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

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In recent studies of "low natural killer (NK) cell syndrome," low NK activity was measured in individuals who were symptomatic, and therefore a causal relationship between low NK activity and infectious or other disease manifestations could not be concluded. However, preliminary work by members of our collaborative team (S.L. and R.H.), provided some indications for chronic low NK activity preceding and predicting subsequent infectious morbidity. This present study was designed to address this causal question in a larger sample, using a longitudinal design. Subjects were 106 healthy normal volunteers from the community. They were examined medically and psychosocially at baseline, and were then followed over a six month interval, with serial monthly assessment over the study period. The results supported our hypothesis that individuals who were currently healthy, but who exhibited a pattern of natural immunity characterized by persistently low NK cytotoxicity would be at risk for development of infectious sequelae over a six-month follow-up period. The results also showed that younger age and the perception of more severe "hassles" or stressors also predicted more infectious morbidity during the six-month study period.

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FINAL REPORT

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

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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 (Visintainer, Volpicelli, and Seligman, 1982; 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 (Palmblad, 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 biological 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 as 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.

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The Principal Investigator and Co-Principal Investigator on this 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 catecholamine 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) and immune function (specifically NK activity) may interact to increase risk for infectious illness. 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. Final Report

One hundred and six individuals, between the ages of 18 and 45 (mean age=28.8 years), were accrued to this study. Approximately 63% of the sample were female, and 90% of the sample were caucasian. Sixty-one percent of the sample were single, 30% married, and 9% of the sample were divorced. Average years of education were 15.7 years, with a range of 12 to 27 years. Subjects were excluded on the following bases: History of alcohol or drug abuse; history of psychiatric hospitalization; current use of prescribed psychoactive agents; medically documented chronic disease (e.g., cardiovascular disease, diabetes, cancer), or recent (within the past two weeks) or current acute infectious or other physical disease.

Normal individuals were recruited from the university and local community through newspaper ads and other media announcements, and, after signing a consent form, were interviewed regarding current and past health history. Baseline assessment included a screening interview to determine past and current psychiatric history, past and present medication use, and life style information (e.g., exercise and substance use habits), and a complete physical examination and laboratory work-up, in order to exclude anyone ill at the time of enrollment (or in the previous two weeks), providing complete physical status information on all subjects at the time of accrual.

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Procedures

Subjects were serially tested, at baseline, and then again at two weeks and four weeks into the study. They were then assessed monthly (except for a weekly health record, described below), including an abbreviated physical exam at three and six months post-accrual. In order to enhance compliance, and to compensate subjects for their time consuming participation, individuals were paid $10. for each completed assessment session, plus a $25. bonus for completion of the entire six-month assessment schedule. These payments, along with phone prompts, minimized loss of data in this prospective study. Complete data on all variables were provided by eighty-three subjects over the prospective follow-up period, but using mean illness morbidity rates per week, information from all 106 subjects were utilized in the statistics reported below.

Psychological Measures

Mood and the perception of environmental stressors were assessed at baseline induction into the study, and at biweekly or monthly follow-up intervals, as specified. Specifically, Spielberger's State/Trait Personality Inventory (STPI) was used as a measure of current and dispositional mood characteristics in the subjects. The Profile of Mood States (POMS) (McNair, et al., 1971), composed of six clinical subscales (tension/anxiety, depression/dejection, anger/hostility, vigor/activity, fatigue/inertia, and confusion/bewilderment), has the advantage of having been used extensively in studies of both physically and psychiatrically ill populations.

The Hassles Scale (Kanner, et al., 1981) is a 117-item questionnaire in which respondents are instructed to indicate the occurrence of any items (e.g., misplacing things, troublesome neighbors, problems with fellow workers) which have "hassled" them within a specified period of time (e.g., in the past week). Participants rated each hassle on a 3-point scale as having been "somewhat," "moderately" or "extremely" severe. From this information, three scores were created: 1) a frequency score, which is a simple count of the number of items checked, 2) an intensity score, which is the mean severity reported by the participant for all items checked, and 3) a severity score, a total severity rating across all items checked. Mean severity scores over the three baseline assessments were entered here in the results reported below.

Laboratory Measures

Blood samples were drawn between the hours of 9:00 a.m and 2:00 p.m. Seventy-five percent of the samples were drawn before noon. An examination revealed no significant difference in NK activity between morning and early afternoon sample (t=.4,NS). All assays were carried out on fresh samples held overnight to ensure comparable viability across samples. NK activity, leukocyte counts and lymphocyte subpopulations in the circulation (percent T cells, B cells, and NK cells, measured by Leu 4, Leu 12, Leu 11a, and Leu 19 antibody markers, respectively) were measured at baseline and follow-up periods.

Natural Killer Cell Assay. The K562 erythroleukemia cell line was maintained in culture in RPMI 1640 medium supplemented with 10% v/v fetal bovine serum (FBS). Cells were subcultured as needed, and the cells in the log phase were used for cytotoxicity assays. K562 targets were labeled with 100-150 uCi of sodium ^{51}chromate (5mCi/mM, New England Nuclear, MA) for 1-2 hours at 37°C. Cells were then washed 4x in tissue culture medium (TCM) consisting of RPMI 1640, supplemented with 5% v/v FBS, 2mM L-glutamine, penicillin (100 u/ml), streptomycin (100ug/ml), all from Gibco, Grand Island, NY. Cells were resuspended in fresh medium, counted and aliquoted at 5 x10^3 targets/well into 96-well U-bottom plates (Costar), into which the effector cells (PBMC) had been previously added at the predetermined concentrations. The effector:target cell ratios ranged from 50:1 to 6:1. Plates were centrifuged at 65g for 5 minutes and incubated in 5% CO_2 in air at 37° for 4 hours, after which medium was harvested from each well using a Skatron supernatant harvesting apparatus (Skatron, Sterling, VA). All determinations were done in triplicate. Radioactivity was counted in a gamma counter and percent specific lysis was determined according to the formula:

$$\frac{\text{Mean experimental cpm - mean spont. release cpm}}{\text{Mean maximal cpm - mean spont. release cpm}} \times 100$$

Lytic units were calculated according to the formula of Pross et al., (Pross, et al., 1981). One lytic unit was defined as the number of effector cells, out of 10^7 effector cells, that were required to kill 20% of 5 x 10^3 target cells. The data variability of the NK cell assay was monitored as described by us recently (Whiteside and Herberman, 1989).

Flow Cytometry. The cells were adjusted to 0.5x10^6/ml in phosphate buffered saline (PBS)-0.1% sodium azide buffer and stained with fluorescein-or phycoerythrin-labeled monoclonal antibodies against various surface markers on human mononuclear cells. The monoclonal antibodies were purchased from Becton-Dickinson (Mountain View, CA) and included: Leu 4, Leu 19, Leu 11a, Leu 12 and isotype controls. The cells were incubated with monoclonal antibodies, which were preitered to give optimal staining, for 15 min. at 4°C. The stained cells were washed twice with PBS-azide buffer and resuspended in 200 ul of 1% paraformaldehyde in the same buffer for two-color flow-cytometry analysis in a FACScan.

B-Endorphin Measurements in Plasma. Separate blood samples were drawn into 13x100 mm Vacutainers containing EDTA. Immediately, 0.3ml Aprotinin was added to each tube (30 TIU/ml, Sigma Chemical Company, St. Louis, MO), the tubes were inverted several times, and then refrigerated briefly (30-60 min) for transport to the radioimmunoassay (RIA) lab. The tubes were centrifuged at low speed (2200 rpm) for 20 minutes, and the plasmas removed and stored at -70°C. Plasma samples (1 ml) were assayed for B-END using an extraction and radioimmunoassay procedure obtained from Incstar (C/N 46065; Stillwater, MN). All values are corrected for recovery in the extraction (recovery $\geq$ 90%). The sensitivity of the RIA is 3 pmol/l; the coefficients of variation are 13.7% (within assay) and 18.1% (between assay). This assay shows less than 0.01% cross-reactivity with beta lipotropin, leucine and methionine enkephalins, and ACTH.

Health Records

All subjects were asked to complete weekly illness, as well as lifestyle inventory records, developed during our pilot work. This record is displayed in Figure 1.

They were instructed to record daily symptoms of infectious illness experienced, as well as the amount of sleep per night, daily exercise, and daily alcohol, drug, caffeine, and tobacco consumed. Females also indicated presence or absence of menses. These records were collected by mail on a weekly basis, and phone prompts were made for subjects who failed to mail in their recording. As can be seen, presence/absence of symptoms reflecting colds, influenza, pneumonia, cold sores, gum infections, mononucleosis, strep throat, and gastro-intestinal illnesses, plus the direct reporting of symptoms such as fever and sore throat, were included on the record. If on follow-up physical exam, subjects reported illness in the preceding period, and if they reported seeing a physician, physician records were obtained in order to corroborate self-report. As discussed in more detail below, for the 30 physician office visits during the study period, there was a 97% agreement between reported symptoms on the daily health record and chart documentation of presenting symptoms by the physician. It is recognized that the measure used here for illness episodes has all the limitations associated with self-report. However, it is also recognized that many individuals do not report to a physician, despite rather disabling acute infections. Thus, for free-living community volunteers, it is difficult to avoid reliance on self-report. In fact, past and current research has demonstrated that such report correlates rather well with clinical ratings of illness (Totman, Reed, and Craig, 1977; Roden, 1958; and Maddox and Douglass, 1974), viral shedding (Forsyth et al., 1963 and Totman, et al., 1980), and biochemical indicators of infection (Nalclerio, et al., 1988).

For the purpose of this present study, illness variables examined included overall days of illness morbidity for colds, flu, gum infections, gastro-intestinal or "stomach" flu, and fever reported over the six month follow-up period, as well as days reported with upper respiratory morbidity (e.g., symptoms of cold and influenza) over follow-up. There were no reported cases of pneumonia or mononucleosis in our sample during the study period, and hence, these categories were not included in the morbidity data. Further, strep throat was eliminated from the morbidity tabulation because the two cases that were reported were not corroborated by laboratory analysis. Sore throat was eliminated from the health data because of the possibility of confounding with fatigue or other physical stress conditions. Finally, cold sores were also eliminated in these analyses because we wished to examine incidence and/or morbidity associated with acute discrete illness, and we considered herpes viral infections a periodically expressed, chronic condition, interesting in itself, but distinct from the acute illnesses being tabulated over the follow-up period of this study. We chose to focus on reported morbidity, rather than attempt to distinguish between incidence of specific categories of illness, because of the difficulty in determining the validity of self-reported differential diagnosis on the part of the subject. Thus, the total duration of illness morbidity, rather than incidence of discrete infectious episodes, was the health end-point of major interest reported here.

RESULTS

As in our pilot work (unpublished), and in the recent descriptive report of incidence and characteristics of the LNK pattern in this current sample (Levy, et al., 1989), we are here operationally defining the basal LNK profile as NK cytotoxicity, below the mean for the group, at each of three baseline serial assessments. Thirty-nine individuals, or 36% of the sample, showed this LNK pattern. By this definition, we have clearly not segregated out a subgroup of individuals with abnormally low NK activity. Rather, we have defined a subgroup of normal individuals, all of whom have NK activity values below the population mean, but most with NK activity well within the normal range. We are here asking whether such a consistently low pattern in this population places such individuals at illness risk.

In general, serial data showed that the LNK group was primarily distinct in expressing lower proportion of NK cells in the periphery, and significantly lower functional levels of NK cytoxicity, chronically, across the entire follow-up period. There were few other immunological, hormonal, or psychosocial differences that distinguished the two groups over time.

Utilizing reported illness morbidity (overall days reported ill and days with respiratory infection morbidity) as the illness end-point, we used a path modeling technique (James, Mulaik, and Brett, 1982) to evaluate relationships among the predictor variables, to test the utility of a causal hypothesis, and to make inferences regarding causality among the variables.

Time 1 variables included chronological age, the perception of hassles, and basal natural immunity. Time 2 variables included overall morbidity, and URI morbidity, reported over the follow-up period (excluding the first month baseline period). The best fit model is displayed in Figure 2. An identical best fit model emerged when the dependent variable was upper respiratory illness morbidity (with slightly different path coefficients not shown in the Figure). Criteria for best fit selection included the model which yielded the largest coefficient of determination, the smallest Chi Square value, a Goodness of fit Index closest to 1, and a root mean square residual closest to 0. T-test values and regression coefficients for the significant paths are also displayed in Figure 2.

As can be seen, chronological age had both a direct relationship, as well as a somewhat weaker, borderline significant indirect relationship, via natural immunity, on morbidity outcome. Higher age predicted lower URI and overall morbidity; lower age predicted the LNK pattern, which in turn predicted higher follow-up illness morbidity. The most significant path was a direct one linking the hassles severity variable with health outcome. Thus, the perception of more serious environmental stressors appears independently to predict more outcome morbidity. When any of these paths were deleted by setting the path coefficient to 0, the model became invalid. The model was also considerably weakened when the path linking the LNK/other variables and illness outcome was deleted. None of the demographic, mood, life style, or personality variables contributed additionally to the model tested. In addition, we also entered baseline basal values of overall proportion of T cells, B cells, and NK

cells in peripheral circulation into the predictor models to test for any additional association with health outcome. These basal values were operationally defined the same way as the LNK pattern versus other category were defined, i.e., persistently or stably low proportional values versus other categorical membership. These phenotypical values did not contribute significantly to the models tested. Thus, the illness measurement of interest here, morbidity over the follow-up period, was statistically linked in our model with individuals' basal functional patterns of natural immunity at entrance to this prospective study, rather than with characteristics of immune cell subsets as additionally contributive predictor variables.

In a subset of this sample (N=81), we were also able to obtain complete baseline and follow-up plasma beta endorphin values, and examine its association with peripheral natural immunity and infectious disease risk over the prospective study period. These findings have been accepted for publication, and will appear in the January, 1991 issue of Life Sciences. This manuscript is appended to this report.

In short, we found that when we entered beta endorphin values into the path model reported above, for the younger cohort only, average values of baseline beta endorphin entered, along with the LNK pattern, to predict URI morbidity over the follow-up period. Lower values of plasma beta endorphin were associated with the LNK pattern, and the latter, in turn, predicted more infectious morbidity over follow-up.

Thus, it appears that persistently low NK activity is associated with greater infectious disease risk, particularly in younger individuals. In addition, the role that "stress" might play appears to be more complex than has been assumed. Although in the main study findings, the report of perceived everyday stress directly predicted illness outcome, independently from immune variables a "stress"-related neuropeptide, beta endorphin, appeared to be associated with infectious morbidity via its potential effects on natural immunity. And finally, the positive association between circulating beta endorphin levels and NK activity, as well as the positive association between beta endorphin and health, suggests that this peptide might enhance immune function, including NK activity in humans, and act as a buffering agent related to stressful impingement.

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GRADUATE STUDENT/POST-DOC EMPLOYEES

Graduate students:

Male--one

Female--one

Post-doctoral students:

Male--none

Female--one

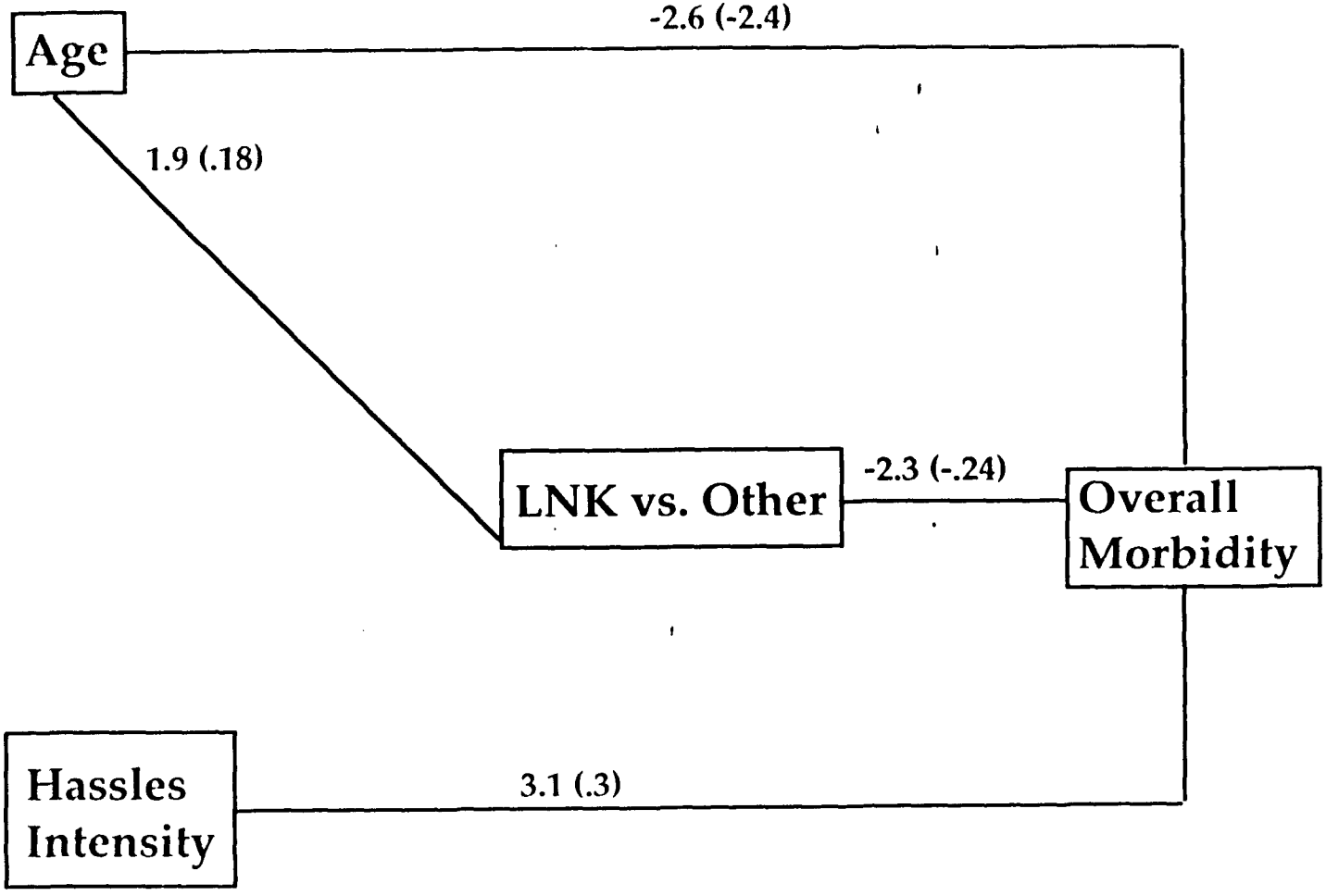
SUBJECT INITIALS	SUBJECT NUMBER

DAILY HEALTH RECORD Date Week No.

Week of _____ - _____ To _____ - _____

ILLNESS INVENTORY (Leave blank if does not occur)	1	2	3	4	5	6	7
1. Cold							
2. Flu							
3. Pneumonia							
4. Cold Sore							
5. Gum Infection							
6. Mononucleosis							
7. Strep Throat							
8. Gastro-Intestinal Virus (Stomach Flu)							
9. Fever							
10. Sore Throat							
11. Other							
LIFE STYLE INVENTORY							
1. Sleep (Hours per Night)							
2. Exercise-Amt. of Time (Type=see below)							
3. Alcohol (Number of Drinks)							
4. Drug Use: Type (see below) & Amount: Include Prescription & Non-prescription							
5. Menstrual Period (Check if Present)							
6. Cigarette Smoking (Number perDay)							
7. Caffeine (Number of Cups)							

*Key: T=Tennis, A=Aspirin (Example: T=Tennis, 1 hr. A=Aspirin, 325 mg)


Age
-2.6 (-2.4)
1.9 (.18)
LNK vs. Other
-2.3 (-.24)
Overall Morbidity
Hassles Intensity
3.1 (.3)