BACKGROUND: BASIC IMMUNOLOGICAL CONCEPTS

Although a thorough discussion of the immune system is beyond the scope of this chapter, we will provide an overview of some important concepts. For more detailed information, the reader can consult any introductory immunology text. For readers with more specialized interests, behavioral influences on immunological functioning are covered in Ader (1981), with perspectives from a number of disciplines. Information specifically on cancer is found in Levy (1982) or Fox and Newberry (1984).

One factor to keep in mind when reading the immunology literature is the age of a study, since knowledge about immunological functioning and the concomitant development of techniques and materials (e.g., monoclonal antibodies) have increased almost exponentially in the past 5 to 10 years. Some hypotheses regarding immunologic function and the data obtained using less precise procedures in earlier literature (including early psychoneuroimmunological research) are inaccurate or misleading when viewed in the context of contemporary knowledge.

The immune system is the body’s defense against infectious and malignant disease. Its two primary tasks are to identify “self” and “nonsel,” and the destruction, inactivation, or elimination of foreign substances or materials.

The two major parts of the immune system are the humoral immune system and the cellular immune system. In the former, B-lymphocytes produce antibodies or immunoglobulins, which are serum proteins that are induced by and react with antigens (molecules, usually proteins, which stimulate the production of particular antibodies). The humoral immune response is important for defense against bacteria and viruses in body fluids.

The cellular immune response, the non-antibody-producing arm of the immune response, is important for defense against intracellular viruses, transplanted tissue, cancer cells, fungi, and protozoans. Malfunctions in cellular immunity are associated with some autoimmune diseases. T-lymphocytes (thymus-derived lymphocytes), a subgroup
of lymphocytes crucial for cellular immune system function, have a number of subgroups. For example, cytotoxic T-lymphocytes migrate to the invasion site in the body, attach themselves to the invading cells, and produce cytotoxic factors which destroy the invaders. Other T-lymphocyte subclasses synthesize lymphokines, essential chemical mediators of various aspects of immunity.

Two T-lymphocyte subpopulations are of particular importance because of their regulatory effects on immunity. Helper T-cells stimulate B-lymphocytes to produce antibody, while suppressor T-lymphocytes act to shut off helper T-cells when sufficient antibody has been produced. Significant disturbances in the helper/suppressor cell ratio can have important consequences for health. Low ratios are found in patients with immunodeficiency disorders (Reinherz & Schlossman, 1980), while high helper/suppressor cell ratios are found in naturally occurring autoimmune diseases, including systemic lupus erythematosus (SLE), hemolytic anemia, severe atopic eczema, and inflammatory bowel disease. In these diseases, the loss of suppressor cells may correlate with the clinical severity (Reinherz & Schlossman, 1980). The loss of suppressor cells may occur for a number of reasons, including their destruction by autoantibodies (antibodies made against self).

Another component of the cellular immune response, natural killer (NK) cells, serves a vital immunologic function; they defend against cancer and virus-infected cells. NK cells form an antitumor surveillance system and appear to be critical in the prevention of tumor growth and metastasis in animal models (Herberman, Ortaldo, Riccardi, Timonen, Schmidt, Maluish, & Djeu, 1982).

When the immune system has identified and processed an antigen, both T- and B-lymphocytes are induced to proliferate and differentiate into functional subpopulations. A given antigen will stimulate this sequence for only a small subset of cells that have compatible receptors. However, the in vitro use of mitogens (substances that stimulate DNA synthesis, cell growth, and cell division for large subsets of cells) provides information on the immune system’s ability to respond to certain foreign substances. The response of both T- and B-lymphocytes to stimulation by mitogens (termedblastogenesis) such as phytohemagglutinin (PHA, which stimulates helper cell proliferation), pokeweed (PWM, which stimulates both T- and B-cells), or concanavalin A (Con A, which stimulates both helper and suppressor cell proliferation) is thought to provide an in vitro model of the body’s response to challenge by infectious agents, such as bacteria or viruses.

Allergy or hypersensitivity is the name given to altered or enhanced responsiveness to an antigen which leads to pathological tissue changes. These reactions occur only after previous exposure to the antigen and are classified as either immediate or delayed, depending on the speed of the response. Immediate hypersensitivity reactions can occur in minutes after exposure to an antigen and involve humoral antibodies; well-known examples include hayfever, asthma, and hives. For hayfever, the deposition of the offending antigen on the mucous membranes of the upper respiratory tract results in the production of IgE antibodies, which prompt mast cells to produce histamine, a chemical producing congested nasal passages, sneezing, and itchy, tearing eyes.

Asthma is a lower respiratory tract allergic reaction. A sensitized person develops wheezing and shortness of breath when exposed to the offending antigen; these symptoms are the result of spasms resulting from constriction of the smooth muscles of the bronchial tubes.

The basic information presented above relates to both sexes. Immunological issues specific to women will follow.
of immunocompetence, including sex hormones. Consistent with the demonstrations of hormone receptors on lymphocytes, there is well-documented endocrine and neuroendocrine (hormones regulated by the central nervous system) mediation of immunity (e.g., Ahlvist, 1981; Blalock, 1984). Of particular relevance to the present discussion is the ability of sex hormones to affect immune function, providing one key pathway through which sex differences influence immune function.

**Infectious Diseases.** We are unaware of evidence suggesting sex differences in the incidence or duration of infectious diseases. However, hormonal variations during menstruation and pregnancy are associated with alterations in the control of herpesvirus latency, including the appearance of both herpes simplex virus type 1 and 2 (HSV-1 and HSV-2) lesions, or virus shedding in the absence of active lesions (Adam, 1982). Although HSV-1 is most commonly associated with oral lesions (cold sores), and HSV-2 with genital lesions, HSV-1 is associated with an increasing percentage of genital lesions, while HSV-2 is being found in oral lesions (Adam, 1982).

HSV is associated with specific health risks for women. Active HSV genital lesions during pregnancy mandate a cesarean section, since the infant’s contact with the infectious virus can result in the development of herpes encephalitis. HSV-2 is a possible oncogenic agent in cervical cancer, although the data are not clear about its etiologic or prognostic significance (Adam, 1982).

Cytomegalovirus (CMV), another herpesvirus, can also pose a serious risk for pregnant women. Viral transmission from a mother with an active infection to the newborn via contact with infected maternal genital secretions results in congenital infections in about 50% of infants. The severe forms of such infections are rare, but result in the newborn’s death within days or weeks; surviving children may be mentally retarded with microcephaly or have other cerebral abnormalities, and/or may have a host of other defects (Sullivan & Hanshaw, 1982).

**Cancer.** There are clear sex differences in the incidence of certain kinds of cancer, as reviewed by Levy and Lippman in this volume. Sex hormones are implicated in some of these differences.

**Autoimmune Disease.** In autoimmune diseases, the immune system is unable to distinguish self from nonself, and therefore attacks certain of the body’s own cells. Most human autoimmune diseases occur with significantly greater frequency in women than in men, and most have age distributions that appear to be related to periods of obvious physiological endocrine alterations. These factors have led researchers to suggest that sex hormones play an important role through their influence on some facets of immunity (e.g., Ahlvist, 1981). Genetic factors are also thought to be important. The two best-known autoimmune diseases are systemic lupus erythematosus and rheumatoid arthritis.

One American woman in 500 (and one tenth as many men) is afflicted with SLE. Estrogenic hormones are implicated, since incidence of SLE is highest during the reproductive years, when estrogen levels are highest. Oral contraceptives that include estrogen can exacerbate the disease, and postpartum exacerbations are common. In addition, men with abnormal estrogen metabolism are at greater risk (Koffler, 1980).

In individuals with SLE, the immune system forms autoantibodies to different types of body cells. Some are directed at DNA in the cell nuclei and may combine with liberated DNA in blood. The resulting antigen-antibody complexes pose a particular risk when they bind in the kidney’s filtration system, resulting in serious kidney damage (Rose, 1981).

Rheumatoid arthritis is a disease that affects the joints, connective tissue, and viscera. There are several subtypes within both the juvenile (O’Dougherty, 1983) and adult on-
set forms of the disorder, and etiological factors are not clear. The female to male ratio for adult rheumatoid arthritis is 3.2 to 1 (Ahlqvist, 1981). Pregnancy often has powerful ameliorating effects, as do oral contraceptives.

**Aging.** There are a number of age-related decrements in immunologic functioning (reviewed in Braveman, in press). The preponderance of women in the aged population make age-related decrements in immunity a particularly salient health issue for women.

**Relationships Between Behavior and Immune System Function**

The competency of the immune system is determined in part by genetic factors. There is also evidence for the mediation of immunity by nutrition, temperature, circadian rhythms, and a number of drugs. There are indications from the animal literature that physical stressors (shock, restraint, rotational stress, etc.) can alter immune function; the wide difference in outcomes appear to be a function of the type and temporal characteristics of the stressor, the degree of control over the stressor, and the degree of stress at baseline (Borysenko & Borysenko, 1982; Riley, 1981).

Stress-related changes in immunocompetence and susceptibility to infectious and malignant disease have been demonstrated in a number of rodent studies (see Borysenko & Borysenko, 1982; Monjan, 1981; Newberry, Liebolt, & Boyle, 1984). The generalization of this work to humans is not clear. Although the functioning of the immune system is similar across mammalian species, there are important differences, including the greater sensitivity of the rodent immune system to the immunosuppressive effects of adrenal glucocorticosteroids (Claman, Moorhead, & Benner, 1971). Moreover, it is not clear how to compare the physical stressor used in animal studies with cognitive stressors in humans.

The human psychoneuroimmunological literature is considerably more limited than the animal literature. The human studies that have measured acute changes in immunological function have most often addressed the effects of infrequent, high-intensity events. Two such studies used very small subject samples and rare events. Kimzey (1975) reported some immunologic changes in astronauts following spaceflights, while Palmbald (1981) reported changes in immunocompetence following 48 or 77 hours of noise and sleep deprivation. Prospective and cross-sectional studies also show that impaired mitogen responsiveness is associated with bereavement (Bartrop, Luckhurst, Lazarus, Kiloh, & Penny, 1977; Schleifer, Keller, Camerino, Thornton, & Stein, 1983). These studies provide valuable preliminary information on the immunological sequelae of novel and intense events.

One human study implicated psychosocial stressors in susceptibility to acute necrotizing ulcerative gingivitis (trenchmouth), an infection associated with normally nonpathogenic indigenous oral bacteria (Cohen-Cole et al., 1983). Compared to controls, these patients showed significantly higher levels of anxiety, depression, and number of negative life events in the previous year. They also had poorer lymphocyte response to mitogen stimulation.

Other researchers have studied the effects of academic stressors on immunocompetence. Jemmott et al. (1983) studied 64 dental students during the academic year. Lower salivary IgA levels at three high stress points contrasted with higher salivary IgA levels found on the low-stress baseline and on the final sample taken on return from summer vacation.

The primary focus of work from our laboratory has been the influence of common stressful events on the immune response. We reasoned that if stress-related immunosuppression were a risk factor for infectious and malignant disease, then significant changes in immune function should be associated with common aversive events, as well
as intense and novel events. We have also studied the extent to which psychosocial variables such as loneliness moderate immunocompetence.

In our first study we found that NK cell activity declined significantly in 75 medical student blood samples drawn during examinations, in contrast to baseline values from the previous month (Kiecolt-Glaser, Garner, Speicher, Penn, Holliday, & Glaser, 1984). Stressful life events and loneliness were also related to NK activity, with high scorers (above the median) on each dimension having lower levels of NK cell activity.

A similar pattern was observed in psychiatric inpatients. Lonelier inpatients had lower levels of NK activity, as well as a poorer response to mitogen stimulation by PHA. No differences were observed in their response to stimulation by PWM (Kiecolt-Glaser, Ricker, Messick, Speicher, Garner, & Glaser, 1984).

We did not find significant sex differences in immune function in either the medical student or psychiatric samples. However, the sex distributions were skewed in different directions for the two studies: Two thirds of the medical students were male, while two thirds of the psychiatric inpatients were female. In addition, there appears to be a sex-related response bias in self-reports of loneliness, which may obscure underlying sex differences. Data from Borys and Perlman (1985) suggest that women are more likely to acknowledge feelings of loneliness than men.

We found additional evidence of stress-related changes in NK activity in research with 40 second-year medical students. Three different assays measuring NK cells showed significant decrements during examinations, compared to baseline levels obtained 6 weeks earlier; these assays were lysis of MOLT-4 cells (a different NK target cell than used in our earlier research), percentage of NK cells as assessed by the monoclonal antibody anti-Leu-7, and percentage of large granular lymphocytes, the NK cell phenotype. In addition, there were significant declines in the production of interferon by Con A stimulated lymphocytes (Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986).

Interferon is a major regulator of NK activity, since it can affect both the growth and differentiation of NK cells from their progenitor cells; the significant decrements in interferon may be related to the decreases in the number of NK cells. Furthermore, interferon can activate the lytic activity of target-binding cells, enhance cytolyis of target cells, and increase the number of target cells that can be killed by an effector cell. There are also data which suggest that NK cells may produce interferon (Herberman et al., 1982).

These interferon and NK data may have important health implications. The modified theory of immune surveillance suggests that cancer cells can develop spontaneously in the body but are normally destroyed by the immune system, with NK cells being the most critical host defense (Herberman et al., 1982). Our data suggest that this host defense can be modified by a common stressor. Therefore, longer-term alterations in cellular immunity may carry increased risk for immunodeficiency disorders and malignant and infectious disease.

To further explore links between distress and health with particular importance for carcinogenesis, we assessed distress-related differences in DNA repair in lymphocytes. Most carcinogens appear to induce cancer by damaging the DNA in cells, thereby producing mutant cells (Miller, 1978); the body’s ability to repair damaged cellular DNA is critical, since faulty DNA repair is associated with an increased incidence of cancer (e.g., Setlow, 1978). Faulty repair of damaged DNA also alters cell growth, cell division, and gene expression, as well as cell death (Hart, Hall, & Daniel, 1978).

We studied psychiatric inpatients because of the high levels of distress associated with psychiatric admission. Newly admitted, nonpsychotic, nonmedicated psychiatric inpatients were divided into high and low distress subgroups based on their MMPI scale 2 (depression). The high distress sub-
group had poorer DNA repair in lymphocytes exposed to X-irradiation than the low distress subjects. While lymphocytes from most "normal" subjects are fully repaired at the end of 5 hours using this assay, the mean repair in the high distress group was only 85% of baseline values. There were no differences between the subgroups in age, sex, DSM-III psychiatric diagnoses, alcohol intake, cigarette smoking duration or intensity, weight loss, sleep disturbance, number of previous psychiatric admissions, or length of their current psychiatric admission (Kiecolt-Glaser, Stephens, Lipetz, Speicher, & Glaser, 1985).

These data suggest that distress is associated with poorer DNA repair in lymphocytes exposed to X-irradiation, at least within a psychiatric population. It is important to place these DNA repair data in the context of the previously discussed evidence regarding stress-related changes in NK cell activity and numbers. Taking the NK cell and DNA repair data together, it appears that distress could contribute to carcinogenesis directly (through faulty DNA repair), as well as indirectly (be affecting immune surveillance or competence).

In the context of possible psychosocial contributions to carcinogenesis, it is noteworthy that a significantly higher incidence of cancer across cancer sites has been associated with higher MMPI depression scores in a 17-year prospective study of over 2,000 nonpsychiatric men, even after accounting for other risk factors (Shekelle et al., 1981). Moreover, institutionalized psychiatric patients may have a greater incidence of cancer mortality than the general population (Fox, 1978).

Herpesviruses. Considerable anecdotal speculation has linked psychosocial stressors with the appearance, duration, and intensity of herpesvirus infections. Previous studies have found an increased risk for Epstein-Barr virus (EBV) infection in West Point cadets associated with a triad of risk factors: poor academic performance, high levels of motivation, and having a father who was an overachiever (Kasl, Evans, & Niederman, 1979); EBV, a herpesvirus, is the etiologic agent for infectious mononucleosis. In other research, Luborsky, Mintz, Brightman, and Katcher (1976) found that general unhappiness was predictive of the frequency of herpes labialis lesions (cold sores) among student nurses.

We found changes in antibody titers to three latent herpesviruses in blood samples obtained from medical students following their return from summer vacation in September, in comparison to samples taken the previous May during final examinations (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985). There were significantly higher antibody titers to EBV, HSV, and CMV during examinations. In addition, lonelier medical students had significantly higher antibody titers to two EBV antigens. The transformation of B-lymphocytes by EBV also showed alterations during exams, and there were again significant differences between the high and low loneliness student subgroups (Kiecolt-Glaser, Speicher, Holliday, & Glaser, 1984). Additional data from a geriatric population (Kiecolt-Glaser et al., 1985) show a significant decrease in antibody to HSV associated with a relaxation intervention, as discussed below.

These changes in herpesvirus antibody titers reflect the ability of the cellular immune system to control the latent herpesviruses. The competency of the cellular immune response is thought to be important in both the limitation of the primary infection and in the control of latent herpesviruses (Glaser & Gotlieb-Stematsky, 1982). Elevated herpesvirus antibody titers may occur in response to enhanced expression of latent virus due to changes in, or dysfunction of, the cellular immune response. Increased virus replication provides a larger load of viral antigens, which stimulate the production of antibody. Consistent with this, patients with immunosuppressive diseases and patients on immunosuppressive therapies have elevated herpesvirus antibody titers. The reestablishment of control over virus replication and
latency is ultimately followed by a drop in antibody titers (reviewed in Glaser & Gotlieb-Stematsky, 1982).

Treatment Applications

Intervention studies that include immunological measures are rare. In contrast, a number of studies have used health-related indices ranging from longevity to patient or physician health ratings (e.g., Blaney, in press; Rodin, 1980). The limited immunological treatment literature provides some enticing hints about the potential value of psychological interventions.

Conditioning. There is now evidence that both humoral and cellular immunosuppression can be classically conditioned (Ader, 1983) and that immunosuppression has survival value for autoimmune disorders. One rodent study suggests potentially important applications of such conditioning in humans. Using an animal model of SLE, Ader and Cohen (1982) showed that development of autoimmune disease in female New Zealand hybrid mice could be significantly moderated by classically conditioned immunosuppression. Groups of mice received weekly solutions of sodium saccharin, used as the conditioned stimulus. One group received injections of cyclophosphamide (the unconditioned stimulus, an immunosuppressive drug) on half of the weekly occasions after administration of the saccharin solution (conditioned animals). Other groups included weekly saccharin administration without cyclophosphamide (untreated animals), weekly saccharin administration paired with weekly injections of cyclophosphamide, and weekly saccharin unpaired with cyclophosphamide given on half the weekly occasions (unconditioned animals).

The conditioned animals survived significantly longer than the unconditioned animals that received the same dosage of cyclophosphamide, and did not differ significantly from animals that had received twice the dosage of the drug. The conditioned animals also differed significantly from the unconditioned animals in the rate of development of autoimmune disease, while nonconditioned groups were not significantly different from non-treated controls.

The differences between the conditioned and unconditioned groups are noteworthy. The conditioned animals showed delays in disease onset and mortality using a drug quantity that would normally have little impact on the course of the disease (Ader, 1983).

Recent data are consistent with possible classical conditioning effect on the delayed hypersensitivity response to tuberculin in humans (Smith & McDaniel, 1983). Conditioning was also suggested as a possible mechanism in a study of asthmatics’ changes in airway resistance (Luparello, Leist, Lourie, & Sweet, 1970).

Relaxation. We assessed the enhancement of immunocompetence by relaxation and social contact in 45 geriatric residents (36 women and 9 men) in independent living facilities (Kiecolt-Glaser et al., 1985). Subjects were randomly assigned to one of three protocols: (a) relaxation training, (b) social contact, or (c) no contact. Subjects in the relaxation and social contact conditions were seen individually three times a week for a month. Blood samples and self-report data were obtained at baseline, at the end of the intervention, and at a 1-month follow-up.

There were significant immunological changes associated with relaxation. NK cell activity increased in the relaxation group at the end of the intervention, with nonsignificant changes in the other two groups; NK levels returned to baseline levels at the 1-month follow-up. There was a decrease in antibody titers to HSV in the relaxation group at the end of the intervention, with the lower titers maintained at the follow-up but without significant changes in the social contact or no contact groups. These data suggest that relaxation may enhance cellular immune function.
The enhancement of immunocompetence may have particular importance for older populations, in which women are the clear majority. The decrements in various facets of immunocompetence associated with aging (Braveman, in press) are associated with the increased risk of mortality from infectious disease, as well as the increased incidence of malignant disease. Poorer cellular immunocompetence is associated with higher mortality in individuals over 80 years of age (Roberts-Thomson, Whittingham, Youngchaiyud, & MacKay, 1974).

Hypnosis and Suggestion. Several hypnotic studies addressed presumably immunologic events such as the treatment of warts. Most have methodological flaws such as inadequate control groups or the failure to assess base rates for spontaneous remission. The studies cited below provide a sampling of some of the better-documented research, not an exhaustive review of relevant work. Moreover, we will not address the possible effects of simple suggestions versus hypnosis, or hypnosis versus other forms of relaxation. Fry, Mason, and Pearson (1964) reported that asthmatic patients who were sensitive to known allergens had smaller wheals following hypnotic suggestions when compared to controls. In a second study, 29 of their subjects were randomly assigned to one of three conditions: (a) hypnotic suggestions that the right arm would not react to skin tests, (b) hypnotic suggestions that both arms would be nonreactive, and (c) hypnosis without suggestions. All groups showed differences in wheal size, but no differences were noted among the treatment groups.

Use of the “double arm” technique provides some of the better-controlled hypnotic research suggesting modulation of some facets of immunoresponsiveness. Using this paradigm with delayed hypersensitivity reactions, a presensitized subject is injected with the same antigen in both arms, and suggestions are made that one arm will show the characteristic changes (wheal, erythema, itching, burning, and swelling), while the other will not. Data from different laboratories suggest that such effects are replicable (Black, 1969; Good, 1981) but may be dependent on the hypnotic responsiveness of subjects as well as use of subjects with more “labile” skin reactivity (Beahrs, Harris, & Hilgard, 1970). Hypnotic mediation of immediate hypersensitivity reactions has also been reported using the same paradigm (Black, 1969).

**IMPLICATIONS: IMMUNE FUNCTION AND HEALTH**

We use medical students as subjects because the increased distress experienced during examinations appears similar to that evoked by other common stressful events. For this reason, the medical students’ immunological responsiveness during examinations provides a good model for the “real world” outside the laboratory. If the quality and intensity of an individual’s emotional response to an event is similar to that of our medical student subjects, there may be similar immunological changes.

Although no reliable sex differences in immune function have been reported in conjunction with stressors, it is certainly possible that there are interactions among stressors, female hormone changes, and health. Such interactions might be particularly important for immunologically mediated conditions that appear to have strong endocrine correlates, such as certain of the autoimmune diseases described previously.

While immunological changes are only infrequently associated with increased illness in our young and healthy medical students, such changes may have important consequences in individuals whose health is already impaired, in individuals who are exposed to an infectious agent or carcinogen, in individuals who already have undetected tumor cells, or in older (predominantly female) populations with decreased immunocompetence. In these and other at-risk groups, both commonplace and novel and intense stressful events may affect morbidity...
and mortality. Consistent with these data are the increased rates of morbidity and mortality in highly distressed populations such as bereaved spouses and psychiatric patients (Babigian & Odoroff, 1969; Jacobs & Ostfeld, 1977; Rees & Lutkins, 1976). Longer-term stress-related alterations in cellular immunity may carry an increased risk for immunodeficiency disorders and malignant and infectious disease.

REFERENCES


Herbermann, R.B., Ortaldo, J.R., Riccardi, C., Timonen, T., Schmidt, A., Maluish, A., &


