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Cynical Hostility and Stimulated Th1 and Th2 Cytokine Production

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Abstract

Hostility has been associated with heightened proinflammatory activity. However, it is not known whether greater hostility contributes to greater inflammation by promoting higher Th1 activity, lower Th2 activity, or both. The present study examines the relation of hostility to mitogen-stimulated Th1 and Th2 cytokine production *in vitro*. Participants were 193 healthy men and women (mean age 37.3; 44% nonwhite). Hostility was assessed with a 20-item version of the Cook-Medley Hostility Scale (CMHS). PHA-stimulated interleukin (IL)-2, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ were used to measure Th1 activity; PHA-stimulated IL-4, IL-5, and IL-10 were used to measure Th2 activity. Greater hostility was related to greater production of two of the three Th1 cytokines, TNF-α and IFN-γ. Hostility was not associated with any measure of Th2 cytokine production. Associations with Th1 cytokines were independent of age, sex, race, socioeconomic status, body mass index, depressive symptoms, and health-related behaviors, and were consistent across men and women. Associations were not explained by social network characteristics, social support, or personality traits closely associated with social behavior. Exploratory analyses substituting the CMHS cognitive, affective, and behavioral subscales for total hostility revealed that associations between hostility and Th1 cytokine production were primarily driven by the cognitive component of hostility (i.e., cynicism). Results suggest that a unique dimension of hostility, particularly the cynicism subcomponent, that is unrelated to social factors, may influence inflammation by promoting greater Th1 cytokine production. This effect on stimulated cytokine activity may have implications for a role of hostility in exacerbating immune-related disease.

Keywords

hostility; cynicism; Cook-Medley Hostility Scale; cytokines; PHA; mitogen stimulation; inflammation

1. Introduction

Hostility long has been recognized as an independent risk factor for morbidity and mortality from all causes and from coronary heart disease (CHD) in particular (Everson-Rose & Lewis, 2005; Miller, Smith, Turner, Guijarro, & Hallet, 1996). Hostility is a multidimensional, trait-like personality characteristic comprised of cognitive (e.g., cynicism, hostile attributions),

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affective (e.g., anger, annoyance, resentment), and behavioral (e.g., aggression, antagonism, insult) components (Barefoot, 1992). Several processes have been suggested as potential mediating pathways through which hostility might influence disease risk. Examples include poor health behaviors (Everson-Rose et al., 2006), excessive cardiovascular activity in response to stress (Suls & Wan, 1993), and dysregulated beta-adrenergic receptor function (Hughes, Sherwood, Blumenthal, Suarez, & Hinderliter, 2003). While each presents a pathway by which psychological factors might be translated into physiologic effects, these processes in and of themselves may not be sufficient to link hostility with some pathologic outcomes.

Elevated proinflammatory activity may constitute an additional down-stream step in the pathway linking hostility to CHD (Everson-Rose & Lewis, 2005; Miller, Freedland, Carney, Stetler, & Banks, 2003; Suarez, 2003). A clear association has been established between lowgrade systemic inflammation and clinically manifest CHD, with the risk for future morbidity increasing with increasing concentrations of proinflammatory markers (Blake & Ridker, 2001; Ridker, 2003). Also, recent evidence shows that circulating proinflammatory cytokine levels are greater at higher levels of hostility (Marsland, Prather, Petersen, Cohen, & Manuck, 2008; Ranjit et al., 2007). Taken together, findings from these two literatures support a mediating role for inflammation in linking hostility and disease. However, the extant literature does not inform as to which components of the immune system hostility influences to promote a persistent proinflammatory state.

Immune-mediated inflammation is dependent upon the counter-regulatory activities of two subpopulations of helper T lymphocytes, Th1 and Th2. Whether T lymphocytes are categorized as belonging to one subpopulation or the other is determined by which cytokines are released subsequent to activation (Elenkov & Chrousos, 1999). Th1 cytokines are those that express proinflammatory properties, whereas Th2 cytokines are those expressing anti-inflammatory properties. A disproportionate amount of either Th1 or Th2 response activity increases vulnerability to immune-related disease, with excessive Th1 activity increasing susceptibility to inflammation-mediated and autoimmune diseases, and excessive Th2 activity increasing susceptibility to infection and allergy. Thus, resistance to disease ultimately depends upon an optimal balance of Th1 to Th2 activities (Mosmann, Cherwinski, Bond, Giedlin, & Coffman, 1986).

The atherosclerosis component of CHD is thought primarily to be a Th1-driven process (Ross, 1999). However, deficient Th2 activity may be just as important as excessive Th1 activity in the pathogenesis of atherosclerotic disease (George, 2008; Hansson & Libby, 2006). Support for a potentially protective role of Th2 response mechanisms in CHD pathogenesis is provided by findings from case-control studies wherein concentrations of IL-10, a Th2 cytokine, were lower in angina patients relative to healthy controls (Yamashita, Shimada, Seki, Mokuno, & Daida, 2003), and in patients with unstable angina relative to those with the stable form of the disease (Smith, Irving, Sheldon, Cole, & Kaski, 2001). These findings have been corroborated by the cumulative findings of experimental mouse research where IL-10 consistently has been shown to have antiatherogenic effects (Kleemann, Zadelaar, & Kooistra, 2008).

In regard to the enhanced inflammation associated with higher levels of hostility, an obvious question is whether higher levels of hostility contribute to the creation of a proinflammatory state by increasing the production of Th1 cytokines, decreasing the production of Th2 cytokines, or both. A recent study partially addressed this question by examining the association of hostility and its cognitive, affective, and behavioral subcomponents with mitogen-stimulated production of tumor necrosis factor (TNF)-α, a Th1 cytokine, in a sample of healthy, non-smoking men (Suarez, Lewis, & Kuhn, 2002). Results showed that higher levels of total hostility, and its cognitive and behavioral subcomponents were associated with greater stimulated TNF-α production (Suarez et al., 2002). In a second study that employed a

female sample, greater hostility also was associated with greater stimulated TNF-α production, but only when combined with higher levels of depressive symptoms (Suarez, Lewis, Krishnan, & Young, 2004). In combination, these findings suggest that hostility may influence circulating inflammatory marker concentrations in part by promoting greater Th1 activity. However, given that previous studies did not include measures of Th2 cytokines, it is not known whether hostility is associated with a proinflammatory state as indexed by greater Th1 cytokine production and an imbalance in the ratio of Th1 to Th2 cytokines.

The primary objective of the present study was to examine the association of hostility with mitogen-stimulated production of Th1 and Th2 cytokines. In light of the previous research, our expectations were that greater hostility would be associated with greater Th1 cytokine production. Given the lack of data on hostility and stimulated Th2 cytokine production, we made no predictions regarding those associations. In exploratory analyses, we examined whether associations of hostility with Th1 and Th2 cytokine production can be accounted for by the specific contributions of the cognitive, affective, or behavioral subcomponents.

Fundamental to the hostility construct is that the characteristic negative thoughts, attitudes and behaviors are directed *toward other persons*. This negative interpersonal dimension of hostility has been demonstrated by hostile persons scoring lower on measures of agreeableness, a positive social personality characteristic (Barefoot, Dodge, Peterson, Dahlstrom, & Williams, 1989) and reporting lower levels of social support (Hardy & Smith, 1988; Scherwitz, Perkins, Chesney, & Hughes, 1991). Given that positive interpersonal characteristics have been associated with better health (Cohen, 2004) , it is possible that associations between hostility and proinflammatory cytokine production might be due to lower levels of these factors rather than higher levels of hostility, per se. Thus, a second objective was to determine whether associations between hostility and cytokine production were independent of social relationship characteristics and personality traits closely related to social behavior.

We also conducted two additional sets of exploratory analyses. First, we examined whether associations between hostility and cytokine production were moderated by sex. Both hostility and CHD risk have been found to differ between men and women, with men being both more hostile (Barefoot et al., 1991; Scherwitz et al., 1991) and at greater risk for CHD (Lerner & Kannel, 1986). Moreover, it has been suggested that sex moderates the magnitude of the association of hostility with CHD, with the association being stronger in men than women (Consedine, Magai, & Chin, 2004). Thus, it is possible that sex may moderate the association of hostility with a potential mediating mechanism, such as stimulated cytokine production. Finally, because a lack of balance in the *ratio* of Th1 to Th2 response processes has been suggested to play a role in the development and progression of CHD (Chenga et al., 2008; Szodoray et al., 2006), we conducted a second set of exploratory analyses to determine whether greater hostility was associated with a higher ratio of Th1 to Th2 cytokine production.

2. Methods

2.1. Participants

We report a secondary analysis based on data collected at baseline in a clinical trial designed to assess psychosocial predictors of resistance to viral infection (Cohen, Doyle, Alper, Janicki-Deverts, & Turner, 2009; Cohen, Doyle, Turner, Alper, & Skoner, 2003). Participants were recruited by newspaper advertisements soliciting subjects for an experimental study of the psychosocial risk factors that moderate viral upper respiratory infection and illness. The study was conducted between 2000 and 2004 as eleven cohorts of between 2 and 39 participants each. The study protocol was approved by the IRBs at the University of Pittsburgh and Carnegie Mellon University. All subjects provided written informed consent and were paid $820 for completing the study.

Only healthy adults were included in the study. Potential subjects received an initial health screen by telephone and later were interviewed and examined by a physician. They were excluded if they had any acute or chronic medical condition, were pregnant or lactating, or had a recent or current upper respiratory infection. Individuals also were excluded if regularly taking medication, with exception of birth control, hormone replacement therapy, analgesics, and topical eczema/psoriasis medications, or had specific antibody titers to the challenge virus (influenza A or rhinovirus 39) of > 4. All data reported here were collected at baseline, prior to virus exposure.

The study population included 95 men and 98 women, aged 21 to 55 years (mean age=37.3, SD=8.8) and 108 (56%) were white, 72 (37%) were black, and 13 (7%) indicated other racial/ethnic categories. The mean education was 13.8 years (SD=2.2), 47% of subjects were smokers, and mean body mass index (BMI) was 29.0 (SD=7.1). A subset of 155 of the 193 participants provided blood samples for assessment of mitogen-stimulated cytokine production. Of these, data from 2 participants were excluded from the present report due to missing body mass information. Thus, the total sample described here was comprised of 153 participants. Not all participants had data on all stimulated cytokine measures. To maximize the power to detect significant associations, we included in each analysis the maximum number of participants with complete data (range = 138-149).

2.2. Measures

Stimulated cytokines—Blood samples for stimulated cytokines were drawn on two occasions, two months apart. For the present analysis, stimulated cytokine values obtained from these two samples were averaged, and then the average was subjected to a $\log_{10}$ transformation to approximate a normal distribution.

The Luminex 100 multiplex bead-based immunoassay system, which is based on the principle of solid phase sandwich immunoassays, was used to measure stimulated cytokine levels. Multiplex analysis permits simultaneous quantification of different cytokines in a small sample volume. Luminex multiplex technology has been demonstrated to be a valid alternative method for the quantification of cytokines (DuPont, Wang, Wadhwa, Culhane, & Nelson, 2005). Peripheral blood mononuclear cells (PBMCs) were stimulated with PHA at a final concentration of 20 μg/mL and incubated at 37°C for 48 hours in the atmosphere of 5% CO2 in air. PHA-stimulated and unstimulated plasma samples were analyzed using Biosource multiplex immunoassay kits (Biosource International, Camarillo, CA), which contained combined antibodies for 10 different cytokines. The kits were validated by the manufacturer and determined to be free of Ab cross-reactivity. All reagents, working standards, and samples were prepared as per the manufacturer's specifications and were run in duplicates. The plates were read within 24 hours using the Bio-plex Reader (Luminex 100, Luminex Corporation, Austin, TX). Stimulated levels of Th1 (IL-2, TNF-α, and INF-γ) and Th2 (IL-4, IL-5, and IL-10) cytokines were determined using Bio-Plex Manager Software (Bio-rad Corporation, Hercules, CA), interpolating from the standard curve (Logistic-5PL curve fit, Brendan Technologies, Carlsbad, CA). Pooled plasma controls also were included on all plates to further assure assay reliability. In all cases, stimulated cytokine production was quantified by subtracting cytokine levels in unstimulated samples from the stimulated levels. Cytokine assays were performed at the IMCPL, University of Pittsburgh Cancer Institute. The IMCPL has an established QA/QC program for cytokine determinations and a long-standing expertise in cytokine measurements for both clinical and research programs.

Hostility—Hostility was measured on two occasions: two weeks after the first blood draw for stimulated cytokine measurement, and then again on the day of the second blood draw for

stimulated cytokine measurement. Mean hostility scores were computed by taking the average of hostility scores obtained on these two occasions. Mean scores were used in all analyses.

Hostility was assessed using a modified 20-item version of the CMHS. The modified CMHS is comprised of three subscales each of which has been found to be better predictors of health outcomes than the total score on the original 50-item scale: *Cynicism* (6 items; e.g., "I think most people would lie to get ahead"), *Hostile Affect* (5 items; e.g., "People often disappoint me"), and *Aggressive Responding* (9 items; e.g., "I would certainly enjoy beating a crook at his or her own game") (Barefoot et al., 1989; Boyle et al., 2004). These three subscales are thought to capture the cognitive, affective, and behavioral dimensions of hostility, respectively. Items are presented in a true/false format; higher scores indicate higher levels of hostility.

Health behaviors—Health behaviors included current smoker status (smoker, nonsmoker), average alcohol consumption (drinks/day), and usual leisure-time physical activity (kcal/week). Alcohol consumption was estimated by averaging across participants' reports of daily consumption during evening telephone interviews that were conducted over a 14-day period. Physical activity was assessed using the Paffenbarger Physical Activity Questionnaire (Paffenbarger, Wing, & Hyde, 1978).

Depression—The Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977) was used to assess depressive symptoms. Participants were asked to indicate on a fourpoint scale (0 = rarely or none of the time to 3 = most or all of the time) how often they have experienced given symptoms during the past week. Four positively worded items were reversescored (e.g., *I felt happy*) and then a depressed mood score was created by summing responses across the twenty items (possible range 0-60).

Social personality characteristics—Trait extraversion and agreeableness were assessed using an eight-item subscale from an abbreviated version of the Goldberg Big Five Questionnaire (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997; Goldberg, 1992).

Social relationship characteristics—Two standardized questionnaires were used to measure social relationship characteristics. The Social Network Index (SNI; (Cohen et al., 1997)) assessed the number of social roles in which respondents were regularly engaged (e.g., spouse, friend, family member, worker) and the number of people within these roles with whom participants were in contact (in person or on the phone) at least once every two weeks. The 12-item version of the Interpersonal Support Evaluation List (ISEL; (Cohen, Mermelstein, Kamarck, & Hoberman, 1985)) assessed participants' perception that others would provide them with support when faced with stressful situations.

Standard covariates—All multivariable analyses included a set of standard control variables. These covariates included variables that previously have been found to correlate with immune function in the present sample: age, sex, race (white, non-white), body mass index (BMI; weight [kg]/height $[m]^2$) and socioeconomic status (SES; composite variable computed as the sum of standardized education [years] and household income [$US/year] values). In order to ensure that associations between hostility and stimulated cytokine production were independent of poor health behaviors, we also included smoker status, alcohol consumption, and physical activity as additional standard control variables. Because depression has been associated both with hostility (Biaggio & Godwin, 1987; Felsten, 1996) and inflammation (Maes, 1999), depressive symptoms were covaried as well. In the present sample, depression and hostility were modestly correlated ($r = .25$, $p < .01$).

2.3. Statistical analyses

All analyses were conducted using SPSS version 13.0 (SPSS, Inc., Chicago, IL). Pearson correlations were conducted to assess the intercorrelations among total hostility and the three hostility subscales (cynicism, hostile affect, aggression). Multivariate linear regression analysis was used to examine whether the associations of hostility with stimulated cytokines were independent of standard covariates (sociodemographic characteristics, BMI, depression, and health-related behaviors) and social personality and relationship characteristics. All stimulated cytokine concentrations, social support score, and BMI were $\log_{10}$-transformed to normalize their respective distributions.

3. Results

3.1. Intercorrelations among hostility subscales

Descriptive statistics for and intercorrelations among total hostility and the three hostility subscales are presented in Table 1. Total hostility scores were strongly correlated with scores on each of the three subscales. Subscales were moderately intercorrelated, thus suggesting that the cynicism, hostile affect, and aggression subscales measured related but not identical constructs.

3.2. Multivariate associations of total hostility with Th1 and Th2 cytokine production

We used linear regression analysis to examine the multivariate associations of total hostility with stimulated production of Th1 and Th2 cytokines. All models included controls for sociodemographic characteristics (age, sex, race, SES), BMI, depression, and health-related behaviors (smoker status, alcohol consumption, physical activity). Results showed that greater total hostility was related to greater production of two of the three Th1 cytokines: TNF-α (B = .02, SE = .007, *b* = .20, $p < .03$) and IFN-γ (B = .03, SE = .013, *b* = .20, $p < .03$). IL-2 production also was greater at high levels of hostility, but that association failed to achieve statistical significance (B=.03, SE = .017, *b* = .16, $p < .08$). By comparison, total hostility was unrelated to production of any of the three Th2 cytokines (IL-4, B = .01, SE = .012, *b* = .07, $p = .39$; IL-5, B = −.002, SE = .013, *b* = −.02, $p = .85$ IL-10, B = .01, SE = .009, *b* = .06, $p = .49$).

3.4. Control for social personality and social relationship characteristics

It is possible that greater Th1 cytokine production with greater hostility is due to more hostile persons lacking the health benefits associated with positive social personality and social relationship characteristics. To rule out this possibility, we conducted two sets of linear regression models which controlled sequentially for social personality characteristics (agreeableness and extraversion) and social relationship characteristics (social support and social integration), and then a third fully-adjusted model that included both sets of social variables. All models also controlled for sociodemographic variables, BMI, depression, and health-related behaviors. We report the results of the fully-adjusted models here. Results showed that the addition of both sets of social variables had little effect on the association with TNF-α (B = .02, SE = .008, *b* = .21, $p < .05$) or on the association with IFN-γ (B = .03, SE = .015, *b* = .21, $p < .04$), thus suggesting that the association of hostility with Th1 cytokine production is independent of these factors.

3.5. Exploratory analyses

3.5.1. Multivariate associations of hostility subscales with Th1 cytokine production—Having determined that greater hostility is associated with greater Th1 cytokine production, we explored whether this association is driven primarily by one or more of the three subcomponents of hostility, cynicism, hostile affect, and aggression. Results of

multivariate linear regression analyses examining the associations of the three hostility subscales with stimulated Th1 cytokine production are displayed in Table 2. Analysis of individual subscales revealed that greater cynicism was associated with greater production of all three Th1 cytokines, and greater hostile affect was associated with greater production of IFN-γ. This latter association, however, failed to achieve statistical significance ($p < .06$). Hostile affect was not related to either IL-2 or TNF-α. Aggression was unrelated to production of any of the three Th1 cytokines. These results suggest that the contribution of the cynicism subscale to the total hostility score largely accounts for the association of hostility with Th1 cytokine production.

3.5.2. Moderating effect of sex—To determine whether the strength of the associations of hostility with stimulated cytokine production differed by sex, we conducted a set of regressions that included a sex-by-hostility interaction term in addition to terms for hostility, sex, and the standard control variables (sociodemographics, BMI, depression, and health-related behaviors). Results of these analyses indicated that sex did not moderate any of the associations of hostility with Th1 or Th2 cytokines (*p*s > .25). Findings were similar when cynicism was substituted for total hostility (data not shown).

3.5.3. Multivariate associations of total hostility with the ratio of stimulated Th1/Th2 cytokine production—Unsurprisingly, higher total hostility was associated with greater ratios of IFN-γ to IL-5 (B = .03, SE = .013, $b = .20$, $p < .03$) and IFN-γ to IL-10 (B = .02, SE = .007, $b = .20$, $p < .03$). When scores on the cynicism subscale were substituted for total hostility, these associations were slightly stronger (IFN-γ/IL-5, B = .08, SE = .027, $b = .25$, $p < .01$; IFN-γ/IL-10, B = .03, SE = .014, $b = .21$, $p < .03$).

4. Discussion

Among a sample of healthy, middle-aged men and women higher levels of hostility, as assessed by total scores on the CMHS, were associated with greater stimulated production of Th1 but not Th2 cytokines. Specifically, productions of TNF-α and IFN-γ were greater at higher levels of hostility. These associations were independent of age, sex, race, SES, BMI, smoker status, alcohol consumption, physical activity, and symptoms of depression. Associations also could not be explained by social relationship characteristics or personality traits closely related to social behavior. Investigation of the individual cognitive, affective, and behavioral subscales of the CMHS revealed that cynicism, the cognitive component of hostility, appeared to be driving the associations of hostility with Th1 cytokines. That high levels cynicism in particular should be associated with greater Th1 cytokine production may be due to psychological vulnerability resulting from cynical cognitions. The “hostile other” schema characteristic of cynical thinking may prime highly cynical persons to be easily provoked by the actions of others, resulting in frequent and exaggerated physiological responses (Allred & Smith, 1991).

Our findings are consistent with previous research demonstrating associations between hostility and greater stimulated proinflammatory cytokine production (Suarez et al., 2004; Suarez et al., 2002). Interestingly, whereas the present results suggest that cynicism, the cognitive component of hostility, is the most reliable correlate of Th1 cytokine production, the results reported by Suarez and colleagues (Suarez et al., 2002) suggest that both the cognitive and behavioral (aggression) components of hostility predict stimulated TNF-α production. Inconsistencies between studies may be due in part to differences in methodology. First, Suarez and colleagues used the Buss-Perry Aggression Questionnaire (BPAQ) to assess hostility and its cognitive, affective, and behavioral subcomponents. The present study employed the CMHS, which is thought to be a less than optimal measure of behavioral components of hostility, such as overt aggression (Smith & Frohm, 1985). Accordingly, the aggressive responding subscale of the CMHS may not have tapped the same construct as that estimated

by the aggression subscale of the BPAQ. Nevertheless, the CMHS—in particular the cynicism subscale, has been associated with greater circulating inflammatory marker concentrations (Ranjit et al., 2007), coronary artery calcification (Iribarren, Sidney, & Bild, 2000), and progression of carotid artery atherosclerosis (Julkunen, Salonen, Kaplan, Chesney, & Salonen, 1994), all important markers of CHD risk. Second, whereas the present study examined cytokine production from stimulated PMBCs, Suarez et al. examined cytokine production from stimulated monocytes. It is possible that the response patterns of these two cell populations are differentially influenced by psychosocial factors.

The present findings also expand upon previous research in several ways. First of all, we included three separate measures of Th1 cytokine production (IL-2, TNF-α, and IFN-γ), three separate measures of Th2 cytokine production (IL-4, IL-5, and IL-10), and three measures indicating Th1/Th2 balance (IFN-γ/IL-4, IFN-γ/IL-5, and IFN-γ/IL-10). That hostility, in particular the cynicism subcomponent of hostility, should consistently show a positive relation across several measures of stimulated Th1 production provides convincing evidence for hostility being associated with a bias toward Th1 dominance in response to novel stimuli. Also, the present study showed that the association of hostility with stimulated cytokine production is independent of social network characteristics, social support, and personality traits closely related to social behavior. Given the inverse association of hostility with these psychosocial variables (Barefoot et al., 1989; Hardy & Smith, 1988), the independent effect of hostility on stimulated cytokine production suggests that some unique dimension of hostility unrelated to these interpersonal factors may be driving the link with immune function.

Whether and to what extent the present findings provide a plausible link in the mechanistic chain connecting hostility with CHD remains open to question. It has been argued that hostility may contribute to early CHD pathogenesis via elevated expression of TNF-α (Suarez et al., 2002). Th1 cytokines have been found to be present at all stages of the inflammatory processes contributing to atherosclerosis (Ross, 1999). However, much of the increase in local cytokine concentrations is due to production by resident macrophages, disrupted endothelium, and proximal smooth muscle cells (Barath et al., 1990). Thus, our findings only support the plausibility of this pathway insofar as the facilitative effect of cynicism on Th1 cytokine production by PBMCs can be extended to Th1 production by other cell types.

Although stimulated cytokine production has not yet been identified as a risk marker for future disease in initially healthy humans, it is possible that the findings reported here have implications for the exacerbation of pre-existing conditions, specifically autoimmune disorders. For example, persons with multiple sclerosis, especially those in the midst of a relapse, show higher Th1 cytokine production in response to stimulation with mitogen relative to healthy controls (Ferrante et al., 1998). Given that certain proinflammatory cytokines including TNF-α have been proposed to play an instrumental role in driving the inflammatory processes that lead to demyelination in multiple sclerosis (Lock, Oksenberg, & Steinman, 1999), it is possible that the greater Th1 cytokine production associated with hostility may increase the likelihood of a proinflammatory phenotype, and thus contribute to increased disease activity.

A limitation to interpreting the results of the present study concerns how well they might be generalized to the larger population. At this time, measurement of stimulated cytokine production does not allow for inter-laboratory comparisons. Factors such as amount and type of mitogen used to stimulate cells and the half-lives of measured cytokines can influence results substantially. Given the lack of an absolute normal standard, it is possible that the present sample is producing cytokines well above or well below the optimum. Moreover, within the present sample, it cannot be determined whether hostile persons are producing excess Th1 cytokines in response to stimuli or whether they simply are demonstrating a higher response

within the range of normal. The latter being the case would not necessarily preclude the greater cytokine production seen here from being clinically significant. For example, increased CHD risk has been identified among individuals showing levels of circulating inflammatory markers within the pre-morbid range. Specifically, individuals with CRP concentrations of 2-3 mg/L —a level well below the accepted cut-point of >10 mg/L used to identify acute infection (Pearson et al., 2003), have been found to be at moderate to high risk of future CHD (Danesh et al., 2000).

In addition to those cited above, a few additional limitations of the present study should be acknowledged. First, the data are cross-sectional so the direction of causation cannot be determined. We did control for several factors (BMI, health behaviors) that may be related both to hostility and immune function, thus rendering unlikely the possibility of the more obvious third factor explanations. However, the influence of other psychological factors, such as depression, that are known to be related both to hostility and to cytokine production, also could provide a plausible alternative explanation for our findings. This possibility was ruled out as well because hostility emerged as an independent correlate of Th1 cytokine production when depressive symptoms were controlled for in the analyses. Second, the study did not include measures of circulating cytokine levels, and thus we could not determine whether elevated stimulated production is associated with elevated circulating levels. Finally, our sample did not include individuals with especially high CMHS scores, i.e., scores that exceeded the range of the normal adult population. However, increasing CMHS scores within the normal range have been associated with increased risk of premature mortality (Barefoot et al., 1989). Accordingly, insofar as we are interested in identifying a potential mechanism to link hostility with morbidity and mortality, physiologic changes associated with variations in hostility within the normal range may be more relevant than changes associated with high hostility.

In sum, the present study provides evidence to support an association of cynical hostility with elevated stimulated production of Th1 cytokines, measured in several ways. These findings are consistent with those of previous research, and with a model suggesting that hostility may be linked with increased CHD risk via a pathway involving inflammatory activity. Furthermore, they suggest that hostility contributes to a proinflammatory phenotype by up-regulating Th1 activity rather than down-regulating Th2 activity.

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Table 1

Intercorrelations among Cook-Medley total and subscale scores[a]

	Total hostility	Cynicism	Hostile affect	Aggression
Total hostility	-	.79	.73	.80
Cynicism		-	.47	.34
Hostile affect			-	.41
Mean (SD)	9.47 (3.42)	3.13 (1.65)	2.21 (.99)	4.08 (1.75)
Median	10.00	3.50	2.50	4.00
Range[b]	1.00-17.50	.00-6.00	.50-5.00	.50-8.50

[a] All correlations significant at $p < .001$.

[b] CMHS score ranges: total, 0-20; cynicism, 0-6; hostile affect, 0-5; aggression, 0-9.

Table 2

Linear regression coefficients describing the associations of CMHS subscale scores with three measures of Th1 cytokine production.

	Associations with stimulated Th1 cytokine production								
	IL-2			TNF-α			IFN-γ		
	B(SE)	*b*	*p*	B(SE)	*b*	*p*	B(SE)	*b*	*p*
Cynicism	.09 (.04)	.23	.01	.04 (.01)	.27	.01	.09 (.03)	.28	.01
Hostile affect	.03 (.06)	.05	.58	.02 (.02)	.08	.37	.08 (.04)	.15	.06
Aggression	.02 (.03)	.05	.61	.01 (.01)	.07	.42	.01 (.02)	.04	.67