Influence of Brain and Behavior on the Immune System

The effect of hypothalamic lesions on immune processes is described.

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Although clinicians now have an increased understanding of the immunological basis of a variety of illnesses, little attention has been paid to the psychophysiological aspects of immune processes. The immune system, similar to the nervous and endocrine systems, plays an important role in biological adaptation contributing to the maintenance of homeostasis and to the establishment of body integrity. The similarity between the function of the immune and central nervous systems maintaining the integrity of the organism in relation to the external environment has been pointed out by Salk (*1*).

In this article we consider chiefly the influence of brain and behavior on the immune system, with primary emphasis on the effect of the central nervous system—and, specifically, the hypothalamus—on the humoral immune response.

Psychosocial Factors and Infection

It has been noted clinically that psychosocial factors modify host resistance to infection (*2*). In addition to clinical observations, there is a growing body of experimental data supporting the hypothesis that psychosocial factors play a role in infectious diseases. Rasmussen and collaborators (*3*–*7*) in an extensive series of studies have primarily employed avoidance learning procedures as the experimental model for investigating the effects of psychological stress. This procedure requires mice to jump a barrier once every 5 minutes at the presentation of a signal to avoid an electric shock delivered to their paws, a response the animals quickly learn to perform. Daily exposure for 6-hour periods to these conditions resulted in an increased susceptibility to herpes simplex virus (*3*), poliomyelitis virus (*4*), coxsackie B virus (*5*), and polyoma virus infection (*6*). Physical restraint also increased the susceptibility of mice to herpes simplex virus (*3*), and high-intensity sound stress resulted in a transient diphasic susceptibility pattern in mice inoculated intranasally with vesicular stomatitis virus (*7*).

Social factors, such as the effect of differential housing, have been studied. Mice housed alone are significantly less susceptible, as compared with animals housed in groups, to parasites such as *Plasmodium berghei* (*8*), *Trichinella spiralis* (*9*), and *Microphallus pygmaeus* (*10*). The type of pathogenic agent may determine the nature of the immune response since mice housed alone are more susceptible to a virus such as the one responsible for encephalomyocarditis (*8*). Intense fighting among male mice also results in decreased resistance to the parasite *Hymenolepis nana* during the immune induction phase (*11*). When mice are stressed by exposure to a predator there is a depression in the acquired immunity to *H. nana*. This immunosuppressive effect correlated with significantly higher concentrations of corticosterone in the plasma (*12*).

Psychosocial Factors and Neoplasia

Internal and external host factors appear to play a role in the development, course, and outcome of neoplastic disorders. Among these factors psychosocial influences have been shown both experimentally and clinically to be determinants in neoplasia (*13, 14*). There is considerable experimental evidence that early experiential factors not only have a profound influence on behavior and on the endocrine and immunological responsivity of small mammals, but that they also influence the development and course of experimentally induced cancer. Furthermore, the findings show that the outcome of the relation between the host and the neoplastic process depends on the species and the nature of the experimental intervention. Brief daily handling and mild electric shock administered early in life, for instance, differentially modify the rate of tumor development and the survival of rats injected with Walker 256 sarcoma (*15*). Infantile stimulation also shortens the survival time of mice after transplantation of lymphoid leukemia (*16*), but does not modify the mortality rate of murine leukemia virus (*17*). Similarly, differential housing and sex-segregated groupings modify the incidence of mammary carcinomas in mice (*18*), decrease the survival time to injections of subcellular material (*19*), but do not influence the development of Walker sarcoma tumors (*17*).

Psychosocial Factors and Immune Processes

Some of the psychosocial situations that modify the susceptibility to infection and the development of neoplasia also influence immune processes. Avoidance learning, for example, decreased the susceptibility of mice to passive anaphylaxis (*20*). Overcrowding, but not the stress of electric shock, initiated prior to immunization of rats with flagellin, a bacterial antigen, reduced both the primary and secondary antibody response (*21*). Vessey (*22*) found that grouped mice have significantly lower titers of circulating antibodies than isolated mice and, by identifying social rank, he demonstrated that dominant mice had higher titers than the other mice in their groups. In contrast, it has been reported that individually housed mice had significantly lower precipitin titers in response to bovine serum albumin than animals housed in groups (*23*). In primates, exposure to a complex pattern of visual, auditory, and somesthetic stimulation was observed to increase the plasma cortisol concentrations and to decrease the magnitude of the circulating antibody response to immunization with bovine serum albumin (*24*). The effects of psychological mechanisms on antibody titers have also been reported (*25*). Petrovskii (*26*), for example, studied changes in agglutinin titers associated with behavioral disturbances induced in immunized dogs and baboons by stressful stimuli or by conflict conditioning techniques. He observed a parallelism between the intensity and duration of the behavioral disturbances and the fall in circulating antibody titers. Several studies (*27*)

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have demonstrated that stress modifies the delayed hypersensitivity response elicited in mice and guinea pigs to 1-chloro-2,4-dinitrobenzene. Wistar and Hildemann have shown that an avoidance learning stress results in a prolonged survival time of skin homotransplants in mice (*28*). Under certain conditions psychological stimulation can enhance the immune response. Brief handling of rats, for example, during the preweaning period increased both the primary and secondary antibody response to flagellin immunization (*29*). The exposure of rats to electric shock results in a significant increase in blood histamine, which is one of the pharmacological mediators of immediate hypersensitivity. Handled infant rats and rats living in groups after weaning had significantly higher blood histamine levels in response to electric shock (*30*).

The physiologic mechanisms that mediate the psychosocial influences on host resistance are complex and need further clarification. Perhaps the demonstrated effect of psychosocial stress on the modified susceptibility to some infections and some neoplastic processes may be due to the modification of humoral and cell-mediated immune responses.

There is evidence that the hormonal and reticuloendothelial systems are involved in the mediation of psychological influences. Avoidance learning or confinement is accompanied by adrenal hypertrophy, lymphocytopenia, and a slowly developing involution of the thymus and spleen occurring in temporal relation with the increase in susceptibility to viral infection (*31*). Immune reactivity is decreased in in vitro cultures of spleen cells derived from donor mice exposed to stress prior to explantation of the spleen (*32*). The degree of immunosuppression was correlated with an increase in plasma corticosterone following the stress in the mice (*33*). The pituitary-adrenocortical system, which is known to be altered by psychosocial stimulation, has been the focus of considerable attention because of evidence primarily derived from pharmacological studies that adrenal steroids may modify susceptibility to infectious disease, alter immune reactions, or depress inflammatory responses (*34*). In addition, both psychological stress and adrenocortical steroids have been reported by some investigators (*35*), although not by others (*36*), to suppress interferon production.

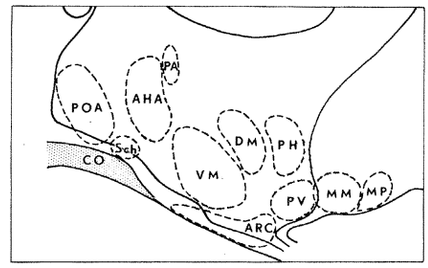

Fig. 1. Sagittal diagram of guinea pig hypothalamus. Lightly shaded areas correspond to regions damaged by lesions.

Whether changes in endogenous adrenal hormones occurring in response to environmental stimulation are responsible for some of the effects on host resistance and immune processes requires further analysis in the context of the different experimental models investigated. On the basis of studies with stressed, adrenalectomized animals, it appears that adrenal steroids are responsible for the increased resistance to passive anaphylaxis (*37*), while the retarded rate of disappearance of vesicular stomatitis virus from the site of inoculation and the increased susceptibility to this viral agent seems independent of adrenal activity (*38*). These findings demonstrate the complexity of the field. Little information is available on the role played by other hormonal systems and physiological processes in the mediation of psychologic and environmental stimulation.

Central Nervous System and Immune Processes

The neurophysiological mechanisms which may mediate the psychosocial influences on immunological reactions have been experimentally studied. At the turn of the century the central nervous system (CNS) was considered to be involved in the development of immune phenomena. The brain was thought to be the organ initiating the anaphylactic reaction. A series of studies conducted between 1910 and 1920 demonstrated, however, that the characteristic signs of anaphylaxis could occur in decerebrated guinea pigs and dogs. With the development of immunological and biochemical techniques, an impressive amount of knowledge on the cellular and chemical aspects of immune processes evolved, and the participation of the CNS in this phenomena was largely overlooked. The consideration of the integrative capacity of the CNS on a number of physiological functions has revived interest in the role of the CNS in relation to immune processes.

Studies on the effect of sectioning the spinal cord on immunogenesis have shown changes such as decreased antibody formation after sensitization (*39*) and lowered histamine sensitivity (*40*). These findings may be the secondary result, however, of peripheral disturbances in temperature control and blood circulation. The depression of the hemolysin response in rats to sheep red blood cells after spinal cord sectioning was prevented when the animals were maintained at body temperature (*41*).

The effect of midbrain lesions on the course of anaphylaxis in the guinea pig has been investigated by Freedman and Fenichel (*42*). Bilateral electrolytic lesions of the midbrain reticulum inhibited death by anaphylaxis. Szentivanyi and Filipp (*43*) were among the first to study the role of the hypothalamus on anaphylaxis. They demonstrated that lethal anaphylactic shock in the guinea pig and the rabbit can be prevented by bilateral focal lesions in the tuberal region of the hypothalamus. Luparello, Stein, and Park (*44*) investigated the effect of hypothalamic lesions on rat anaphylaxis and found that anterior, but not posterior, hypothalamic lesions inhibited the development of lethal anaphylaxis in the rat.

We have conducted a series of studies on the effect of hypothalamic lesions on immune processes in the guinea pig. The effect of hypothalamic lesions on both immediate (humoral) and delayed (cell-mediated) hypersensitivity was investigated (*45*). Bilateral electrolytic lesions were placed in the anterior, median, or posterior basal hypothalamus of male Hartley strain guinea pigs. Controls included sham-operated and unoperated animals. Each group was sensitized with picryl chloride, a hapten or incomplete antigen, in Freund's adjuvant, 1 week after operation. By this method of immunization delayed cutaneous reactions to picryl chloride and tuberculin (purified protein derivative), cir-

Table 1. Effect of anterior hypothalamic lesions on immune processes.

Groups	Circulating antibody titer*	Anaphylactic death†	Delayed hypersensitivity reactions	
			Picryl chloride contact‡	Tuberculin§
Nonoperated	2.54 ± 0.14	20/27	27/29	18.2 ± 0.6
Anterior sham-operated	2.51 ± 0.12	12/18	18/20	19.1 ± 0.8
Anterior hypothalamic lesions	1.85 ± 0.18	3/17	14/20	15.7 ± 0.4

*Mean $\log_{10}$ of the reciprocal of the antibody titer. †Ratio of the number of animals that died to the number tested. ‡Ratio of animals with a 4+ reaction (or more) to the number tested. §Size of reaction (means ± standard error).

culating antibodies to the picryl hapten, and anaphylaxis were studied consecutively in each of the groups. Brain serial sections were made for lesion localization. Significant protection against lethal anaphylaxis ($P < .001$), a lower titer of circulating antibody ($P < .01$), and depressed delayed hypersensitivity reactions were found in the animals with electrolytic lesions in the anterior basal hypothalamus (Table 1). Lethal anaphylaxis occurred in 71 percent of the control animals and in only 18 percent of the guinea pigs with anterior hypothalamic lesions. In the control groups the titer for antibody to picryl chloride, as measured by passive cutaneous anaphylaxis (PCA), was fourfold higher than that for the experimental group. Delayed hypersensitivity reactions in animals with anterior lesions were diminished as shown by the fewer intense skin test reactions to picryl chloride (significantly different from nonoperated control group $P < .05$) and the smaller tuberculin reactions (significantly different from sham-operated $P < .001$ and from nonoperated $P < .01$ groups) (Table 1). The median and posterior hypothalamic lesions had no significant effect on lethal anaphylaxis, circulating antibody, or the delayed hypersensitivity response (*45*).

The localization of the hypothalamic lesions is projected on a sagittal diagram of the guinea pig hypothalamus (Fig. 1). All the animals included in the group with anterior hypothalamic lesions presented various degrees of damage to the anterior hypothalamic region and the suprachiasmatic nuclei, with the lesions impinging, in some guinea pigs, on the preoptic area and the rostral portion of the ventromedial nuclei. The animals with lesions in the median hypothalamus showed damage to the ventromedial nuclei and the arcuate nuclei. The lesions in the posterior hypothalamus damaged the premammillary region and the medial mammillary nuclei. The lesions in the three hypothalamic areas were of comparable size, and there was minimal overlapping of lesions among the three experimental groups (Fig. 1).

Subsequent studies were focused primarily on the humoral immune response and immediate hypersensitivity. The effect of anterior hypothalamic lesions on lethal anaphylaxis was investigated after the animals were sensitized with ovalbumin, instead of picryl chloride (*46*). In sham-operated guinea pigs challenged with 0.25, 0.5, and 1.5 mg of ovalbumin the percentage with lethal anaphylaxis was 17, 25, and 73 percent, respectively (Fig. 2). In contrast, when the animals with anterior hypothalamic lesions were injected with the two lower doses of antigen there were no deaths; and in animals injected with 1.5 mg

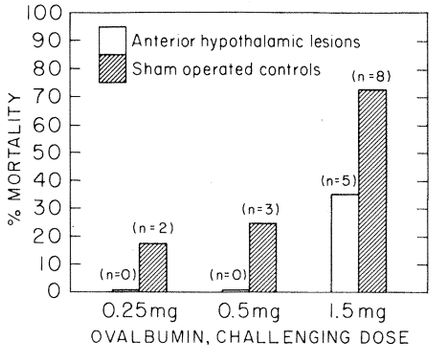

Fig. 2. Anaphylactic mortality of sensitized guinea pigs with anterior lesions and sham-operated controls challenged with three antigen doses. Figures in parentheses refer to number of dead animals per group.

of ovalbumin the mortality was only 36 percent. The difference in mortality ratios between the anterior hypothalamic and sham-operated group was significant (χ^2, 6.73; $P < .01$). Furthermore, surviving animals with anterior hypothalamic lesions had significantly less severe anaphylactic reactions (Fig. 3). These results are consistent with those from the study with picryl chloride (*45*) in which sensitized guinea pigs with anterior hypothalamic lesions were markedly protected against lethal anaphylaxis. These results suggest that the protective effect of anterior hypothalamic lesions is not related to the nature of the antigen.

Little is known about the mechanisms whereby hypothalamic lesions protect against anaphylaxis. Several investigators using a variety of techniques have considered the effect of lesions on the levels of circulating antibodies. Filipp and Szentivanyi (*47*) have reported that circulating as well as tissue-fixed antibodies were reduced in tuber-injured guinea pigs. Korneva and Khai (*48*) found that lesions in

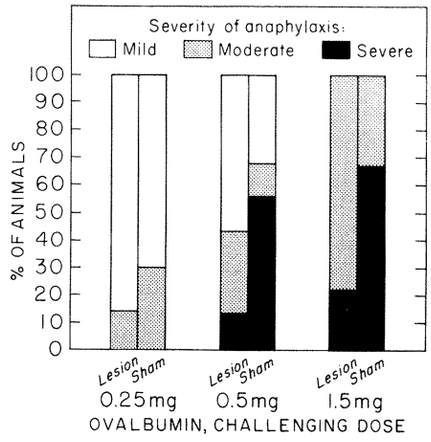

Fig. 3. The effect of anterior hypothalamic lesions on the severity of anaphylaxis of sensitized guinea pigs surviving antigen challenge.

the posterior ventral hypothalamus of rabbits completely suppressed the production of complement-fixing antibodies and induced a prolonged retention of the antigen in the blood. In cases where the areas of destruction were localized in other parts of the hypothalamus, the thalamic structures, the caudate nucleus, and the posterior commissure, the course of immune processes was similar to that in control animals. Ado and Goldstein (*49*), on the other hand, reported that anterior, medial, and posterior hypothalamic lesions in rabbits had no effect on the titer of complement binding and hemagglutinating antibodies after the animals were sensitized with egg albumin.

In a study of the effect of hypothalamic lesions on lethal anaphylaxis after the animals were sensitized with ovalbumin (*46*), protection was not associated with significantly lower titers of antibody to ovalbumin as measured by PCA at the time of challenge. As noted above, we have found in guinea pigs that anterior, but not posterior or median hypothalamic, lesions (Table 1) were associated with significantly lower titers of PCA antibody in response to picryl chloride (*45*). Qualitative differences in the nature of the antigen (protein as compared to chemical hapten) might account for the differences in the antibody response. Differences in the method of picryl chloride and ovalbumin studies, such as the time between the lesioning of the animals and the determination of circulating antibodies, may account for the discrepancy in the antibody findings.

The significance of low circulating antibodies in the decreased anaphylactic response, however, remains to be determined. If the antianaphylactic effect was due solely to diminished antibody production, then no protection would be expected in animals passively immunized and provided with sufficient antibody to produce lethal anaphylaxis. Szentivanyi and Filipp (*43*) have reported that guinea pigs passively sensitized with homologous as well as with heterologous (rabbit) serum are protected by hypothalamic lesions. These investigators did not identify the hypothalamic structures damaged by the lesions, nor did they quantify the amount of antibodies injected in the animals. We have found that guinea pigs passively sensitized with heterologous (rabbit) antibody to ovalbumin are also afforded significant protection ($P < .02$) against lethal anaphylaxis after lesions in the anterior hypothalamus (*50*).

Furthermore, in a study in which anterior hypothalamic lesions were placed in guinea pigs 1 month after sensitization, significant protection was afforded when the animals were challenged 48 to 72 hours

after the placement of lesions. This effect was found even when there were no differences in circulating PCA antibodies to ovalbumin at the time of challenge between lesioned and sham-operated controls. These observations and those found in passive anaphylaxis suggest that the effect of anterior lesions may be related to nonspecific aspects of the humoral immune response.

The lesions may interfere with antibody binding to host tissues, they may modify the antigen-antibody union, they may alter the content and release of histamine and other vasoactive substances by the tissues, or they may diminish the responsiveness of the target tissues to the pharmacological agents liberated by the antigen-antibody reaction. We have studied the effect of anterior hypothalamic lesions on some of the nonspecific aspects of the humoral immune response by in vitro techniques (*46*). The contraction of isolated ileum from lesioned and control guinea pigs was compared in response to the addition of a specific antigen, ovalbumin, after passive sensitization in vitro, and the addition of ovalbumin to ileum from actively sensitized animals. The study showed that anterior lesions of size and location comparable to those providing protection against lethal anaphylaxis do not modify the anaphylactic response of isolated ileum passively sensitized in vitro (Fig. 4) or ileum from guinea pigs actively sensitized.

Using passive cutaneous anaphylaxis we studied the effect in vivo of anterior hypothalamic lesions on some of the nonspecific components of the immune response. Serial saline dilutions of rabbit antiserum to ovalbumin were injected intradermally on the clipped backs of guinea pigs 2, 15, and 30 days after the placement of anterior hypothalamic lesions. Eighteen hours after intradermal passive sensitization, the ovalbumin antigen, mixed with a dilute solution of the dye Evan's blue, was injected into the jugular vein. The diameter of the bluing reaction at the site of the injection of the antibody provided a measure of the skin anaphylactic response. There were no significant differences between the anterior hypothalamic lesioned animals and the sham- and nonoperated controls on each of the days tested. Our findings in the studies in vivo and in vitro do not support the hypothesis that the protective effect of lesions in the guinea pig is due to impairment of antibody binding capacity or due to interference with the intracellular processes responsible for the release of histamine or other mediators of anaphylaxis. In the rat, however, hypothalamic lesions did influence passive cutaneous anaphylaxis (*51*).

In guinea pigs the immediate cause of anaphylactic death is anoxia due to intense bronchospasm primarily resulting from the liberation of histamine and other pharmacologic agents after the antigen-antibody reaction. Several investigators have reported that the central nervous system modifies the susceptibility of animals to histamine. Whittier and Orr (*52*) found that bilateral lesions of the caudate nuclei of rats were associated with a significant increase in survival time after the intraperitoneal administration of histamine phosphate; sham operations and lesions in the cerebral cortex did not modify the time of survival. Przybylski (*53*) investigated the effect of the removal of the region of the quadrigeminal bodies and of the cerebral cortex on histamine toxicity in guinea pigs. The animals in which the quadrigeminal bodies were removed showed a decreased susceptibility to histamine administered either intravenously or by the inhalation of an aerosol. Removal of the cerebral cortex did not modify the reactivity of the animals. Szentivanyi and Szekely (*54*) found that lesions in the tuberal region of the guinea pig hypothalamus provided protection against lethal histamine shock.

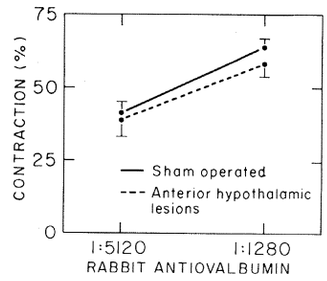

Fig. 4. The percent of maximum contraction of passively sensitized ileum segments from guinea pigs with anterior hypothalamic lesions and sham-operated animals. The values represent mean anaphylactic responses ± the standard error of three segments per animal sensitized with each of two concentrations of rabbit antiserum to ovalbumin.

We have studied the effect of bilateral electrolytic lesions in the anterior and posterior medial hypothalamus of guinea pigs on histamine toxicity as measured by dose-mortality curves and the median lethal dose (LD_{50})(*55*). The animals with anterior lesions were afforded significant protection against histamine toxicity (Fig. 5). The observation that guinea pigs with anterior lesions are less susceptible to exogenous histamine led to the hypothesis that the protective effect of lesions is mediated by a decreased smooth muscle response to histamine. This hypothesis was tested in an in vitro study (*46*). The contractions of isolated ilia from anterior hypothalamic lesioned and control guinea pigs were measured in response to graded doses of exogenous histamine. Comparison of dose-effect relationships showed no significant differences between both groups of animals. The above study suggests that hypothalamic lesions do not modify the smooth muscle response to histamine challenge. There may be, however, differences in the target organ response of ileum and bronchiolar smooth muscle.

The integrity of the autonomic nervous system may be essential for the mediation of hypothalamic influences on the bronchospastic reaction. An increasing body of data indicates that the autonomic nervous system plays an important role in the mediation of the physiological changes observed during anaphylaxis (*56*). Mills and Widdicombe (*57*), in a study on vagotomized guinea pigs, provide specific evidence that a vagal reflex is partially responsible for the bronchoconstriction that occurs in anaphylaxis and follows intravenous administration of histamine. These authors reviewed the evidence that anaphylaxis and exogenous histamine, in addition to having a direct action on the airway's smooth muscle, trigger a vagus reflex which superimposes its respiratory and bronchomotor effects on the local bronchoconstriction. Maslinski and Karczewski (*58*) have shown that electrical stimulation of the brain of guinea pigs through temporal electrodes significantly reduces the mortality of guinea pigs subjected to anaphylaxis and histamine shock. The protective effect is accompanied by a depression in the afferent and efferent activity of the vagus. This and other observations led Karczewski (*59*) to postulate that the protection against anaphylaxis and histamine shock is due to a depression in the activity of the parasympathetic nervous system which, by interfering with the vagal reflex, leads to a reduced response of the airway's smooth muscles to constricting

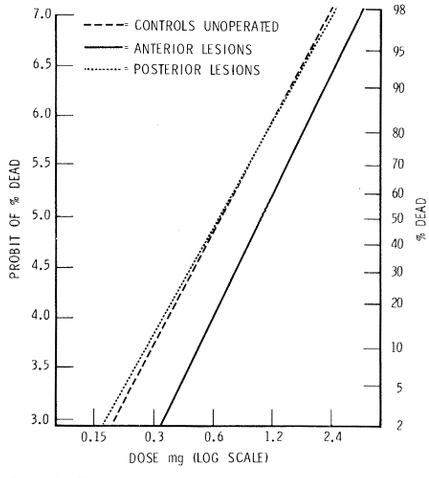

Fig. 5. Dose-effect curves for hypothalamic lesioned and control guinea pigs injected with histamine phosphate.

stimuli. Przybylski (*60*) has studied in the guinea pigs the effect of stimulation and ablation of the midbrain reticular formation on the bronchial smooth muscle response to histamine. Stimulation of the dorsocaudal regions of the midbrain reticular formation produced bronchoconstriction and potentiated the constrictor effect of histamine, whereas ablation of this area diminished the bronchoconstrictor response to histamine. Przybylski has suggested that the effect of the dorsocaudal midbrain region on histamine susceptibility is mediated by parasympathetic activity.

In a recent series of studies Gold (*61*) investigated the role in canine asthma of vagus reflexes in antigen-induced bronchoconstriction. He studied the airway response after complete, efferent, and afferent vagal blockade. The findings suggest that the classical concept of bronchoconstriction being the direct result of the interaction of antigen with cell-fixed antibodies and the release of histamine must be altered. Gold's findings suggest that the major factor in antigen-induced bronchoconstriction is a vagally mediated reflex with an afferent component triggered by stimulation of airway receptors and an efferent limb producing airway smooth muscle contraction.

Several lines of evidence (*62*) indicate that bronchomotor tone is the result of a balance between parasympathetic and sympathetic influences. Damage to the region of the anterior hypothalamus, which is thought to mediate primarily parasympathetic responses, may decrease vagal bronchoconstrictor tone, resulting in the predominance of bronchial β-adrenergic receptor activity. In keeping with this hypothesis, inhibition of vagal activity (*63*) or β-adrenergic stimulation (*64*) decreases histamine-induced bronchoconstriction while blockage of β-receptors potentiates histamine bronchospasm (*65*). Filipp has reported (*66*) that propanolol and pertussis vaccine, both β-receptor blockers, diminish the protective effect of tuberal hypothalamic lesions in guinea pig anaphylaxis.

Szentivanyi (*67*) has postulated that the hyperactivity observed in bronchial asthma may be due to the reduced functioning of the β-adrenergic system leading to α-adrenergic dominance and the consequent increase in bronchial responsiveness to the various pharmacological mediators. Orange and Austen have reported (*68*) that increased intracellular concentrations of adenosine 3′,5′-monophosphate (cyclic AMP) after activation of β-adrenergic receptors inhibit the immunoglobulin E–mediated immunologic release of histamine and slow reactive substance (SRS-A) from lung tissues. Hypothalamic lesions may produce a functional imbalance in the two adrenergic effector systems or increase the concentrations of cyclic AMP, resulting in an inhibition of release of histamine and SRS-A. At present, however, there are no data to support these possibilities.

The influence of the CNS on immune mechanisms may be due, at least in part, to changes in neuroendocrine function induced by the destruction of specific hypothalamic structures. In the rat, the anterior medial hypothalamus is involved in the regulation of the secretion of thyroid stimulating hormone (TSH) by the anterior pituitary (*69*). Electrolytic lesions in this area induce low plasma levels of TSH and decreased thyroid function. A number of investigators have demonstrated, in the rat and guinea pig, a relation between thyroid physiology and immune processes. It has been noted (*70*) that the resistance to the anaphylactic reaction is increased in thyroidectomized rats. Similar findings were observed by Nilzén in the guinea pig after thyroidectomy or administration of ^{131}I. Suppression of thyroid activity inhibits local and systemic anaphylaxis, abolishes circulating precipitins, and decreases the susceptibility of the animals to exogenous histamine (*71*). Little is known about the effect of anterior hypothalamic lesions on thyroid function in the guinea pig.

Hypothalamic lesions can also modify adrenocorticotrophic hormone (ACTH) secretion and blood corticoid levels. Adrenal steroids have a protective effect against anaphylactic shock and an inhibitory effect on antibody formation in the rat (*72*). Tyrey and Nalbandov (*73*) have found that antibody titer depression in the rat that follows anterior hypothalamic lesions can be significantly blocked by either hypophysectomy or adrenalectomy. These observations led Tyrey and Nalbandov (*73*) to postulate that the effect of anterior lesions is mediated by an increase in pituitary-adrenal activity. The enhanced pituitary-adrenal function after lesions is in keeping with the current concept that ACTH release is controlled by inhibitory and facilitatory neural mechanisms.

Adrenocortical hormones also have a profound action on the metabolism and effects of histamine. They have inhibitory effects on histamine decarboxylase activity (*74*), tissue binding of newly formed histamine (*75*), and on the amount of histamine released by the tissues (*76*). Although adrenal steroids have a protective effect against histamine toxicity in mice and rats, the findings regarding the effect of corticosteroids on the susceptibility of guinea pigs to anaphylaxis and to exogenous histamine are contradictory (*77*).

It has been suggested that the protective effect of anterior lesions may also be due to simultaneous changes in thyroid and adrenocortical function. Filipp and Mess (*78*) reported that exogenous administration of thyroxin partially restored the sensitivity to anaphylaxis of actively immunized guinea pigs with lesions in the tuberal area of the hypothalamus. They also studied the combined effect of thyroxin and metopirone, an inhibitor of adrenocortical hormone synthesis, on the anaphylactic response of sensitized guinea pigs with lesions in the tuberal region (*79*). The observation that the administration of both substances completely abolished the protective action of the lesions led them to hypothesize that the antianaphylactic effect of hypothalamic damage is due to the combined effect of decreased thyroid function and increased adrenocortical activity. There have been very few studies concerned with the neuroendocrine effects of localized hypothalamic damage in guinea pigs. Additional information is necessary on plasma levels of thyroid, adrenocortical, and adrenomedullary hormones in guinea pigs with well-defined hypothalamic lesions that decrease anaphylactic reactivity.

Summary

It has been shown experimentally that psychosocial processes influence the susceptibility to some infections, to some neoplastic processes, and to some aspects of humoral and cell-mediated immune responses. These psychosocial effects may be related to hypothalamic activity. Reviewing the mechanisms that may be involved in the role of the hypothalamus in immune responses indicates that there is no single mediating factor. Various processes may participate, including the autonomic nervous system and neuroendocrine activity. The research reviewed has been limited primarily to a consideration of the effect of hypothalamic lesions on humoral immune responses. There is some evidence (*45, 80*) indicating that hypothalamic lesions also modify cell-mediated immune responses. Further research is required to evaluate the effect of the hypothalamus on cell-mediated immunity.

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National Parks: The Dilemma of Development

Many variables affect development in the national parks. Compromise is needed to maintain park quality.

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The national parks of the American West have traditionally been the subject of much debate; such debate persists largely because of the popularity of the parks themselves and the resulting intrusions of human artifacts on park landscapes. Development centers are the major example of such intrusions, and much of the debate has focused on the extent to which these concentrations of tourist, administrative, and supportive facilities detract from scenic resources of the parks and what, if anything, can be done about it (*1*). A frequently suggested solution involves the use of alternatives to the traditional development center sites. On the basis of work done in 16 western national parks, I shall outline some of the circumstances that led to the locational pattern of today's development centers and discuss advantages and disadvantages associated with the use of alternative locations that are aimed at reducing depreciation of scenic resources (*2*). I then suggest a general approach that emphasizes compromise among those variables that are relevant to the issues involved.

Current cultural landscapes are products of past perceptions of needs, reactions to conditions, and decisions about ways of meeting demands—regardless of whether the landscape in question is urban, agricultural, or a development center in a western national park. In general, today's development centers were established many decades ago and resulted from decision-making that occurred under circumstances far different from present condi-

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