NS	.48**	.56**	.66**
Leu 19											NS	NS	NS	NS
Hassles-Freq.													.97	.27
Hassles-Sev.														.44

\* p .05

\*\* p .01

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