Developmental Psychoneuroimmunology

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Every major organ system or homeostatic defense mechanism is subject to the influence of interactions between psychological and physiological events. In many instances, psychobiologic interactions occurring during the course of development are of particular importance. The complex mechanisms underlying these interactions and their relationship to behavior, physiologic function, and even to organic disease are imperfectly understood. The most imperfectly understood, perhaps, are the interrelations between behavioral and immunologic processes. Why should this be so? For one thing, immunology is a relatively new biologic specialization and, perhaps, the fastest growing of the biological sciences. It is probably more accurate, then, to state simply that immunology is one of the few subspecialty areas of basic science into which the behavioral sciences have not *yet* ventured. A better reason may relate to the fact that the immune system is viewed by many immunologists as an autonomous agency of defense, a self-regulating system directed solely to the recognition of what is "self" and what is "not self." Little or no attention has been devoted to the central nervous system or to psychosocial factors which, operating through the nervous system, could influence immune function. That situation, however, is changing rapidly. Converging data from a variety of disciplines suggest that the immune system is integrated with other physiological systems and, like all such systems operating in the interests of homeostasis, is sensitive to regulation or modulation by the brain. Thus, the immune system stands as a potential mediator of a variety of psychophysiologic effects.

The evidence for this assertion is, I believe, overwhelming. It includes (a) neuroanatomic and neurochemical evidence for the innervation of lymphoid tissue; (b) observations that lesioning or stimulation of the hypothalamus result in changes in immunologic reactivity and, conversely, activation of an immune response results in measurable changes within the hypothalamus; (c) the finding that lymphocytes bear receptors for hormones and neurotransmitters; (d) evidence that alterations of hormone and neurotransmitter function modify immunologic reactivity and, conversely, elicitation of an immune response is accompanied by changes in hormone and neurotransmitter levels; (e) recent data documenting the effect of behavioral interventions, including conditioning,

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on various parameters of immune function; and, finally, (f) experimental and clinical studies in which psychosocial factors have been found to influence the predisposition to and/or the precipitation or perpetuation of disease processes that involve immunocompetence. Much of this information is now readily available (Ader, 1981).

With respect to psychosocial factors and disease, there are abundant clinical (mostly retrospective) data documenting a relationship between "life change" or "stress" and a variety of disease processes including some that are immunologically mediated (Gunderson & Rahe, 1974; Weiner, 1977). Both susceptibility to and recovery from infectious, allergic, and autoimmune disease have been related to life stresses in humans (e.g., Plaut & Friedman, 1981).

Over the past 25 years, there have been several studies of the effects of "stress" on infectious disease in animals, and the recent interest in immune processes as the mediator of these effects has renewed interest in this older literature. Briefly, a variety of environmental circumstances (e.g., avoidance conditioning, physical restraint, auditory stimulation, and the manipulation of social interactions) have been found to modify the susceptibility or response to a variety of infectious (Friedman, Glasgow, & Ader, 1969; Rasmussen, 1969), parasitic (Davis & Read, 1958; Friedman, Ader, & Grota, 1973; Hamilton, 1974; Plaut, Ader, Friedman, & Ritterson, 1969), and autoimmune (Amkraut, Solomon, & Kraemer, 1971; Rogers, Trentham, McCune, Ginsberg, Rennke, Reich, & David, 1980; Rogers, Trentham, & Reich, 1981) diseases in experimental animals. The effects of these "stress" situations are not unitary. Not only is the direction of any effects a function of the nature of the particular environmental stimulation and pathogenic stimulus, but it depends upon several biological characteristics of the host (e.g., species, strain, gender, age) as well as the psychophysiological state of the individual upon which such stimulation is imposed. Friedman, Ader, and Glasgow (1965), for example, found that neither "stress" nor an inoculation of Coxsackie B virus, alone, was sufficient to induce infection in adult mice. However, the combination of stress and inoculum could elicit symptoms of disease.

A related area involves the susceptibility or response to neoplastic processes. It is not entirely clear to what extent which kinds of cancer have a viral etiology or involve immunosurveillance. Some neoplastic disease does appear to involve immune processes (e.g., Riley, Fitzmaurice, & Spackman, 1981). Amkraut and Solomon (1972), for example, used the Moloney sarcoma virus and found increases and/or decreases in the course of tumor growth depending upon the nature and timing of stress in relation to infection. A role for the immune system is suggested by the observation (Fefer, McCoy, Perk, & Glynn, 1968) that immunologically immature mice (younger than 2 weeks of age) die from Moloney sarcoma virus, whereas fully immunocompetent mice (animals over 4 weeks of age) reject the tumors and survive. There are, of course, differences between immature and mature mice beside their levels of immunocompetence.

Experientially, the manipulation of early life experiences, social factors, and noxious environmental stimulation or, conversely, the minimization of environmental disturbances can influence the development and/or course of spontaneously developing or experimentally induced neoplastic disease. Reviews of this literature have been prepared by Fox (1981), LaBarba (1970), and Riley et al. (1981). More recent studies (Sklar & Anisman, 1979; Visintainer, Volpicelli, & Seligman, 1982) have shown that the capacity to cope with stressful environmental circumstances can attenuate tumor growth and mortality. Considering the high level of sophistication that characterizes such research, there is likely to be a renewed interest in this field, particularly with respect to the immunologic mediation of the effects of psychosocial (e.g., "stress") factors in altering the predisposition to, the precipitation of, or the perpetuation of spontaneous or experimentally induced disease.

More relevant to my present focus is the influence of psychosocial factors in immunologic reactivity *per se.* I will, then, review this material briefly before proceeding to describe related developmental data. These data are quite preliminary, but they give some indication of the potential of a developmental approach for understanding the interrelations among behavioral, neuroendocrine, and immune processes.

Psychosocial Factors and Immunologic Reactivity

The available literature concerning psychosocial influences on immunologic reactivity is relatively sparse and has, for the most part, been published in just the last few years. On man, one of the more dramatic studies is that of Bartrop, Lazarus, Luckhurst, Kiloh, and Penny (1977), who conducted a semiprospective study of the impact of bereavement on "immune function." Blood samples were obtained approximately two and eight weeks after the death of a spouse from illness or injury. Controls were hospital personnel (matched for age, sex, and race) who had experienced no such loss within the previous two years. Lymphocyte responsivity to mitogenic stimulation with phytohemagglutinin (PHA) and Concanavalin A (Con A), stimulators of thymus-derived or T lymphocytes, was measured *in vitro.* Although mitogenic reactivity is not synonymous with immunologic reactivity, it does reflect the availability of normally functioning subpopulations of circulating lymphocytes for responses to antigenic stimulation, cell interaction, and antibody production. Lymphocytes from the bereaved group showed a significantly suppressed mitogenic reactivity, particularly on the second of the two tests. It is noteworthy that there were no changes in serum concentrations of thyroxin, cortisol, prolactin, or growth hormone corresponding to the change in immunologic responsivity in the bereaved spouses. Data currently being collected by Schleifer, Keller, McKegney, and Stein (1980) are confirming and extending the findings on the immunologic effects of bereavement. Another example of the effects of bereavement is provided by a study of women who had experienced abortions (Assael, Naor, Pecht, Trainin, & Samuel, 1981). These women were divided into those who were effectively coping with the loss of the fetus and those who had not (as yet) adjusted to the consequences of the abortion. Psychometric testing revealed a number of differences between these groups, primarily with respect to depression. Those who were not coping effectively, who could also be characterized as being depressed, showed significant suppression of mitogen-induced lymphocyte proliferation. Again, differences in responsivity could not be related to differences in adrenocortical hormone levels.

These studies provide dramatic illustrations of the impact of psychological factors on immune function. To be sure, bereavement may induce changes in eating and sleeping habits, caffeine or alcohol consumption, smoking, and the use of tranquilizers and other drugs. The contribution of such variables needs to be clarified since they have been implicated in modifying immunologic reactivity. While it is difficult to separate nutritional influences, for example, from the environmental and psychosocial circumstances with which they are frequently associated, changes in nutritional state (in either direction) influence immunocompetence (e.g., Chandra, 1981; Palmblad, 1981).

An increasing number of studies have been initiated to examine the effects of environmental stimulation ("stress") on immune processes. Most of these studies have been conducted on animals, but there has been no standardization with respect to experimental treatments or immunologic measures and, as a consequence, there has been little uniformity in the results.

Gisler, Bussard, Mazie, and Hess (1971) reported a suppression of *in vitro* immunologic reactivity in mice exposed to either acceleration or ether anesthesia, depending upon

the strain of mouse that was used. These *in vitro* effects could be reproduced by treatment with ACTH (Gisler & Schenkel-Hulliger, 1971). In another study (Pavlidas & Chirigos, 1980), nonspecific immunopotentiators such as interferon or bacterial lipopolysaccharide (LPS) were used to activate resting peritoneal macrophages, rendering them tumoricidal for MBL-2 lymphoblastic leukemia cells. In the absence of "stress," interferon, for example, results in an inhibition of tumor growth. Subjecting mice to physical restraint, however, resulted in an impairment of tumoricidal activity when peritoneal macrophages were activated *in vitro* with interferon or bacterial LPS. Corticosteroids were implicated in this effect by the finding that the addition of hydrocortisone or prednisone attenuated and dexamethasone almost completely blocked the inhibition of tumor cell growth resulting from interferon alone. The extent to which the endogenous release of corticosteroids is involved in the effects of "stress" on macrophage function remains to be determined. With respect to the effects of stimuli such as acceleration or ether, Solomon and Amkraut (1981) reported that neither they nor Gisler were able to suppress the *in vivo* immune response by hormone administration.

Studies on *in vivo* cellular responses have yielded seemingly disparate results. Guinea pigs subjected to a topically applied chemical irritant show increased reactivity as a consequence of electric shock stimulation (Guy, 1952; Mettrop & Visser, 1969). In mice, "crowding" or "auditory stress" has been reported to reduce inflammatory responses (Christian & Williamson, 1958; Funk & Jensen, 1967; Smith, Molomot, & Gottfried, 1960). Decreases in delayed hypersensitivity reactions in response to high temperature (Pitkin, 1966) prolonged survival of skin allografts in mice subjected to avoidance conditioning (Wistar & Hildermann, 1960), and a suppressed graft-versus-host response to a limited feeding schedule (Amkraut, Solomon, Kasper, & Purdue, 1973) has also been reported. Additional experiments by Amkraut et al. (1973) using adrenalectomized or ACTH-treated recipients provided no evidence that the effects of a restricted feeding regimen could be attributed to altered adrenocortical steriod levels. In an especially interesting series of experiments, Blecha, Barry, and Kelley (1982) found that two cell-mediated responses (delayed-type hypersensitivity to sheep erythrocytes and contact sensitivity to 2,4-dinitro-1-fluorobenzene) were differentially affected by immobilization, heat, and cold, and the temporal relationship between the stressful and immunogenic stimulation. Immobilization-induced suppression of delayed-type hypersensitivity was blocked by adrenalectomy or metyrapone, but the enhanced contact sensitivity following immobilization could not be attributed to corticosteroids (Blecha, Kelley, & Satterlee, 1982).

Mice subjected to daily avoidance conditioning sessions are less susceptible to anaphylactic shock (an immediate hypersensitivity response) than unstimulated controls. The "stress"-induced resistance to anaphylaxis does not occur in adrenalectomized animals but can be restored by hydrocortisone treatment (Rasmussen, Spencer, & Marsh, 1959; Treadwell & Rasmussen, 1961), suggesting adrenal involvement in the mediation of this effect. As the authors acknowledge, however, such a conclusion would be premature; steroid levels were not measured; corticosterone, not hydrocortisone, is the endogenous corticosteroid secreted by mice; and adrenal medullary influences were not examined. Since "crowded" animals were reported to show elevated corticosteroid levels, Treadwell and Rasmussen (1961) tested for anaphylactic responses in group- and individually housed mice. Contrary to expectations, they observed that, under the smaller of two challenge doses of antigen, group-housed mice were the more susceptible. They did not, however, question the hypothesis of an adrenocortical mediation of "stress"-induced changes in susceptibility to anaphylaxis. They inferred, instead, that the results were due to the "incidental stress of isolation."

Several studies document the effects of a variety of experiential manipulations on antibody responses. Monkeys exposed to a sequence of noxious stimuli show a reduced antibody response to different immunogenic stimuli (Felsenfeld, Hill, & Greer, 1966; Hill, Greer, & Felsenfeld, 1967). In mice, Glenn and Becker (1969) found that group housing resulted in higher antibody levels than individual housing when animals were given a booster injection of antigen. In rats, Solomon (1969) observed a reduced primary and secondary response to a bacterial antigen. Edwards and Dean (1977) found a decreased antibody response among mice housed in high- as compared to low-density groupings, and Vessey (1964) observed less precipitating antibody in mice that were moved from individual to group cages relative to those that remained individually housed. Edwards, Rahe, Stephens, and Henry (1980) have confirmed that *changes* in the psychosocial environment can suppress antibody formation; mice moved from individual to group housing had lower antibody titers than mice that remained individually housed, and mice moved a second time (from a group back to an individual cage) displayed a further depression of humoral immunity. Changing housing conditions, incidentally, also differentially influences adrenocortical reactivity (Plaut & Grota, 1971). Other recent data indicate that the effects of "stress" in altering immunologic reactivity are a function of the chronicity (Monjan & Collector, 1976) as well as the intensity (Keller, Weiss, Schleifer, Miller, & Stein, 1981) of stimulation.

The above studies represent only a sampling of the available literature. Several more complete reviews are available (Ader, 1980; Monjan, 1981; Plaut & Friedman, 1981; Solomon & Amkraut, 1981). Despite the disparity in the results, some conclusions can be derived from these studies. First of all, *some* environmental circumstances that can, for the sake of simple communication, be referred to as "stressful" are capable of influencing humoral and cell-mediated immunologic reactivity. In general, the effects of "stress" are immunosuppressive. The relative contribution of different "stress-induced" neuroendocrine changes in the modulation of immunologic reactivity, however, remains to be analyzed. Despite the richness and modern-day appreciation of the network of neuroendocrine interactions, there is a common tendency to relate all "stress" effects to adrenal responses and to attribute any immunosuppression due to environmental stimulation to elevations in adrenocortical steroids. Complete reviews of this literature (e.g., Comsa, Leonhardt, & Wekerle, 1982), however, reveal that endogenous levels or physiological doses of corticosteroids can be immunoenhancing as well as immunosuppressive. The effects depend upon such obvious variables as level of corticosteroid, amount of antigen, and the temporal relationship between steroid and antigen—in addition to host factors such as species, strain, sex, age, circadian rhythms, etc. Whatever the mechanisms may be, the data that are available thus far with respect to behavioral influences on immune function suggest that parametric research will be necessary to examine effects that relate to (a) the quality and quantity (and the individual's "perception" or "interpretation") of naturally occurring or experimentally imposed environmental circumstances; (b) the quality and quantity of the immunogenic stimulation to which the organism is exposed; (c) the temporal relationship between experiential and immunologic events; (d) the selection of outcome variables and measurement parameters, and the choice of sampling times; (e) the myriad host factors upon which the environmental and immunogenic stimuli are superimposed; and (f) the interaction among the above factors.

Except for the analysis of dose-response relationships and the central importance of aging within immunology, it would not be unfair to point out that immunologic research does not attend to the above factors to any great extent. It appears, though, that immunocompetence is sensitive to adaptive processes that are regulated by the brain.

Thus, there is reason to study the psychobiologic processes that influence the immune system in much the same way as psychobiological contributions to other homeostatic processes have been elaborated. Not only is there a rationale for a developmental orientation, but there are data that address the potential of this particular line of inquiry.

Developmental Factors and Immunologic Reactivity

Several years ago, there was a rash of experimental studies involving psychological factors and cancer, some of which were devoted to the effects of early life experiences. There were also a few studies on early experience and virus infection (Friedman et al., 1969) and autoimmune disease (Amkraut et al., 1971). I suspect, however, that even those of us who were engaged in such studies did not appreciate at the time the implications that they might have for CNS-immune system interactions. Solomon, Levine, and Kraft (1968) had even reported a study in which rats handled throughout the preweaning period were subsequently immunized with a bacterial antigen. Both the primary and secondary antibody responses were greater in handled animals than in unmanipulated controls.

The situation is different today. The evidence for CNS-immune system interactions enumerated at the outset provides a basis for expecting relationships among the brain, behavior, and the immune system. In particular, there is reason to suppose (and data to suggest) that neural and neuroendocrine development may be important determinants of adult immunocompetence.

Pierpaoli (1981) has written extensively about the hormonal regulation of immunity and the parallel development of endocrine and immune function, emphasizing the reciprocal effects of variations in one or the other system. He presents evidence, for example, that the thymocytes of newborn animals need exposure to hormones to acquire their full immune capacity. By careful selection of the parameters of stimulation, the sequential inoculation of mice with different allogeneic cells during the neonatal and perinatal period can prolong the stage of immunologic immaturity during which infants normally display tolerance (Pierpaoli, Kopp, Muller, & Keller, 1977). These developmental changes were accompanied by alterations in some measures of endocrine function, suggesting that the generation of tolerance and immunity (the recognition of what is "self" and "nonself") is part of the genetic programming of neuroendocrine and immune functions by the brain. Except for the thymus, there is actually a paucity of data with respect to the immunologic effects of early disruptions of endocrine function. What data are available support the notion of an intimate connection between these systems.

The pituitary defect of dwarf (Snell-Bagg) mice, for example, results in a hereditary deficiency of somatotropic hormone and thyroxine. These animals are also immunologically crippled. Treatment with somatotropic hormone and thyroxine, however, restores humoral and cell-mediated immunity. Immunologic blockage of hypothalamic-pituitary function (i.e., with antipituitary serum) also induces a wasting disease, but only when introduced during the first weeks of life; there is no impairment of cellular immunity when antipituitary serum is given to adult animals (Pierpaoli, Fabris, & Sorkin, 1970). It is of additional interest that the prolonged nursing of dwarf mice by foster mothers attenuates the deleterious effects of pituitary deficiencies on lymphoid tissue and partially restores the animals' response to antigenic stimulation. To what extent this is due to an hypothesized maternal milk factor that promotes immune competence, nutritional factors, or a maternally mediated hormonal modification (Pierpaoli et al., 1970, 1977) requires examination. In any case, it illustrates the dependence of immunologic development on extraimmune influences.

Mother–Young Interactions

Developmental psychobiology has devoted considerable attention to the critical nature of mother-young relationships for the development and maintenance of homeostasis at several biopsychosocial levels of organization. What we have overlooked in our analysis of adaptive processes is that immunocompetence is a crucial element for survival of the organism and that the development of immunocompetence is, in part, accomplished through the transfer of cells and antibodies from mother to young (Stini, 1981). In addition to warmth, nurturance, etc., the intimate contact of mother and young during suckling, for example, simultaneously exposes mother and young to pathogens. The licking of young also assures that pathogens present on the neonate enter the mother's respiratory and gastronintestinal tracts. The lymphatic circulation of the gastrointestinal tract (in humans, at least) also supplies the mammaries. Immunologic changes elicited by antigens derived from the infant are present in breast milk and immunity is thereby transmitted to the infant. Therefore, in seeking the stimuli responsible for the increase in maternal behavior that rats display to experimentally manipulated pups, one might ask if such behavior serves to protect the pup from the environmental pathogens to which it may be exposed when away from the nest. More speculatively, perhaps, one might even ask if the recognition (i.e., acceptance and/or rejection or cannabilism) of young is mediated by the major histocompatibility complex which has already been implicated in mate selection (Andrews & Boyse, 1978; Yamaguchi, Yamazaki, & Boyse, 1978; Yamazaki, Yamaguchi, Andrews, Peake, & Boyse, 1978).

The potential for hazard also exists in mother-young relationships. In neither the rat nor the human is the blood-brain barrier fully developed at birth, and maternal specific antibodies can be detected in the cerebrospinal fluid (CSF) of infants (Thorley, Holmes, Kaplan, McCracken, & Sanford, 1975). When labelled IgG antibodies against brain antigens are injected into adult and infant rats, transfer into the CSF is observed only in infants (Adinolfi & Dodd, 1981). These authors have speculated that abnormal maternal states involving endocrine and immune perturbations (e.g., the presence of antibrain antibodies) might cause changes in the brain during fetal or early life that ultimately result in specific neurologically based behavioral disorders. It may well be, as suggested elsewhere (Ader, 1981), that the study of CNS-immune system interactions may teach us as much about the normal and abnormal function of the brain as about the regulation and disregulation of the immune system.

Few data have been collected thus far on changes in immunocompetence as a function of alterations in mother-young interactions. The importance and potential of such studies, however, has been recognized. It was recently reported (Reite, Harbeck, & Hoffman, 1981) that peer separation in pigtailed monkeys results in an impairment of cellular immunity. As with the studies of bereavement in humans, concomitant endocrine measures yielded no immediately evident correlations. In a second experiment (Laudenslager, Reite, & Harbeck, 1982), the effects of mother-young separation were studied in bonnet monkeys. In two mother-infant pairs, mothers were removed to another room for two weeks and then returned. Relative to a two-week baseline, the period of separation was characterized by a depressed lymphocyte response to mitogenic stimulation in both infants. One of the two mothers also showed a depression of cellular immunity during separation. Both infants and mothers recovered normal immune responses following reunion. This study, too, failed to uncover evidence that the change in immunologic reactivity might be due to an elevation in adrenocortical steroids in response to the separation experience.

In another recent study (Michaut, Dechambre, Doumerc, Lesourd, Devillechabrolle, & Moulais, 1981), maternal deprivation in mice was accomplished by a combination of

factors. Lactating females were absent from their litters 4 hr each day during the first week and 8 hr each day during the second postpartum week, and weaning was imposed at 15 days postpartum. Controls remained unmanipulated with the lactating female until 21 days of age. Between 7 and 8 weeks of age, all mice were immunized with sheep erythrocytes. There were no differences in body weight or adrenal weight, but maternally deprived animals showed a depressed antibody response to the antigenic stimulation.

Early Infectious Disease

Not only may experiential events influence susceptibility or responses to infectious disease as noted above, but infectious disease may influence behavior. Furthermore, the effects of viral infection on behavior may be a function of the age at which the infection is experienced and may be modified by mother-young interactions. In a study by Hotchin, Benson, and Gardner (1970), mice were inoculated with lymphocytic choriomeningitis (LCM) virus when they were two days old. When the pups were nine days old, a mother not previously exposed to LCM virus was substituted for the litter's natural mother. This intervention resulted in a 20% decrease in mortality. The introduction of two "normal" mothers resulted in a 32% reduction in mortality. Conversely, if a mother from LCM-infected mice was substituted for the natural mother of uninfected animals, there was a 15% increase in mortality. Daily rotation of lactating females (within groups) increased the mortality of infected mice but had no effect on control litters. Clearly, the health of the mother influenced survival of the pups. It is not clear, however, by what means this influence was exerted. The mothers of infected mice did receive contact infection that could cause mild illness and these mothers did develop symptoms of disease six days after inoculation of their litters. There is the possibility, then, that survival was influenced by illness-induced behavioral changes in the mother rather than or in addition to any qualitative or quantitative changes in milk secretion. Furthermore, these changes and the daily rotation of mothers which the authors describe as "mildly stressful" had little effect on normal mice, but acted synergistically to potentiate the lethal effects of the viral infection. This interpretation is consistent with the interaction between "stress" and viral infection reported by Friedman et al. (1965).

In a more recent study, McFarland, Sikora, and Hotchin (1981) inoculated weanling mice and eight-week-old mice with herpes simplex type 1 virus. Open-field testing two weeks later revealed hypoactivity in mice inoculated at weaning and hyperactivity in mice inoculated at eight weeks of age. The fact that housing conditions were changed following infection may have differentially affected the four- and eight-week old mice, but these results (together with clinical observations cited by the authors) reinforce the notion that the effects of infectious disease on behavior (like the effects of behavior on infectious disease) are influenced by an interaction between the host (in this case, stage of development) and the infectious agent.

Prenatal Influences

Over the past several years, the public has been made painfully aware of the deleterious effects of some environmental pollutants. The combined efforts of behavioral toxicology and behavioral teratology have provided abundant evidence that the effects of chemical contamination of the environment may be detected in behavioral changes before physical symptoms become evident. There are considerable data to indicate that the immature organism is particularly sensitive to such adverse environmental circumstances. Even so, prenatal exposure to environmental toxins may result in no detectable defects at

birth and still result in behavioral impairments later in life as behavioral processes of adaptation emerge. Presumably, the developing brain is especially vulnerable to chemical insult and alterations in brain development are sensitively indexed by alterations in behavior. More recent data indicate that neuroanatomic or neurochemical alterations in the developing brain are also reflected in the compromised function of immunologic defense mechanisms.

Koller (1979) has provided an exhaustive review of the impairment of immune function resulting from a variety of environmental contaminants (heavy metals, industrial chemicals, and pesticides). Like the alterations in behavior, immune function is modified by levels of contamination that do not produce clinical signs of toxicity; and, like the alterations in behavior, there is evidence to suggest that the effects on immunologic reactivity are greater in infant than in mature animals.

Illustrating a longitudinal research strategy in examining the psychobiologic effects of prenatal exposure to methyl mercury, Spyker (1975) described the behavioral changes that eventually occurred in exposed mice who were "normal" at birth. She also noted an increased incidence of bacterial infection with advancing age in the mice exposed to methyl mercury *in utero*. Specific antigenic challenges were used to assess immunocompetence in another sample of differentially treated animals and revealed an impairment of immune function in the elderly group of prenatally exposed mice.

Another example is provided by the immunomodulating effects of alcohol. Several research programs have been concerned with the growth, developmental, and behavioral effects of prenatal exposure to alcohol (e.g., Abel, 1980; Randall & Riley, 1981). Given the clinical evidence indicating that alcohol intoxication is, among other things, toxic to the immune system, Monjan and Mandell (1980) studied the effects of *in utero* exposure to alcohol on immunologic reactivity of rat offspring. Females were intubated daily with different doses of ethyl alcohol or sucrose beginning two weeks before mating and continuing until parturition. Mitogenic stimulation of splenic lymphocytes from experimental and control offspring occurred at 7, 11, and 18 months of age. There were no differences in B-cell function, but T-cell function as measured by the response to Con A was significantly depressed in the offspring of mothers that received the high dose of alcohol. This suppression was evident at 7 and 11 months of age but not at 18 months. Prenatal exposure to alcohol causes some transient and some relatively long-lasting changes in the steady-state levels, metabolism, or release of several neurotransmitters (Druse, 1981). These, in turn, have been implicated in the modulation of immune function (e.g., Hall & Goldstein, 1981). Whether the patterning of these neurotransmitter changes or direct effects on the thymus could account for the immunosuppressive effects of *in utero* alcohol exposure remains to be examined. It is clear, though, that the teratogenic effects of alcohol intoxication extend to the immune system. The fact that a variety of other psychoactive drugs is capable of influencing immune function in adult organisms (e.g., Ferguson, Schmidtke, & Simmons, 1978; Saunders & Muchmore, 1964) suggests that it would be profitable to determine if the abuse of such agents is also teratogenic for the immune system.

In summarizing the effects of prenatal exposure to methyl mercury, intended, I presume, to be generalized to other kinds of environmental stimulation, Spyker (1975) speculates that the "apparent dysfunction of the immune system may also be an example of how impairment of a system other than the nervous system can affect behavior. On the other hand, decreased immunological competence may be altering nervous system function and thus indirectly affecting behavior" (p. 1843). One must add to this the hypothesis that the effects of alterations in the prenatal environment on immune function are

the result of neuroanatomical and/or neurochemical changes induced by environmental contaminants, pharmacologic agents, and experiential events.

Sexual Development and Hormonal Changes

Sex differences in masculine and feminine *behaviors* appear to be dependent upon differences in neural organization laid down during early development (Gorski, 1979). If the brain is exposed to androgens during the neonatal period, masculine sexual behavior develops and is expressed by genotypic females. At the same time, the ability of the hypothalamus to regulate cyclic gonadotrophin secretion by the pituitary is altered in females treated neonatally with androgens. Ovarian hormones, however, do not play a comparable role in the development of the brain. Sexual dimorphism has also been morphologically confirmed with respect to still another behavior, singing in birds (Arnold, 1981). Only male canaries and zebra finches sing, and there is a specific neural region that controls this behavior. This area accumulates androgen and is larger in males than in females. Neonatal implants of androgen can permanently masculinize the neural morphology of females and enable them to reproduce some song.

Sex differences can also define or be defined by immunologic differences. Females reject skin allografts more rapidly than males, for example, and castration accelerates allograft rejection in males but is less effective in modifying the immune response in females (Castro & Hamilton, 1972; Graff, Lappe, & Snell, 1969). In many aspects of immune function in humans as well as lower animals, females tend to be more reactive and, with age, are more liable to autoimmune diseases (Dubois, 1974). Is this sex difference also related to differences in neural organization? Does the neonatal administration of androgen permanently masculinize the immunologic reactivity of females? Is there a specific region of the brain that controls the dimorphism in immunologic reactivity? Where in the brain might steroids exert such an effect on immune function?

There are some hints that pursuing this line of research would also be fruitful. I have already mentioned the intricate connections that exist between neuroendocrine and immunologic development. Sex differences in the development of immunologic reactivity (see Krzych, Thurman, Goldstein, Bressier, & Strausser, 1979) support this possibility. In a study by Pierpaoli, Haran-Ghera, and Kopp (1977), susceptibility to neoplastic disease was examined as a function of hormonal status. Female SJL/J mice show a high incidence of spontaneous neoplasma and a high susceptibility to lymphosarcomas in response to oral dimethylbenzanthracene (DMBA). In one experiment, masculinization of SJL/3 mice was accomplished by treating females with a single injection of 1 mg of testosterone at either two or three days of age. Animals were given DMBA at 60 days of age. The "early" testosterone treatment reduced the incidence of lymphosarcomas from 82% to 23% and prolonged the latency to develop tumors. That this altered hormonal state was, in fact, an "early" experience effect remains to be determined. Provocative results were also obtained by Tartakovsky and Klimenko (1981). In this study, rats were injected with testosterone on Day 2 and Day 16 of life in an effort to examine the long-term effects of thymus hypofunction. Sixty days later, half the testosterone-treated group and untreated controls were immunized with SRBC. Testosterone treatment reduced complement level and the phagocytic activity of leukocytes (nonspecific defense mechanisms) and, in response to antigenic stimulation, decreased humoral and cell-mediated reactivity. Unfortunately, the gender of the animals used was not specified, and again it remains to be determined if these long-term effects of testosterone are specific to "early" hormonal intervention.

Dieter and Breitenbach (1970) manipulated the hormonal status of immature (three-week-old) white Leghorn cockerels. (The cockerel adrenal gland displays a high corticosterone response to ACTH and "stress" at 4 weeks of age, which is also about the time of lymphoid organ growth and development.) Animals were injected daily with different doses of testosterone proprionate or corticosterone for two weeks. At the end of this period, a dose-related involution of lymphoid organs (bursa of Farbricius, thymus, and spleen) was observed in response to both corticosterone and testosterone, the latter being greater in magnitude. Two weeks later, the weights of the lymphoid organs of cockerels treated with corticosterone were not different from those in control animals, whereas the effects of testosterone were still evident. Histological examination indicated that the effects of testosterone were permanent, particularly with respect to the bursa of Fabricius.

Additional data relating sex hormones and immune function concern the development of autoimmune disease in New Zealand hybrid mice. The female, in particular, develops a lethal glomerulonephritis between 8 and 14 months of age. Several studies (e.g., Roubinian, Talal, Greenspan, Goodman, & Siiteri, 1978; Steinberg, Melez, Raveche, Reeves, Boegel, Smathers, Taurog, Weinlein, & Duvic, 1979) have shown that the immunologic defect that results in manifest disease is sensitive to alterations in sex hormones. In general, castration and/or testosterone treatment of females prolongs survival and castration and/or estradiol treatment of males accelerates mortality relative to sham-treated controls. Of particular interest are the reports (Steinberg et al., 1979) that age is a critical factor in determining the effects of hormonal interventions. Castration of males, for example, results in a marked acceleration of autoimmune disease only if it is performed at two to three weeks of age. Castration at 5 weeks has only a minor effect, and it has no effect when introduced at 14–15 weeks of age. It would appear that the production of hormone early in life—or the effects of the patterning of sex hormones on other endocrine or lymphoid tissue at this stage in the development of the immune system—is critical to the maintenance of immunocompetence.

I mentioned at the outset that part of the evidence for interaction between the endocrine and immune systems comes from the fact that, in addition to the effects of hormones on immune processes, immune responses elicit endocrine changes. Such findings have their counterparts in certain observations of development. In birds, the bursa of Fabricius is a primary lymphoid organ involved in the development of humoral immunity. It is the origin of B cells and is active during embryonic life and in young chickens. The integrity of the bursa of Fabricius may also be required for endocrine development in the chicken (Pedernera, Romano, Besedovsky, & Aguilar, 1980). Looking for a bidirectional link between endocrine and immune function, Pedernera et al. (1980) bursectomized chick embryos after 68 hr of incubation. In addition to sham-operated controls, another group of bursectomized chicks received a graft of bursal tissue at 9.5 days of incubation. Measurements made at 17.5 days of development and at hatching showed that bursectomy diminished the *in vitro* production of corticosterone by the adrenal glands and increased the *in vitro* production of testosterone by the testes. Bursal grafting prevented these endocrine alterations. There is, then, support for the hypothesis that the bursa produces factors that could influence endocrine function during development of the chick embryo. When the bursa of Fabricius is isolated from environmental stimuli by ligation of the bursal duct *in vivo,* there is a marked retardation of bursal development and maturation of immunologic reactivity (Ekino, Nasa, Tanaka, Matsuno, Fujii, & Kotani, 1980). Immunologic competence increases with age in these chickens, although it remains lower than in controls. Considering the observations of Pedernera et al. (1980), it might be hypothesized that these effects and/or the restoration of immunocompetence might depend, in part, on neuroendocrine influences.

General Comments

I hardly need emphasize the extent to which hormones influence behavior, or the extent to which behavior and early life experiences influence hormonal state. Also, it is far beyond the scope of this paper to present all the evidence on the role of hormones in the modulation of immune responses; several recent reviews are available (for example, Ahlqvist, 1981; Comsa et al., 1982). During the past several years, attention has been focused on the role of hormones in the development of immunocompetence (see Pierpaoli et al., 1970). As Comsa et al. (1982) point out, the vast majority of this research has concentrated on the thymus. Indeed, because of its critical function in the ontogeny of immune competence, the endocrine functions of the thymus and its prominent role in the development of neuroendocrine function has probably not received the attention it deserves. Conversely, hormones other than those of the thymus have not received sufficient attention as modulators of immune responses.

Lymphocytes bear receptors for "neurotransmitter" substances as well as for hormones, and the study of the influence of neurotransmitters on immune function (e.g., Hall & Goldstein, 1981) is a rapidly growing field of research. Modulators of neurotransmitter level also influence behavior, particularly, perhaps, when effects are exerted early in the course of CNS development (see Cuomo, Cagiano, Cohen, Mocchetti, Cattabeni, & Racagni, 1981; Shaywitz, Yager, & Klopper, 1976). It will be interesting and important to learn if there are parallel effects on the development and maintenance of immunocompetence. It is likely that some of the effects of behavior in modifying immunologic reactivity are mediated by endocrine and neurotransmitter changes. In turn, it has been hypothesized that these exert influences on the immune system via their action on cyclic nucleotides (e.g., Bourne, Lichtenstein, Melmon, Henney, Weinstein, & Shearer, 1974). Ontogenetic changes in the secretion of behaviorally active neuropeptides could also alter immunologic reactivity through their effects on thymic hormone secretions (MacLean & Reichlin, 1981) or on cyclic nucleotides resulting from changes in neurotransmitter metabolism (Iuvone, Morasco, Delany, & Dunn, 1978; Lichtensteiger & Monnet, 1979; Versteeg & Wurtman, 1975; Weigant, Dunn, Schotman, & Gispen, 1979).

Based on the limited data that are currently available, it would be premature to specify the multiple neuroendocrine pathways through which behavioral processes influence immune processes—and vice versa. There are data, however, to show that behavioral processes, including conditioning (Ader & Cohen, 1981), can influence immune responses; an impressive literature showing that neuroendocrine changes influence immune function; and emerging data on the innervation of lymphoid tissue and the possibility that certain developmental experiences might influence such connections. What is missing at this junction is research to establish the links among these several psychobiological processes.

In its published description of Research Programs, the Developmental Immunology Program of the Genetics and Teratology Section of the National Institute of Child Health and Human Development has expressed particular interest in developmental immunology because (a) abnormal immunologic development leads to immunodeficiency diseases; (b) deficits in bodily defenses result in intrauterine and postnatal infections which are known teratogens; and (c) immunologic interactions between mother and fetus are possible causes of intrauterine growth retardation, abortion, premature births, and congenital malformations. Given the extensive behavioral literature on the effects of prenatal maternal stress, early postnatal experiences, and pre- and postnatal endocrine interventions, I would expand upon these issues and point out that (a) environmental stimulation during early (postnatal) life is capable of altering immune development and may thereby influence the likelihood of developing immunodeficiency diseases; (b) "stressful" stimulation

experienced by pregnant females can influence bodily defenses including immunocompetence and increase susceptibility to intrauterine and postnatal infections that are, in turn, potentially teratogenic; and (c) prenatal maternal "stress," plus a variety of other postnatal environmental circumstances, are capable of influencing behavioral interactions between mother and young and, thus, the immunologic interactions between mother and young, thereby influencing a variety of psychobiologic processes. To these, I would add that early infectious disease has behavioral consequences that differ from those that follow infectious disease in the older individual.

The areas of concern in developmental immunology were promulgated without consideration of the possible role of behavioral influences. They are issues that derive from a practical concern with development, aging, and health and disease within the conceptual framework of an autonomous, self-regulating immune system. Psychobiologists, too, are concerned with development, aging, and health and disease. However, we operate from the conceptual base of an integrated psychobiologic system, a system in which behavioral and physiological processes act in concert to maintain homeostasis. There is now abundant evidence that the immune system, like all other physiological systems operating in the interest of homeostasis, is integrated with all other physiological processes and therefore subject to regulation or modulation by the brain. It is true that the immune system is capable of considerable autoregulation. Many immune responses can be made to take place in a test tube. The phenomena of real concern, however, are those that take place within living organisms—within a neuroendocrine milieu that is demonstrably sensitive to experiential events. It should not be surprising, then, to find that behavioral factors—particularly those that occur during early development—are capable of influencing immune processes, or even that immune processes may be capable of altering behavior. Study of the ontogeny and phylogeny of the immune system should be broadened to include the role of behavior in these processes. Indeed, it would appear to be critical to do so. Psychoneuroimmunology is a new field of interdisciplinary research, and developmental psychobiology is in a unique position to make substantial contributions to an understanding of the complex developmental processes that influence immunoregulation.

Notes

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