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Psychoneuroimmunology: Past, Present, and Future

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Provides a brief overview of the history and current status of behavioral immunology research, as well as speculation on likely future directions, and suggests that the field may have broad implications for basic biological sciences and medicine. In addition, the field has clear relevance for health psychology; its relevance to actual health outcomes, however, is not yet known.

Key words: psychoneuroimmunology, stress, emotion, immunity

The genesis of behavioral immunology can be traced to work that began in the 1960s. Solomon coined the term *psychoimmunology* in 1964 and published a key article that was far ahead of its time: "Emotions, Immunity, and Disease: A Speculative Theoretical Integration" (Solomon & Moos, 1964). Moreover, in several pioneering studies, he has shown stress-related suppression of primary and secondary immunity in rats (Solomon, 1969) and has also demonstrated that early handling could have lasting consequences for humoral immunity (Solomon, Levine, & Kraft, 1968).

Ader and Cohen's (1975) landmark article showed that immune function could be classically conditioned. This report was viewed with considerable skepticism initially; in fact, several laboratories designed replications of the original experiment, assuming that the original data were erroneous. The

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reliability of the phenomena has now been demonstrated by several laboratories.

Consistent with the interest in major stressful life events, the primary focus of human behavioral immunology research in the 1970s was the investigation of very intense and novel events. Researchers studied the immunological sequelae of astronauts' space flights (Kimzey, 1975), bereavement following the death of a spouse (Bartrop, Luckhurst, Lazarus, Kiloh, & Penney, 1977), 44 or 77 hours of noise and sleep deprivation (Palmblad, 1981), or new cadets' adjustment to life at a military academy (Kasl, Evans, & Niederman, 1979).

An additional impetus to the development of the field was the explosive growth in immunology during the 1970s and 1980s. Several key immunological developments, such as the production of monoclonal antibodies (permitting identification of subpopulations of white blood cells), allowed immunologists far greater specificity in characterizing different facets of the immune response and in demonstrating their functional significance.

The dramatic increase in research exploring behavioral influences on immunity in this decade has been fueled by two other factors. The National Institute of Mental Health, particularly the Health and Behavior Branch, has had a significant impact on the growth of the field through additional funding and encouragement of longer term developmental efforts such as postdoctoral training grants.

In addition, the AIDS epidemic has focused attention on interactions between immune function and behavior. Because there is considerable variability in rates of HIV progression following seroconversion, one question of current interest is whether psychological variables may act as co-factors (Kiecolt-Glaser & Glaser, 1988b).

CONTEMPORARY RESEARCH WITH HUMAN SUBJECTS

Research with human subjects has become considerably more sophisticated in recent years. Researchers have used several different populations, and both acute and chronic stressors appear to have immunological consequences. For example, one series of studies used medical students who were undergoing a very commonplace stressor, academic examinations. Blood samples taken during examinations showed poorer immune function compared to baseline blood samples taken 1 month earlier (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985; Glaser et al., 1987; Kiecolt-Glaser, Garner, Speicher, Penn, & Glaser, 1984).

Psychiatrists have searched for possible immunological markers for various disorders by comparing data from psychiatric patients, particularly depressed patients, with data from asymptomatic control subjects. Depressed

patients typically have poorer immune function than their nondepressed community counterparts (Stein, Keller, & Schleifer, 1985).

Several investigators are pursuing programmatic research with individuals whose health is already impaired, particularly HIV-infected individuals (Coates, McKusick, Kuno, & Stites, 1989; Fletcher et al., 1988; Temoshok, Zich, Solomon, & Stites, 1988). Levy, Herberman, Lippman, and d'Angelo (1987) examined psychosocial variables and immune function in breast cancer patients.

In an elegant series of studies involving behavioral, endocrinological, and immunological data, Baum has shown that there may be long-term consequences following a major urban stressor (McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989). Other data similarly suggest that chronic stressors may promote continued immunological down-regulation (Kiecolt-Glaser, Fisher et al., 1987; Kiecolt-Glaser, Glaser et al., 1987).

Although the abundant animal literature is well beyond the scope of this article, two areas have particular relevance for health psychology. Coe, Lubach, and Ershler (1989) showed that infant monkeys separated from their mothers can show distinctive immunological changes. In addition, evidence from Laudenslager, Ryan, Drugan, Hyson, and Maier (1983) suggests that controllable shock may have different immunological consequences than uncontrollable shock.

Some data suggest that relaxation may have positive immunological consequences (Kiecolt-Glaser et al., 1986; Kiecolt-Glaser et al., 1985). Another intervention study provided preliminary evidence that disclosure of traumatic or troubling events might have positive immunological consequences (Pennebaker, Kiecolt-Glaser, & Glaser, 1988).

Across several laboratories, it now appears that distressing psychological responses are one common denominator through which psychosocial events or psychological variables might have an impact on immunity. It is thought that these effects are mediated, at least in part, through the endocrine system, because there is good evidence for endocrine–immune interactions (Felten, Felten, Carlson, Olschowka, & Livnat, 1985; Hall, McGillis, Spangelo, & Goldstein, 1985).

RESEARCH PROBLEMS AND PROSPECTS

The primary problem in the area at present is the scarcity of researchers who have interdisciplinary training and expertise. Although many psychologists and psychiatrists have a strong interest in the field, they often have trouble establishing collaborative relationships with immunologists. Cross-discipline training is essential because psychologists are otherwise unable to communicate with immunologists, and the converse is true as well.

Cross-training can lead to a better appreciation of other differences

(e.g., the different research strategies that are generally used in the social and biological sciences). Basic biology scientists frequently rely on replication of an experiment as the primary method of ensuring reliability of a phenomenon, whereas behavioral scientists typically use statistical significance as their benchmark.

Psychologists who have not performed biologically oriented research are often unaware of the expense or the labor-intensive nature of immunological assays (Kiecolt-Glaser & Glaser, 1988a). For example, setting up routine assays using blood from several individuals generally takes a technician the better part of a day. Immunologists must consider the potential payoffs before investing their time and resources in a collaboration.

The expertise provided by an immunologist can make a critical difference in a collaboration. As one illustration, the collection and measurement procedures used in most studies for secretory IgA that do not appear to have included a person with immunological expertise have not been sufficiently reliable or valid so as to produce interpretable data (Stone, Cox, Valdimarsdottir, & Neale, 1987).

Although researchers who enter the area face several obstacles, there are also some very promising new developments. One of the markers of the growth of a field is the emergence of its own journal. In 1987 the first issue of *Brain, Behavior, and Immunity* (edited by Robert Ader, Nicholas Cohen, and David Felten) was published.

Although the clinical relevance is not known, Ader and Cohen (1982) demonstrated one very important potential application of conditioning phenomena in mice with an autoimmune disease. Their data suggest that it may be possible to obtain clinically significant drug effects with lower drug dosages; it is also possible that the noxious side effects of certain drugs might be attenuated somewhat through conditioning, although these are both quite speculative hypotheses at present.

It should also be emphasized that the actual health implications are still unclear and that down-regulation of immune function does not necessarily imply poorer health. There are very few studies that have simultaneously shown a confluence among psychosocial variables or stressors, down-regulation of immunity, and actual health changes (Glaser et al., 1987; Kasl et al., 1979; Pennebaker et al., 1988). The central problem in establishing actual health consequences (or lack thereof) is the relatively low frequency with which infectious disease occurs in most populations; longitudinal studies using at-risk individuals are critical. Alternatively, if one can actually control infection of subjects, then it is much easier to collect data that may help in understanding the health implications: Sheldon Cohen and a co-worker are performing such a study with the Common Cold Unit in England.

The field is growing at a very rapid rate. Although there are still many central questions for which there are little data, the prospects for learning

about the interactions among the central nervous system, the endocrine system, and immune system appear virtually limitless.

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