

Close Relationships and Immunity

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I. INTRODUCTION

Our lives tend to be centered around close relationships with significant others, family, and friends. It is increasingly apparent that the existence and quality of such relationships and the support they provide have a strong impact not only on our psychological well-being (Glenn and Weaver, 1981) but also our physical health. A number of prospective studies have reported remarkably similar patterns of increasing risk for all-cause mortality with a decreasing number of social ties, even after controlling for sociodemographic characteristics and health (e.g., Berkman and Syme, 1979; House et al., 1982; Kaplan et al., 1988). The existence and quality of key close relationships, such as marriage, are also predictive of morbidity and mortality from a range of chronic and acute conditions (Johnson et al., 2000; Kiecolt-Glaser and Newton, 2001; Verbrugge, 1979). One key pathway underlying the association between social relationships and health outcomes appears to be changes in immune function (Kiecolt-Glaser, 1999), an area of research which holds great promise for further clarifying the role of close relationships and health and which will be the focus of this chapter.

The current review is organized around three aspects of close relationships: social integration, social support, and negative aspects of social ties. These topics map relatively well onto three models by which social relationships can affect health in relation to psychological stress: the main effects model, the stress-buffering model, and the social strain model (Cohen, 2004; Orth-Gomer, 2000; Rook, 1990). In this literature, psychological stress is most often determined by self-reported perceived stress, as well as by objective indicators of life stress and reports of life events. We first present work on *social integration*, including in this category broad measures of network size as well as studies focused on marital status, a key social tie. In line with the main effects model (Lazarus and Folkman, 1984), measures of social integration are typically associated with health benefits independent of stress (Cohen, 1988; Cohen, 2004). Next, we review literature focused on *social support*. In contrast to quantitative measures of network size, social support is typically defined as the perception that assistance would be available if and when it is needed, as well as the receipt of assistance during such times. Such assistance can include, but is not limited to, the provision of material aid, assistance with tasks, information, or emotional support. In line with the stress-buffering model, the benefits of perceived social support are frequently seen only (or primarily) when a person encounters stress of a sufficient magnitude (Cohen, 1988). Relevant work on the related constructs of loneliness and intimacy is also covered briefly in this section. Finally, we review work that best fits with the social strain model, which holds that relationships can sometimes serve as a source of stress

themselves (Coyne and Bolger, 1990), with accompanying negative implications for health and immunity. This section includes a brief review of the relatively large body of work on marital conflict, in addition to evidence that other social ties and some forms of social support can be problematic.

Experimental designs and clinical interventions provide some of the best evidence that aspects of close relationships are causally related to immunity in both healthy and clinical populations. Such studies are briefly reviewed in a subsequent section. The topics covered in this intervention section and, indeed, throughout the review, sometimes have overlapping content. In a concluding section, we address more broadly what is currently known about the mechanisms common to reviewed findings. As other chapters in this volume cover the relevance of physiological responses and phenomena, such as hypothalamic-pituitary-adrenal (HPA) axis reactivity and glucocorticoid responsiveness, our focus is on the major psychological and behavioral pathways by which relationship factors may affect health and immune function in relation to acute and chronic stress. In that context, we discuss how relationships may affect immunity indirectly by impacting cognitions, affect, manners of coping, and health behaviors. We conclude by suggesting promising future research directions.

II. KEY FINDINGS IN CLOSE RELATIONSHIPS AND IMMUNE FUNCTION

A. Social Integration

Social integration refers to the degree to which a person is linked to or involved with his/her social environment at different levels, including community, individual network of social ties, and intimate relationships. The converse of social integration would be isolation, or the lack of regular contact with friends, neighbors, co-workers, family members, and social groups.

1. Network Size

A key aspect of social integration, network size can be measured by assessing the number of different types of relationships (e.g., a spouse, a parent, a friend, a co-worker), the total number of individuals in one's social network, and the frequency of contact with network members. Such quantitative measures are associated with mortality and morbidity from a range of conditions, including certain cancers and respira-

tory diseases with a clear immunological component (for a review, see Berkman and Glass, 2000). In addition, larger social network size predicts better functional and perceived health 30 years later, even after controlling for age and previous health (Moen et al., 1992). The relationship between network size and health outcomes rivals that of well-established health risk factors, such as smoking, blood pressure, blood lipids, obesity, and physical activity (House et al., 1988).

Strong evidence of an impact of network size on immune function comes from work on virus susceptibility by Cohen and colleagues, in which healthy individuals were experimentally exposed to the common cold virus and subsequently observed under controlled conditions. One such study showed that increasing social network size was associated with decreased susceptibility to infection (Cohen et al., 1997), although this association has not been found consistently (e.g., Cohen et al., 2003). A link between network size and cold susceptibility raises the question of whether these effects may be explained by personality variables. For example, sociability, the trait tendency to seek out and maintain social ties, is also associated with greater resistance to the cold virus (Cohen et al., 2003). However, preliminary findings suggest that the effects of sociability and network size are somewhat independent (Cohen, 2004). In addition, smaller social network size was associated with a lower antibody response among healthy undergraduate students; this effect was also independent of personality traits sometimes associated with loneliness, such as self-esteem, hostility, and extraversion, as well as perceived stress, health behaviors, and mood (Pressman et al., 2005). Of note, having more diverse social contacts also increases exposure to infectious agents, potentially increasing the risk of illness (Hamrick et al., 2002). However, in a naturalistic setting where potential of exposure to viruses varies, individuals with more diverse networks show fewer upper respiratory infections only when they also report low stress (Hamrick et al., 2002).

Regular attendance of religious services is one component of many measures of social network size, as many individuals derive close social ties and a feeling of social integration from religious groups. Religious participation is associated with perceptions of a more supportive social network (Ellison and George, 1994) and is associated with lower mortality rates (McCullough et al., 2000; Strawbridge et al., 1997) and with lower levels of interleukin-6 (IL-6), a pro-inflammatory cytokine (Koenig et al., 1997; Lutgendorf et al., 2004). Although the pathways between religious participation and mortality are not well understood,

researchers speculate that increased social integration and immune function play a role. However, some studies indicate that social network size does not account for the relationship between religious participation and immune outcomes, suggesting that the effects of religious participation are explained primarily by other factors (e.g., Lutgendorf et al., 2004).

Evidence for association between social network size and health supports the main effects model of social support: Social network size appears to confer health benefits regardless of the experience of psychosocial stress (Cohen, 2004). However at least one study supports the stress-buffering model—the proposition that social relationships confer benefits especially to those who experience more psychosocial stress. A study of patients with disseminated cancer found that greater social network size related to greater responses to delayed-type hypersensitivity (DTH) tests only for those reporting a high level of life stress (Turner-Cobb et al., 2004). However, among individuals with less life stress, the relationship was reversed: Individuals with smaller network size showed more robust immune responses. One interpretation of these findings is that under conditions of low stress, a greater number of social contacts may have been experienced as stressful due to obligations of the sick individual to those network members or because of unhelpful attempts at support by those network members; in contrast, under conditions of high stress, perhaps social contacts were either able to provide better support or their perceived availability and support were more appreciated. As will be discussed in greater detail later, situations of chronic illness may potentiate problems with social support when they exist.

Much of the literature on social network size has been interpreted in terms of positive benefits that result from social integration. This interpretation is supported by the graduated increases in health that have repeatedly been found with increasing integration (e.g., Berkman and Syme, 1979; Cohen et al., 1997). However, as noted by Cohen (2004), it appears that the most isolated individuals are at “greater risk than one would expect if the relation between social integration and health was linear” (p. 680); that is, it appears that the greatest differences in health are seen between the very isolated as compared to their less isolated counterparts. In concordance with this observation, there is evidence that being able to identify even just one person who functions as a confidante, someone who can be trusted to listen to personal events and feelings, is predictive of better health. For a majority of adults in the United States, the marital relationship serves as a primary source of support (Glenn and Weaver, 1981; Simmons and O’Connell, 2003) and, correspondingly,

a majority of research on specific close relationships has focused on marriage.

2. Marital Status and Divorce

Married individuals consistently experience better health than unmarried and divorced individuals and are at lower risk of mortality from a range of acute and chronic conditions over and above effects of age, income, and other biomedical risk factors (Gordon and Rosenthal, 1995; Johnson et al., 2000; Verbrugge, 1979). Interestingly, older individuals who become divorced appear to be at greater risk of both mortality and morbidity than younger people, perhaps in part because they typically lack a support network sympathetic to such concerns (Schulz and Rau, 1985).

The association between physical health and marriage remains after controlling for selection effects, (i.e., the tendency for healthy individuals to marry and stay married) (Wu et al., 2003). Although other factors undoubtedly contribute to the association, the support provided by marriage and the stress of marital transitions are widely acknowledged to account for much of the predictive power of marital status on health outcomes (Burman and Margolin, 1992).

In interpreting studies more specifically relevant to immune function, it is important to note that the effect of marital status on both mortality and morbidity is substantially stronger for men than for women (Kiecolt-Glaser and Newton, 2001); non-married women have a 50% greater risk of mortality than their married counterparts, compared to a 250% greater risk for non-married compared to married men (Ross et al., 1990). In fact, men show greater benefit from social integration in general (House et al., 1988). There are several plausible explanations for why marriage confers greater health benefits to men than women (Johnson et al., 2000; Kiecolt-Glaser and Newton, 2001), most of which involve differences in actual supportive functions and which are described in the section titled “Perceived Marital Support.”

Research focused on marital status and immune function is limited, with a greater body of work focusing on marital quality. However, one study suggests that married women may have more adaptive immune function than comparable recently separated or divorced women (Kiecolt-Glaser et al., 1987), with the latter showing lower percentages of natural killer (NK) cells (Kiecolt-Glaser et al., 1987) and higher antibody titers to latent Epstein-Barr virus (EBV), indicating poorer cellular immune function control over the steady state expression of the latent virus. These effects were not explained by differences in drug or alcohol use, diet, or sleep. Similar results were found with

men, with divorced or separated men showing higher antibody titers to two herpes viruses—EBV and herpes simplex type 1 (HSV-1) (Kiecolt-Glaser et al., 1988). Individual variation in responses to divorce, which can include acute as well as long-lasting depression in addition to other stress responses, are likely to play a role in these immune changes (Kiecolt-Glaser et al., 1987). The potential impact of depression on immune function (for a review, see Irwin, 2001) is discussed in the following section, as well as in our conclusion section.

Rheumatoid arthritis (RA), a systemic autoimmune disease, provides other immune-relevant data relevant to marital status. Among this population, increases in aspects of immune function are maladaptive because they are associated with disease flare-ups (Zautra et al., 1994). In both men and women with this disease, married individuals demonstrate slower progression of functional disability than the unmarried (Ward and Leigh, 1993). No one category of unmarried individuals (e.g., never married, separated, and widowed) appeared to drive the effect in this study (Ward and Leigh, 1993).

3. Bereavement

The emotional and physical health consequences of surviving a close other can be profound. As with divorce, there are many complicated issues surrounding bereavement other than the loss of social connectedness and social support. Sadness, anxiety, and rumination are common and often long lasting (Weiss, 2001). Some studies have focused on bereavement in general. For example, Gerra and colleagues (2003) found that individuals experiencing unexpected bereavement from a close other (parent, child, spouse) demonstrated alterations in functional (as opposed to quantitative) immune measures post-bereavement as compared to non-bereaved matched controls. However, the majority of health-relevant work on bereavement focuses on sequelae subsequent to the death of a spouse. Spousal bereavement is associated with an increased risk for inflammatory disorders (Sternberg et al., 1992) and increased all-cause morbidity and mortality. Similar to gender differences in social integration described earlier, men appear to be at a greater risk of mortality following spousal bereavement (Kiecolt-Glaser and Newton, 2001). A particularly well-controlled and comprehensive study found that surviving one's spouse led to increased risk of mortality among men but not women over a 10-year period (Helsing et al., 1981). Interestingly, older individuals tend to be at less risk for both mortality and morbidity from spousal bereavement than younger people (for a

review, see Schulz and Rau, 1985), perhaps because of their expectations and a tendency to have social networks prepared and able to provide support following this event. As the majority of studies of bereavement have been of older women, the association between bereavement and health in younger individuals may be underestimated.

A number of studies have demonstrated dysregulation of immune function following the death of a spouse. The first such study demonstrated that bereaved women had significantly lower lymphocyte responses to two mitogens (Concanavalin A [Con-A] and phytohemagglutinin-A [PHA]) two months after the death of their spouse (Bartrop et al., 1977), followed by a study of men which found such effects after the death of a spouse from breast cancer (Schleifer et al., 1983). While the former study was not able to control for baseline levels, in the latter study lymphocyte responses were not suppressed in the men prior to their spouses' death, despite their reported increase in life stress due to coping with the disease. More recent studies have shown that bereavement is associated with a decrease in NK cell activity (e.g., Hall and Irwin, 2001; Irwin et al., 1987b). Although the clinical relevance of such dysregulation of immune function is not clear, the potential importance of these findings is highlighted by the morbidity and mortality rates associated with bereavement.

Clinically relevant changes in immune function are more clearly demonstrable in HIV seropositive (HIV+) individuals for whom subtle changes in CD4+ T-cell numbers and proliferative responses of T-cells to mitogens are associated with morbidity and mortality. HIV+ men who had lost their partner to AIDS in the previous year evidenced greater serum neopterin levels (produced by activated macrophages and linked to progressive HIV infection) and a decreased T-cell proliferative response as compared to seropositive non-bereaved, seronegative bereaved, and seronegative non-bereaved men (Kemeny et al., 1995). Bereavement status in this population predicts decreases in CD4+ cells across a 4-year period, and NK cell cytotoxicity between 6 to 12 months post-bereavement (Kemeny and Dean, 1995; Goodkin et al., 1996). Limited research has compared bereavement from different types of close relationships. Data from HIV+ populations indicate that close romantic partnership is particularly significant: Although loss of a partner predicts immune changes in HIV+ men in the following year (Kemeny et al., 1995), loss of a close friend to AIDS does not predict immune changes (Kemeny et al., 2004).

Factors including depression, elevated cortisol levels, and sleep may account for the association

between bereavement and immunity (Hall and Irwin, 2001; Herbert and Cohen, 1993). Although the direction of causality has not yet been established, depression appears to play a particularly prominent role. A large longitudinal study of older adults found a nine-fold increase in major depression and a four-fold increase in depressive symptoms among the recently bereaved as compared to married individuals (Turvey et al., 1999). A rise in depressive symptoms following bereavement is particularly common among those for whom the loss of spouse was unexpected (Carnalley et al., 1999) and for whom social support is lacking (Wortman et al., 2004). More severe depressive symptoms among bereaved women are associated with lower lymphocyte proliferative responses to mitogens, less adaptive NK cell activity, a decrease in the number of T-cells, and an increase in the ratio of CD4+ to CD8+ cells (Irwin et al., 1987a).

B. Social Support

One reason that the existence of social ties is related so strongly to health outcomes is that they provide many forms of positive social support. The term *social support* refers to support from a variety of domains: instrumental support (including both financial and assistance with tasks), emotional (appraisal) support, information, companionship, and self-esteem support (Cohen and Hoberman, 1983; Cohen et al., 1985). A distinction is frequently made between perceived and received support, with perceived support referring to the degree to which an individual believes that support would be available if and when necessary, and received support referring to the actual amount of support that has been recently provided. Because measures of social support tap into the quality of social ties, they are often but not always correlated with social network size. For example, an individual with only one close relationship may feel that all of his/her needs are met, while another individual with 10 relationships may report low perceived social support. While higher levels of social integration (e.g., social network size) are typically beneficial regardless of stress level, measures of perceived support appear to operate in tandem with psychological stress (Uchino et al., 1996). Furthermore, the stress-buffering effects of social support may depend on the degree to which the functions provided by the social network match the specific needs elicited by the stressful event (Cohen and Wills, 1985).

An important consideration is that these measures may correlate with and possibly interact with socioeconomic status (SES); individuals with higher SES may be better able to provide a variety of types of support due to a variety of factors, including greater

time, money, and health. Individuals with higher annual earnings report providing more support to others than do those in middle or lower income categories (Krause and Borawski-Clark, 1995). Individuals with higher incomes also report greater satisfaction with the support they receive from others (Krause and Borawski-Clark, 1995). While individuals in lower social classes tend to provide support to others less frequently, they simultaneously rely more heavily on support provision; older low-SES adults tend to turn to others for assistance at relatively low levels of stress, while older high-SES individuals tend to rely on their own personal resources, turning to others only in times of greater need (Krause, 1997). Thus, not only is social class an important construct to consider in studies of social support, but social support interventions may be especially beneficial to individuals of lower social class.

1. Perceived Social Support

As compared to other measures of social support (e.g., received support), perceived social support is most reliably and strongly associated with well-being (Wills and Shinar, 2000) and most research relevant to immunity has employed such measures. Although there have been null findings, a meta-analytic review of studies predominantly based on perceived support concluded that higher support is associated with better immune system function overall (Uchino et al., 1996). For example, higher perceived support has been associated with a robust antibody response to a hepatitis B vaccine among medical students (Glaser et al., 1992). Among healthy men, perceived support, but not network size or actual utilization of support, is positively correlated with NK cell numbers (Miyazaki et al., 2003). Similarly, among spouses of those with cancer, higher perceived support on a variety of dimensions was associated with higher NK cell activity as well as better proliferative responses to one of two tested mitogens over and above any effect of depressed mood (Baron et al., 1990). In one of few studies to examine gender differences, however, the perceived availability of a confidante was associated with a stronger proliferative response for women but not men (Thomas et al., 1985). Finally, low perceived support has also been correlated with an increase in self-reported episodes of upper respiratory infection (for a review, see Biondi, 2001).

A broader view of the health-promoting effects of social support suggests that perceived support largely operates via a stress-buffering model, with the greatest and most reliable benefits of support found under conditions of psychological stress, when the support is

most needed (Cohen, 2004). The majority of data with immune relevance appears to follow the same pattern. Supporting the stress-buffering model, social support buffered the negative effects of minor daily stressors on total lymphocyte counts and mitogen-induced proliferative responses of lymphocytes in an elderly sample (Thomas et al., 1985). Additionally, examination stress effects on NK cell activity were also ameliorated by high perceived support (Kang et al., 1998).

In a population representing chronically stressed individuals, caregivers of spouses with dementia who reported low perceived support and less closeness with others demonstrated poorer augmentation of NK cell activity to two cytokines (Esterling et al., 1994b; Esterling et al., 1996). Caregivers who reported lower levels of perceived support demonstrated more negative changes in immunity 1 year later if they were distressed by their spouse's dementia-related behavior (Kiecolt-Glaser et al., 1991), indicating again that social support may be particularly important for those experiencing greater subjective distress.

Among cancer patients, lack of social support is associated with increased mood disturbance, decreased life expectancy, and decreased NK cell activity (Ell et al., 1992; Jensen, 1991; Levy et al., 1992; Waxler-Morrison et al., 1992). Among ovarian cancer patients there is a negative correlation between social well-being and vascular endothelial growth factor (VEGF) levels, a cytokine associated with tumor angiogenesis and poorer survival (Lutgendorf et al., 2002).

As noted earlier, social integration tends to benefit men in terms of health significantly more than it does women. While gender disparities related to supportive functions provided by men versus women have been posited as explanations for these effects, in most cases these disparities have not been directly linked to health or immune outcomes and represent an area ripe for future research. In terms of general social integration, women tend to provide support more to others in general. In addition, most caregivers of both children and older adults are women (for a review, see Mancini and Blieszner, 1989). As will be addressed later, providing long-term care to others, even loved ones, can be a considerable source of stress.

2. Perceived Marital Support

The marital relationship represents a relatively stable resource for all of the supportive functions one may derive from a support network. However, little research has focused on the relationship between support functions provided by one's spouse and immune parameters. Among breast cancer patients, NK cell activity was associated with the perceived

quality of emotional support provided by a spouse or intimate partner (Levy et al., 1990a). Another study found that, averaging across support domains, newlywed wives who reported greater satisfaction with the support provided by their spouses demonstrated smaller increases in negative affect, blood pressure, and cortisol in response to a conflict interaction with their spouses (Heffner et al., 2004). These data suggest that satisfaction with spousal support may be a unique predictor of physiological outcomes, above and beyond support from an overall social network.

Gender disparities in the supportive functions spouses provide have been posited as explanations for noted gender differences in the health benefits of being married. Although no data are available to support the contention that such gender disparities relate to immune-relevant outcomes, this represents an important area to target future research. For example, wives tend to influence their spouses to improve health behaviors to a greater extent than do husbands (Umberson, 1992), which can be interpreted as a form of informational support (the conferring of advice, recommendations, and feedback). In addition, married women do a greater percent of housework and child care than their spouses (Bittman et al., 2003), an aspect of the marital relationship that can be interpreted as disparity in provision of instrumental support. Evidence suggests that this disparity is more stressful for women who hold egalitarian ideals; these women report less satisfaction with their marriages and demonstrate more adverse cardiovascular and catecholamine responses than others (Kiecolt-Glaser and Newton, 2001).

Finally, men tend to rely more heavily on their wives for emotional support. For example, one study found that although men and women were equally likely to confide their main concerns with others in the weeks following cancer diagnosis, 40% of men reported confiding *only* to their partner, as compared to 15% of women who reported this pattern (Harrison et al., 1995). Because women tend to have broader support networks in whom they confide personal problems or difficulties, husbands may receive greater relative benefits from receiving emotional support from their spouses. Future research focused on the relative benefits of specific support functions from the spouse may provide a way of determining what elements of social support are key to health and immune benefits.

Other types of close relationships provide many of the same supportive functions as do married relationships. Of note, the number of individuals living as if married (which includes but is not limited to same-sex couples) has increased dramatically in recent years (Simmons and O'Connell, 2003). Recent evidence sug-

gests that such unmarried romantic partners share many of the physical and psychological benefits of married individuals, after controlling for income and age (Wu et al., 2003). Non-romantic close relationships (e.g., parents, children, friends) certainly also provide key aspects of support. However, family relations tend to provide for different supportive functions than do friendships, and the relative importance of family versus friends depends on age. Although relatives provide more instrumental support than do friends, friendships are central to emotional support and reducing feelings of loneliness (Lee and Ishii-Kuntz, 1987). Relatives, rather than friends or neighbors, are more likely to provide long-term assistance (Greenblatt et al., 1982); it is estimated that 80–90% of care of older persons is provided by family members (Brody, 1981). Additional comparisons of the marital relationship to other types of close relationships would be helpful in determining the underlying mechanisms behind health correlates of marriage.

3. Received Support

In humans, received support can be measured by assessing the degree to which certain types of support were provided to an individual over a given time period, such as the previous 4 weeks (Wills and Shinar, 2000). Literature on received support is much more limited than that on perceived support, in part because there are some limitations of utilizing received support as a measure that make results difficult to interpret. Received support reflects not only the availability of support and willingness to access available support but also the need for support. Perhaps because individuals experiencing greater need tend to receive more assistance, received support is sometimes correlated positively with functional disability and mortality (Dunkel-Schetter and Bennett, 1990; Krause, 1997). However, self-reports of receiving support when one is ill have been associated with health benefits. Social support provided by volunteers is associated with increased survival time in terminally ill patients by 80 days (Herbst-Damm and Kulik, 2005). Additionally, breast cancer patients who actively seek social support as a coping strategy show greater NK cell activity than those who do not (Levy et al., 1990a). Seeking instrumental support at diagnosis of ovarian cancer is associated with lower concurrent IL-6 as well as better clinical status and less disability 1 year later (Lutgendorf et al., 2000). However, in this study IL-6 did not mediate the effects of social support on these health outcomes.

Another reason the human literature on received support is limited is that interventions involving

received support are unethical and direct observations of support are difficult. Primate studies provide perhaps the strongest evidence that received support is adaptive for immune function. Rhesus monkeys housed with familiar peers during maternal separation show a smaller decrease in CD4+ and CD8+ cell numbers as compared to those housed alone (Coe, 1993). Primates exposed to the social stress of re-housing had poorer mitogen responses than those that were not re-housed. Further, among those who were re-housed, those demonstrating higher levels of naturally occurring affiliative behavior had better immunological responses (Cohen et al., 1992).

4. Loneliness and Intimacy

One reason social integration and social support may be beneficial is their association with the more specific constructs of loneliness and intimacy (Reis and Franks, 1994). Indeed, loneliness can be interpreted as a perceived lack of support. However, although loneliness is often related to social network size, the association is by no means perfect. One can feel isolated from others despite having a large number of social contacts, or feel very socially connected due to a particularly good social contact. There is some evidence that feelings of loneliness can be immune dysregulating (Cacioppo et al., 2003). In a population of psychiatric patients, loneliness was related to lower NK cell and PHA responses (Kiecolt-Glaser et al., 1984b). In addition, loneliness in medical students is associated with lower NK cell activity (Kiecolt-Glaser et al., 1984a). More recently, feelings of loneliness among college freshmen were associated with poorer antibody responses to one of three tested vaccines (Pressman et al., 2005). The effect of loneliness on antibody responses was not mediated by cortisol, increases of which correlated with reports of loneliness close in time to the cortisol measures, but was partially attributable to the higher perceived stress of lonely individuals (Pressman et al., 2005).

In contrast to loneliness, intimacy refers to the perceptions of closeness with a social partner. Evidence suggests that the majority of the health-promoting benefits of intimacy are accounted for by differences in social support, while benefits of social support are not mediated by intimacy (Reis and Franks, 1994). However, studies of more specific constructs like intimacy in the context of health are valuable in that they can illuminate more specific mechanisms by which social support is beneficial (Prager and Roberts, 2004). There is very little immune-relevant research on intimacy. Perhaps the most relevant research in this area comes from a prospective study of married rheumatoid

arthritis patients in which self-reported perceptions of positive spousal interaction patterns were associated with less severe increases in disease activity in response to interpersonal stress (Zautra et al., 1998). Thus, as with the bulk of the social support literature, this study supports the contention that the self-reported receipt of support from close relationships serves a protective function in the face of difficulties.

C. Social Strain

Although for most people supportive social contacts outnumber troublesome ones (Rook, 1984), close relationships are often marked by both positives and negatives (Major et al., 1997), and overall networks may be characterized by both support and rejection (Finch et al., 1989). As described by social exchange theory, relationships can be a source of stress due to demands of time, money, and emotional resources (Cook and Rice, 2003). Finally, support may be well intended but provided in a manner that is not helpful. In the current section, we review evidence that negative aspects of social relationships can themselves serve as stressors, with a resulting impact on immune function.

1. Negative or Ambivalent Characterizations of Social Ties

There is substantial evidence that interactions marked by acute conflict and negative emotions have direct physiological consequences. Because close ties tend to be relatively stable (Weihs et al., 1999), conflict within relationships can function as both an acute and a chronic stressor, and may thus dramatically impact health over an extensive time period (Rook, 1992). Conflictive social interactions consistently result in heightened blood pressure and heart rate (Kamarck and Lovallo, 2003), especially for those high in trait hostility (Suls and Wan, 1993). Work with populations suffering from diseases related to immune dysregulation and inflammation supports a link between interpersonal stress and health outcomes. For example, among those with rheumatoid arthritis, interpersonal stress has been linked to both endocrine and immune alterations, changes which were associated with clinician-rated disease activity as well as self-reported joint tenderness in well-designed prospective studies (Zautra et al., 1994; Zautra et al., 1998).

People's negative characterizations of particular social ties or interactions are relatively independent (Ruehlman and Karoly, 1991): One can view someone as being an important and positive member of his/her social network while also acknowledging negative

aspects of the relationship (e.g., a family member who provides valued financial support but who is difficult socially). In fact, almost half of an individual's important social ties can be characterized as *ambivalent* (Uchino et al., 2001), which means they are perceived to be high in both positive and negative aspects. Recent studies indicate that relationships characterized as ambivalent may be just as toxic as those characterized as predominantly negative, in part because people tend to avoid contact with individuals they consider negative but have greater contact with ambivalent ties. Uchino and colleagues found that high numbers of ambivalent relationships in the networks of older adults predicted increased sympathetic reactivity during stress (Uchino et al., 2001). Similarly, compared to interacting with someone characterized as predominantly supportive or aversive, interacting with individuals characterized as ambivalent is related to larger increases in ambulatory systolic blood pressure (Holt-Lunstad et al., 2003).

To our knowledge, research with specific immune measures has not yet explored the possible interactive contributions of positive and negative perceptions toward social network members, which is clearly an important avenue for future research. Ambivalence in the marital relationship may be particularly important, as this is a relationship requiring a great deal of interaction and cooperation.

2. Marital Conflict and Dissatisfaction

Although, on average, being married confers health benefits, the mere existence of a close relationship is not enough to be protective. A particularly strong and reliable association is found between poor marital quality and poor health (Kiecolt-Glaser and Newton, 2001). One commonly used indicator of the quality of marital relationships is satisfaction with marriage, which is typically assessed with self-report scales. In the studies described previously that compared married men and women with separated or divorced individuals, lower marital satisfaction was associated with several indicators of poorer immune function, including levels of EBV antibody titers for women and men and the percentage of CD4+ and CD8+ cells for men (Kiecolt-Glaser et al., 1987; Kiecolt-Glaser et al., 1988). Immune data from these studies were consistent with the epidemiological observation that recently separated individuals have greater incidence of health impairment than individuals who have been divorced for many years (Dohrenwend et al., 1978). Studies with chronically ill populations support a correlation between marital satisfaction and immune function. For example, among wives with chronic fatigue and

immune dysfunction syndrome (CFIDS), marital satisfaction is correlated with health symptoms related to the disease (Goodwin, 1997).

In addition to self-report measures of marital satisfaction, marital quality has increasingly been assessed using observations of behavior during couple interactions. Hostile behaviors, such as interrupting and criticizing, appear to be particularly predictive of physiological outcomes. Hostile behaviors during marital discussions are associated with adverse changes in blood pressure and endocrine levels (Ewart et al., 1991; Kiecolt-Glaser et al., 1993; Malarkey et al., 1994). Moreover, research utilizing a variety of populations provides substantial evidence for immune dysregulation resulting from marital conflict. For example, using a sample of healthy newlywed couples with high marital satisfaction overall, subjects who exhibited more negative or hostile behavior during a 30-minute discussion of marital problems showed greater decrements over 24 hours as compared to other subjects on functional immunological assays (Ewart et al., 1991; Kiecolt-Glaser et al., 1993; Malarkey et al., 1994). Older couples also evidence endocrine and immune dysregulation following marital conflict discussion (Kiecolt-Glaser et al., 1997), with both men and women who demonstrated more negative behavior evidencing the poorest immunological responses across three assays. In another marital interaction study, wives responded to a 45-minute conflictive discussion task with greater increases in depression, hostility, and systolic blood pressure than husbands (Mayne et al., 1997); women's lymphocyte proliferative responses decreased following conflict, while men's increased (Mayne et al., 1997).

Several studies of individuals provide evidence that changes in immune parameters as a response to marital strain have clinical relevance. For example, in a population of predominantly female rheumatoid arthritis patients, negative spouse behavior (e.g., critical remarks) was predictive of poorer pain outcomes, even after controlling for baseline pain (Waltz et al., 1998). Marital strain is also associated prospectively with the development of mouth ulcers (Levenstein et al., 1999; Medalie et al., 1992), an area where the immune system is important; endocrine and immune dysregulation appear to play a role in these effects, in addition to gastrointestinal stress responses and adverse health behaviors. In addition, recent research on the effects of marital interactions has assessed healing of experimentally induced wounds, a clinically important outcome measure. Couples who demonstrated consistently higher levels of hostile behavior during across both conflictive and supportive interactions healed wounds at 60% of the rate of low hostile couples (Kiecolt-Glaser et al., in press).

Some consistent effects of individual differences have emerged from the literature on physiological responses to marital conflict. Notably, trait hostility—a dispositional tendency characterized by aggression, anger, and cynicism—may interact with marital conflict to produce even greater immune dysregulation. Individuals high in trait hostility show greater endocrine and immune responses to marital conflict, but only in part because they demonstrate more negative conflict behaviors during marital interactions (Mayne et al., 1997; Newton et al., 1995). Another study found a significant association between behaviorally coded affect during conflict and cardiovascular, immune, or cortisol data only among husbands who were high on cynical hostility (Miller et al., 1999).

The weight of evidence suggests that women suffer more from poor relationship quality and conflict (e.g., Hibbard and Pope, 1993; Kiecolt-Glaser et al., 1996; Malarkey et al., 1994; Mayne et al., 1997). For example, women who reported that they had considerable conflicts with their husbands and who also reported work conflict had a 2.54-fold risk of work-related disability related to a variety of health problems in the ensuing 6 years; neither work nor marital conflict was a risk factor for men (Appelberg et al., 1996). These differences between wives and husbands do not seem to be a function of gender differences in broader physiological patterns of responding to acute stress (Kiecolt-Glaser and Newton, 2001). One possible explanation for gender differences related to marriage is that conflict may dampen the benefits of being married more for women than men, perhaps because women's self-representations tend to be characterized by greater relational interdependence (Cross and Madson, 1997) and women tend to spend more time thinking about marital events than do men (Burnett, 1987; Ross and Holmberg, 1990).

3. Relationship Burden

Even relationships construed as predominantly positive can function as a source of stress when one individual in the relationship requires substantial care, such as a sick child or a spouse with Alzheimer's disease. In addition to direct demands on time, emotional, financial, and physical resources, care giving often requires dramatic restructuring of the family environment (Ell, 1996). Individuals care giving for a spouse with dementia have higher rates of depression and anxiety, and continue to show these higher levels even years after the loss of spouse for whom they were providing care (Bodnar and Kiecolt-Glaser, 1994). One reason why caregiving may be so emotionally and physically difficult is that caregivers often experience

social isolation, with accompanying reductions in access to social support (Ell, 1996). Converging evidence from a variety of immune markers and outcomes demonstrates that caregiving is consistently associated with immune dysregulation. As compared to well-matched controls, caregivers report more days of infectious illness (Kiecolt-Glaser et al., 1991) and evidence poorer immune responses to virus and vaccine challenges (Glaser et al., 2000; Vedhara et al., 1999). Caregivers also demonstrate slower healing of laboratory-induced wounds, an outcome with clear clinical relevance (Kiecolt-Glaser et al., 1995). In addition, both current and former caregivers had poorer enhancement of NK cell activity in response to recombinant IL-2 and interferon-gamma (INF- γ) *in vitro* (Esterling et al., 1994b; Esterling et al., 1996) and showed a substantially greater increase in IL-6 over a 6-year period as compared to non-caregivers (Kiecolt-Glaser et al., 2003). Caregivers with less positive social support and less emotional closeness among social contacts showed greater dysregulation, suggesting that the stress of caregiving is partially buffered by strong support networks (Esterling et al., 1996).

Caregiving for a chronically ill child is also related to important health outcomes. Telomerase activity and telomere length, two cellular markers associated with aging, were measured in peripheral blood mononuclear cells taken from healthy mothers, a subset of whom were caregivers for a chronically ill child (Epel et al., 2004). Regardless of whether the mother's child was healthy or sick, both perceived stress and chronicity of stress were significantly associated with lower telomerase activity and shorter telomere length (Epel et al., 2004). High stress levels were also associated with higher oxidative stress (Epel et al., 2004). In conjunction with immune dysregulation found among caregivers of spouses, these results provide substantial evidence that chronic stress is associated with premature aging (Glaser and Kiecolt-Glaser, 2005). An important caveat to the caregiver literature is that providing support is not necessarily detrimental to one's health. Indeed, providing social support to others is associated with reduced mortality over a 5-year time period, after controlling for age and gender (Brown et al., 2003). Providing support to others may provide a source of self-esteem and connectedness with others. However, in situations such as caregiving for an individual with chronic illness, stress associated with the provision of support may override the potential benefits.

Relationship burden may help explain some unexpected findings in the HIV literature. While some research has shown that low support is associated with acceleration of the progress of HIV infection (e.g., Leserman et al., 1999; Solano et al., 1993), substantial

evidence suggests HIV+ men who report more loneliness (Miller et al., 1997), less attachment to others (Persson et al., 1994b), or less social support (Persson et al., 1994a) show better immune function, although the immune outcomes are not always related to disease progression or mortality (e.g., Miller et al., 1997). There are several possible explanations for why these latter findings are discordant with the bulk of research reviewed in this chapter showing benefits of social integration and social support. Individuals with HIV and Acquired Immune Deficiency Syndrome (AIDS) are more likely to have social contacts who also have the disease. For this reason, HIV+ individuals are more likely to take on the burden of providing care to their close social ties (Cole and Kemeny, 2001). Those with HIV/AIDS are also more likely to experience bereavement than are members of the general population and report a related increase in depression, anxiety, and general distress (Gluhoski et al., 1997). In addition, gay men in the United States, on whom the majority of research has focused, may suffer strain in their social contacts due to prejudice about homosexuality and AIDS. HIV+ gay men who conceal their homosexuality and who also have high levels of social support have lower CD4+ cell counts than those who do not, suggesting that the strain of concealment is magnified for these individuals (Ullrich et al., 2003).

4. Problematic Received Support

While social support is generally considered to be beneficial, some attempts to provide support may be misguided, potentially causing additional stress. For example, when someone becomes critically ill or loses a loved one, friends and family may avoid discussing the issue (Lichtman et al., 1988), criticize one's responses (Koopman et al., 1998), or be overprotective (Hagedoorn et al., 2000). Among rheumatoid arthritis patients, evidence suggests that responses to pain that are overly accommodating may inadvertently reinforce pain behaviors and encourage less adaptive health behavior (Turk et al., 1992). Rheumatoid arthritis patients who report that their spouses engaged in more solicitous, distracting, and punishing responses reported greater pain intensity and demonstrated more pain behavior during a standardized battery of physical tasks (Williamson et al., 1997). Similarly, in a study of chronic back pain patients, higher spousal ratings of solicitousness were associated with less time spent walking on a treadmill in the partner's presence than when alone (Lousberg et al., 1992).

In addition, regardless of how skillfully support is provided, receiving high levels of support may reduce the recipient's self-esteem, perceived competence, and

perceived control (Matire et al., 2002). The effects of received support may depend on individual differences in the degree to which people desire support and how they adjust to support provision. For example, one study demonstrated that the effects of instrumental support (i.e., physical assistance) from spouses of women with osteoarthritis depended on the centrality of functional independence to the woman. Women who rated physical independence as highly important and who received high levels of support reacted negatively to this support, experienced greater depressive symptoms, and showed fewer self-care behaviors (Matire et al., 2002). This suggests that support interventions need to account for individual difference in how one responds to support provision.

III. INTERVENTIONS

Interventions provide some of the best evidence that social support and key aspects of close relationships are causally related to immune changes and that these changes can be clinically relevant. Here, we highlight findings related to psychosocial interventions aimed at improving aspects of close relationships and which have relevance to immune function.

As described earlier, one way in which close relationships buffer stress is by allowing for the disclosure of negative emotions. Emotional disclosure through journaling and/or verbal accounting of stressful events may allow individuals without sufficient close ties to reap some of the benefits of emotional expression and may augment the effects of supportive ties for others. In both clinical and non-clinical populations, dramatic physical and psychological health improvements result from emotional disclosure interventions (Pennebaker, 1997; Smyth et al., 1999), including objective health outcomes among rheumatoid arthritis patients (Smyth et al., 1999). Changes in immune function appear to play a role in the health benefits of emotional disclosure. For example, among healthy medical students, those assigned to write about a traumatic experience once per day for 4 days prior to receiving a hepatitis B vaccine had higher antibody titers to the vaccine at 4 and 6 months post-vaccination than controls (Petrie et al., 1995). In addition, undergraduate students whose essays about stressful life events evidenced a lot of emotion had lower levels of antibody to EBV, suggesting greater cellular immune control over this latent virus (Esterling et al., 1990). In general, interventions focused on emotional disclosure appear to be more effective if the individual has not already disclosed or come to terms with the circumstances giving rise to their emotions (Pennebaker et al., 2001).

Of course, writing about an event is different from actually expressing emotions to someone else who can respond and provide support. To our knowledge, no study has compared emotional disclosure while alone to disclosure to a close friend or significant other, which would be particularly meaningful to the impact of disclosure in close relationships. However, verbal disclosure of stressful life events may be even more effective than written disclosure. As compared to those assigned to write non-emotionally, healthy undergraduates assigned to express their emotions about stressful events showed lower EBV titers; those assigned to verbally disclose their emotions (alone into a tape-recorder) showed even lower EBV titers than those assigned to write about them (Esterling et al., 1994a). In addition, preliminary evidence with chronic pain patients suggests that writing letters in a directed way about angry feelings can be beneficial in terms of pain severity, control over pain, and depression (Graham et al., 2006).

A number of psychosocial interventions have focused on chronically ill populations. While not entirely consistent, research targeting cancer distress generally demonstrates that psychosocial interventions have strong effects on psychological function. In fact, it has been argued that evidence is strong enough to justify the integration of psychosocial treatment into standard care (Carlson and Bultz, 2004). Data regarding the impact of psychosocial interventions on health outcomes in cancer populations is mixed, and beneficial findings in terms of longevity have not withstood replication (Goodwin, 2004). An important note is that interventions with cancer patients showing beneficial effects have encouraged discussion of negative thoughts and emotions such as fear of dying, hopelessness, and guilt, suggesting that emotional disclosure may be a key mechanism underlying successful interventions in this area as well.

Most support interventions are based on peer support from other individuals with the same disease. However, it may be more effective to focus support interventions on improving utilization of a more naturalistic, existing support network (Cohen, 2004). Given the reviewed data on the particular importance of the marital relationship, it may also be beneficial to target the marital relationship as a source of support. One unique intervention related to marriage, the CanCOPE intervention, was developed specifically for couples in which the women had either early stage breast or gynecological cancer (Scott et al., 2004). The intervention emphasized mutual support and effective communication. The intervention for couples produced significantly greater improvements in couples' supportive communication, greater reduction in

psychological distress, improved sexual adjustment, and improved coping strategies compared to standard care and a similar cognitive behavioral intervention for the women alone.

As noted earlier, bereavement is associated with immune dysregulation. Disclosure of emotion is common after bereavement, but may be constrained if the death was traumatic or stigmatized (e.g., from AIDS or suicide) (Pennebaker et al., 2001). In a correlational study, those who talked about the traumatic death of their spouse reported being in better health than those who had not (Pennebaker and O'Heeron, 1984). In an emotional disclosure intervention, those assigned to write about the recent death of their spouse showed improvement on hopelessness and depression (Pennebaker and Seagal, 1999). More comprehensive interventions with bereaved individuals also result in improved health. For example, bereavement support groups have been demonstrated to result in greater improvements of health-related quality of life in HIV+ individuals than comparable individual therapy (Sikkema et al., 2005). Literature on immune outcomes of such interventions has overwhelmingly focused on HIV+ men, primarily because they are particularly likely to experience bereavement (Gluhoski et al., 1997). In a sample of HIV-1 positive homosexual men, a bereavement support group was demonstrated to buffer against the decrement in CD4+ cell count and the increment in plasma viral burden typically seen as a response to bereavement (Goodkin et al., 1998). Research on the immune effects of support groups for HIV+ women is needed, particularly as they report greater distress, anxiety, and a suicidal ideation in response to bereavement compared to HIV+ men (Summers et al., 2004). In addition, following psychosocial interventions, psychological and quality-of-life improvements appear to be greater for HIV+ women than for men (Sikkema et al., 2005).

The bulk of the evidence indicates that support interventions have beneficial effects. However, support interventions are not always necessary, and may do harm to individuals who are experiencing little distress or who already have adequate support. One study (Helgeson et al., 2000) found that women who began a supportive group intervention with high levels of social support demonstrated decreases in physical function over the course of the intervention. Negative interactions in the group increased over time, so this may not be typical of support groups in general. However, other studies have similarly found that support interventions may result in deleterious effects (Frasure-Smith et al., 1997). In addition, for those who are experiencing support deficiencies, interventions may be most effective if they are tailored to address

the individual's particular support problem (Hogan et al., 2002). For example, while some individuals may benefit from increasing their number of social ties, other individuals may have access to adequate support but difficulty asking for assistance.

There are many other promising areas for interventions focused on close relationships that are not reviewed here. For example, training providers to provide better support (e.g., in a medical setting) may be helpful; one study of cancer patients showed that positive ratings of emotional support from a spouse were related to NK cell function as well as better ratings of emotional support from a physician (Levy et al., 1990b). Also, given the substantial data linking marital conflict to immune dysregulation, another promising avenue is interventions targeting marital distress. Based on emerging data, interventions to reduce interaction conflict and improve interpersonal support and communication may improve wound healing and aid in surgical recovery (Kiecolt-Glaser et al., 1998).

IV. CONCLUSIONS AND FUTURE DIRECTIONS

The research reviewed in this chapter, predominately based on work from the past 20 years, provides powerful evidence that social relationships are associated with immune function. In work focused on the existence and status of close relationships, a small social network, loneliness, divorce, and bereavement are associated with adverse alterations in immune function and related health (e.g., Gerra et al., 2003; Kiecolt-Glaser et al., 1984b; Kiecolt-Glaser et al., 1987; Pressman et al., 2005; Ward and Leigh, 1993). Similarly, considerable work suggests that problematic social relationships can function as a source of stress and be immune dysregulating (e.g., Glaser et al., 2000; Kiecolt-Glaser et al., 1988; Malarkey et al., 1994). In contrast, positive aspects of social support are associated with more adaptive immune function (e.g., Cohen et al., 1992; Uchino et al., 1996), often apparently by buffering the effects of stress.

Several lines of work suggest that such changes have a corresponding impact on health. For example, wound healing is affected by both marital strain and the stress of care giving (Kiecolt-Glaser et al., 1995; Kiecolt-Glaser et al., in press). Research on vaccine responses and infectious illness risk also suggest clinical relevance (Kiecolt-Glaser et al., 2002). Moreover, although the effects of social support interventions have been mixed, some studies have shown clinically meaningful improvements (e.g., Goodkin et al., 1998). Although longitudinal data are available with chroni-

cally ill populations, additional work is needed to link relationship-driven immune changes to longitudinal health outcomes in healthy populations.

In addition, greater delineation of the psychological mechanisms by which relationships affect immune function is needed. Although beyond the scope of this chapter, cognition, affect, and behavior are interrelated domains that are believed to underlie the association between social ties and health outcomes. For example, the degree to which a person perceives a given stressor as challenging or threatening depends on his/her assessment of the difficulty of the task and his/her ability to meet its demands (Blascovich and Mendes, 2001). These appraisals, which can be affected by the degree to which social support is available, in turn influence affective responses and coping behaviors. In terms of health behavior, the influence of close social ties is typically positive; however, relationships marked by conflict or negative social influence can result in detriments to health behaviors with clear relevance to immune function (Kiecolt-Glaser and Glaser, 1988).

In the affective domain, there is substantial evidence that emotional responses, such as anxiety, anger, and depression, are associated with immune function. For example, hostility, which clearly affects social interactions, is uniquely associated with C-reactive protein (Graham et al., in press; Suarez, 2004) and IL-6 for certain individuals (Suarez, 2003). Depression is also associated with production of pro-inflammatory cytokines (for a review, see Kiecolt-Glaser and Glaser, 2002) as well as with both enumerative and, more reliably, functional measures of immune function (Herbert and Cohen, 1993). As depression is associated with social integration, perceived adequacy of social support, and relationship conflict, it may be a particularly important psychological mechanism by which close relationships affect immune function. Moreover, clinical depression involves changes not only in affect, but also in behavior and cognition. Clearer delineation of the degree to which cognition, emotional responses, and behavior interact with each other and ultimately mediate the relationship between social ties and immune function is needed.

Research often treats emotion and behavior as well as biomedical risk factors and demographics (e.g., gender, ethnicity, socioeconomic status) as "spurious" variables that need to be controlled to determine the independent impact of a particular variable of interest. Such attempts are often successful and valuable. However, these factors clearly play an important role in determining health and immune function. Additional research is needed to examine not only the unique effects of these factors, but their interactive effects as well. To that end, we predict that multi-

variate statistical techniques, particularly structural equation modeling, will become increasingly valuable in the field of psychoneuroimmunology. Although use of these methods may be impeded by unfamiliarity as well as difficulty in obtaining adequate sample sizes, they are valuable in that they enable the specification of the multiple converging pathways that exist in reality.

Other areas of research that deserve further investigation include positive aspects of relationship interactions (Robles and Kiecolt-Glaser, 2003) and the impact of ambivalent social ties (those characterized as both positive and negative). Relatedly, the immune relevance of other measures of partner closeness, such as those assessed with pictorial diagrams and unobtrusive reaction time tests (Aron et al., 1992), has not been studied to our knowledge. Interestingly, the activation of feelings of romantic love toward an intimate partner has recently been associated with brain activity in specific regions as determined by fMRI (Aron et al., 2005). As novel methods of assessing social relationships are developed, our ability to conceptualize the association between immune outcomes and social ties will gain even more sophistication.

Even after controlling for potentially confounding factors that make work in this area challenging, there is substantial evidence that key aspects of close relationships are associated with immune function. We are not yet at a point where we can claim that immune changes account for a proportion of the morbidity and mortality risk associated with social integration, social support, and relationship discord. However, it should be clear that psychosocial and behavioral interventions targeted at close relationships should be included in the arsenal of methods we consider as we strive to improve physical as well as psychological well-being.

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