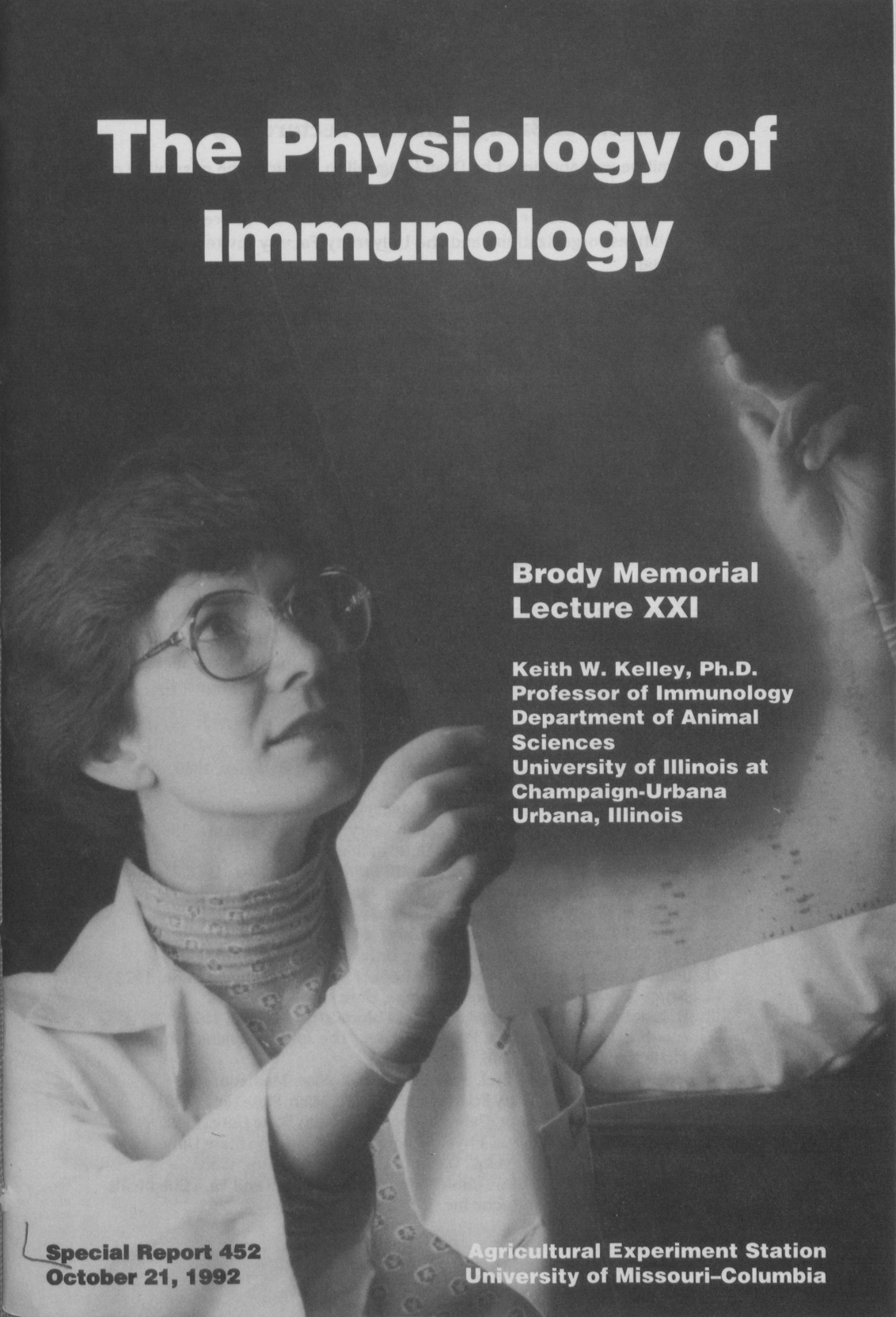
# The Physiology of Immunology



## Brody Memorial Lecture XXI

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Special Report 452
October 21, 1992

Agricultural Experiment Station
University of Missouri–Columbia

## Establishment of Brody Memorial Lectureship

A committee was appointed by Dean Longwell to consider the possibility of creating a memorial for Samuel Brody. It was the opinion of the committee that a permanent lectureship would be most suitable if sufficient funds were obtained from friends, relatives, organizations and the University Faculty invited to contribute to this memorial.

Friends, relatives and organizations interested in recognizing Dr. Brody provided the initial funds, which were supplemented by a generous grant from the King Ranch and matching funds from the Alumni Achievement Funds.

The Board of Curators approved the establishment of the Samuel Brody Lectureship Fund in April, 1959. Lectures have been held as often as sufficient income from the interest provided expenses and a small honorarium for a distinguished lecturer.

The present Brody Memorial Lectureship Committee was appointed by Dean Roger Mitchell.

Dr. Donald E. Spiers, Sigma Xi Representative

Dr. Harold D. Johnson, Department of Animal Sciences

Dr. B. Ann Becker, ARS Representative

Dr. Ralph R. Anderson, Gamma Sigma Delta Representative

The Committee will welcome additional contributions from any individuals or groups in academia or industry. Such funds will be applied to the principal or endowment of the now-established Brody Memorial Lectureship Fund. Any increases in the endowment fund, or course, will allow lectures to be held more frequently.

## Previous Brody Lectures:

I. Max Kleiber, Dept. Animal Science, Univ. of Calif., Berkeley, 1960
II. Knut Schmidt-Nielsen, Dept. Zoology, Duke Univ., 1961.
III. F. W. Went, Director, Missouri Botanical Garden, 1963
IV. K. L. Baxter, Dept. Nutrition, Hannah Dairy Research Institute, 1964
V. C. Ladd Prosser, Dept. Physiol., Univ. of Illinois, 1965
VI. H. T. Hammel, Physiol. Group, John B. Pierce Found. Lab., 1966
VII. H. N. Munro, Dept. Physiol. Chemistry, Mass. Institute of Tech., 1967
VIII. James D. Hardy, Dept. Physiol., Yale University, 1968
IX. Loren D. Carlson, Dept. Physiol., Univ. of Calif.-Davis, 1969
X. R. L. Baldwin, Dept. Animal Science, Univ. of Calif.-Davis, 1971
XI. John R. Brobeck, Dept. Physiol., School of Medicine, Univ. of Penn. 1972
XII. Bruce A. Young, Dept. Animal Science, Univ. of Alberta, 1974
XIII. D. E. Johnson, Dept. Animal Science, Colorado State Univ., 1975
XIV. Albert L. Lehninger, Dept. Physiol. Chem., The Johns Hopkins School of Medicine, Baltimore, 1976
XV. Henry A. Lardy, Dept. Biol. Science, Univ. of Wisc.-Madison, 1979
XVI. H. A. Tucker, Depts. Dairy Science and Physiol., Mich. State Univ., 1981
XVII. H. Russell Conrad, Dept. Dairy Science, The Ohio State Univ., 1982
XVIII. David Robertshaw, Dept. Physiol/Biophysics, Colorado State Univ., 1984
XIX. Allen Munck, Dept. Physiol., Dartmouth Medical School, 1986
XX. Lawrence J. Machlin, Dir. Clinical Nutrition, Vitamins and Fine Chemicals Division, Hoffman-LaRoche Inc. 1988

# The Physiology of Immunology

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This work was supported in part by grants from the USDA (92-37206-7777) and from the National Institutes of Health (AG06246).
Publication number SR 452; new 6/93/300.

# Introduction

Cells that defend animals against infectious diseases are affected by their: a) genome, which is a function of the genetic composition of each parent b) physiologic state, such as pregnancy and lactation, and c) nutritional status, which is modulated by the food that animals eat. Research in the animal sciences has been based on the three traditional disciplines of genetics, physiology and nutrition. Since all these factors influence cells of the immune system, it is only natural that immunological research has now found its way into the animal sciences. However, it has been generally viewed that the immune system is autonomous; that is, it neither affects nor is it affected by other physiologic systems. Research conducted during the past decade has now made it clear that cells of the immune system are inextricably linked with other physiological systems, such as the neuroendocrine, respiratory, reproductive and central nervous systems. Changes in one system evoke changes in the other, and it is likely that communication loops have evolved to coordinate and regulate functional activities of the immune system. The integrated view of immunophysiologists, that cells of the immune system interact with the entire body, rather than existing as a separate physiologic system that operates autonomously, should help to unravel a number of mysteries that are key to solving important problems in the animal and medical sciences.

# Stress and the immune system

Over fifty-five years ago, Hans Selye published a short article titled, "A syndrome produced by diverse nocuous agents" (Selye, 1936). Selye made the original observation that acute stressors, such as exposure to cold, injections of toxic drugs or surgical injury, resulted in a rapid decrease in size of the thymus gland, lymph nodes and spleen. Although not all scientists agree with Selye's interpretation of his data as a "general adaptation syndrome," Selye offered the first morphological evidence to show that acute stressors affect lymphoid tissue. Selye also showed that atrophy of lymphoid tissues did not occur in stressed animals that had been adrenalectomized. It was subsequently shown that acute stressors cause the release of pituitary-derived adrenocorticotropin (ACTH), which augments the release of glucocorticoids from the adrenal gland. Glucocorticoids are well known to suppress a variety of immune responses (reviewed by Munck et al., 1984), and synthetic analogs of adrenal glucocorticoids have been used for years as anti-inflammatory compounds in both humans and domestic animals. It might therefore be considered that the stress-associated adrenal hormones, cortisol and corticosterone, were the first hormones shown to affect lymphoid cells.

The present-day concept that hormones alter functional responses of cells of the immune system is therefore not a new idea. There is now a plethora of data which show that hormones other than glucocorticoids affect lymphoid cells, with some hormones augmenting and others suppressing different immune responses. The newest concept that has emerged from these and other studies is that lymphoid cells are not only affected by hormones from the neuroendocrine system, but that products of lymphoid cells also affect the neuroendocrine system. Therefore, it is appropriate to consider reciprocal systems of communication (or cross-talk) between these two physiologic systems (reviewed by Kelley, 1988).

# An historical perspective

As early as 1878, Louis Pasteur showed that cold-stressed chickens were more susceptible to Bacillus anthracis than the experimental controls (discussed by Kelley, 1985). Selye developed the idea during the 1940s that nonspecific responses of animals to adverse stimuli caused lymphoid tissues to atrophy. During the early 60's, research conducted by Rasmussen, Jensen and Marsh, and subsequent studies by Gross and co-workers (cited by Kelley, 1980; 1985), showed that a number of adverse environmental situations affected the susceptibility of animals to infectious diseases. Experiments conducted by Pierpaoli, Sorkin, Besedovsky and Fabris in the early 1970s established that a number of hormones (e.g., growth hormone,

thyroxine) modulated functional properties of lymphoid cells (reviewed by Kelley, 1989). These workers were also the first to demonstrate abnormal endocrine profiles in mice that were born with a congenital absence of a thymus gland. More recently (in the early 1980s), Blalock published his ideas on reciprocal systems of communication between the immune and endocrine systems. Thus, research that was initiated by Selye in stress physiology provided the conceptual framework for much of the research on hormones and immunity.

Many of the ideas presented by these pioneering scientists preceded the knowledge that was necessary to understand the mechanisms by which hormones affect lymphoid cells. At that time, researchers did not know that lymphoid tissue is innervated and that lymphocytes and macrophages express receptors for a number of hormones and neurotransmitters. Neither was it known at that time that specific brain lesions affect functional activities of lymphoid cells nor that lymphocytes actually secrete their own hormone-like molecules (e.g., interleukin 2; IL-2). The existence of distinct subsets of lymphocytes with different functional activities was also unknown, as was the key function of the thymus in providing the microenvironment for differentiation of T cells by rearrangement of T cell receptor genes.

Future advances in the molecular basis of lymphoid cell regulation will lead to a better understanding of how cross-talk occurs between the immune and neuroendocrine systems. Unlike college courses in which students are taught biological systems in a piece-meal fashion (e.g., physiology, biochemistry, immunology, microbiology, nutrition), the body functions as an integrated unit that is not segregated by departmental boundaries. It seems realistic to view the immune system as an integral and active participant in that process which Walter Cannon called homeostasis, in which lymphoid cells can both affect and be affected by other physiologic systems.

# Animal management and immune responses

A number of environmental situations may occur during the production of livestock that can be regarded as stressful. These environmental situations include heat, cold, crowding, mixing, weaning, limit-feeding, shipping, noise and restraint. In 1980, a comprehensive review article was published which discussed most of the available data on how these management practices affected disease susceptibility and the immune systems of domestic animals (Kelley, 1980). This review has been extended four times (Kelley, 1983; 1985; 1988; Dantzer and Kelley, 1989). In each case, more emphasis was placed on understanding the biochemical events that are responsible for these changes in disease susceptibility. The main theme in all of these papers was that adverse environmental conditions alter the resistance of domestic animals

to infectious diseases by affecting cells of the immune system. Since acute stressors also alter the endocrine profile of domestic animals, and Selye had established that the adrenal gland secretes products which are at least partially responsible for lymphoid involution during stress, it was predicted that these effects on the immune system were caused by stress-induced hormonal changes. When an animal perceives an environmental situation as adverse, it makes appropriate adjustments that are aimed at mastering the challenging situation. These reactions include alterations in hormone secretion that may affect a particular type of cell(s) within the immune system.

The most frequently discussed family of stress hormones that affects lymphoid cells are glucocorticoids, regulated by the hypothalamic-hypophyseal axis. When animals are acutely stressed, the hypothalamus liberates a peptide known as corticotropin-releasing factor. This peptide, in turn, causes the adenohypophysis to secrete ACTH. Cortical cells of the adrenal glands respond to ACTH by synthesizing and releasing glucocorticoids into the blood. Adrenal glucocorticoids and their synthetic analogs are well known to be anti-inflammatory at pharmacologic concentrations. However, even at physiologic levels, these hormones have been shown to be associated with stress-induced reductions in T cell proliferation of pigs, chickens and cattle (e. g., Westly and Kelley, 1984; Blecha and Baker, 1986). Proteins in serum, such as corticosteroid binding globulin and albumin, bind exogenous glucocorticoids and can therefore make it biologically unavailable, as we have demonstrated in chickens (Table 1; Franklin et al., 1987).

**Table 1.**

Corticosterone inhibits phytohemagglutinin (PHA)-induced proliferation of chicken splenocyte only in medium without fetal bovine serum (FBS; Franklin et al., 1987).

| | Percent Reduction | |
|---|---|---|
| Corticosterone Concentration | + FBS | – FBS |
| None | 100 | 100 |
| 1 ng/ml | ND | 94 |
| 2 | 105 | ND |
| 12 | ND | 57* |
| 50 | 113 | 36* |
| 1000 | 100 | ND |

*Indicates difference ($P < .05$) from zero level; ND = Not Done.

# Growth hormone, prolactin and the immune response

Since some hormones can suppress immune responses, we became interested in the possibility that hormones exist which might augment immune events. This idea seemed reasonable in view of the fact that animals without a pituitary gland are extremely susceptible to bacterial infections such as Salmonella typhimurium (Edwards et al., 1991). Growth hormone, prolactin and insulin-like growth factor-I have been shown to augment a number of functional activities of lymphoid cells (reviewed by Berzci, 1986; Kelley, 1989; Arkins et al., 1993). Our experiments were initiated by using a well-described system for inducing growth in rats (Turner et al., 1986). This system involves the use of a pituitary adenoma cell line known as $GH_3$, which secretes both growth hormone and prolactin. We chose to implant these cells into aged rather than young rats because it is well known that the thymus gland atrophies with age. Involution of the thymus gland is associated with a decline in plasma levels of growth hormone that occurs after puberty, and aging is associated with a significant decline in a number of T cell responses. The question we sought to answer was whether $GH_3$ cells could cause thymic growth in aged female rats (Kelley et al., 1988). If so, we wondered whether growth of the thymus gland would be accompanied by augmented T cell responses.

Results of these experiments with both 18- and 24-month old rats were dramatic (Kelley et al., 1986). As expected, we could not find histological evidence of a thymus gland in normal aged rats. However, in both groups of aged rats that were implanted with $GH_3$ cells, we found both gross and histological evidence of thymic growth. Even though the aged female rats have higher T cell responses and IL-2 synthesis than aged male rats (Davila and Kelley, 1988), there was a marked immunosuppression in aged control female rats, as determined by both proliferative responses to T cell lectins and synthesis of IL-2. However, spleen cells from aged female rats implanted with $GH_3$ cells responded significantly greater to phytohemagglutinin (PHA) and concanavalin A (Con A) than the control aged rats, and this effect was accompanied by augmented synthesis of IL-2. In 18-month-old rats, T cell proliferative responses could be restored to those of young control rats. $GH_3$ cells may reverse thymic involution during aging by preventing the accumulation of thymocyte progenitors and enhancing their differentiation into mature, functional cells (Li et al., 1992; Kelley et al., 1992). Defective respiratory burst activity and synthesis of tumor necrosis factor in response to interferon-$\gamma$ that occurs in macrophages of aged rats are also reversed by $GH_3$ cells (Davila et al., 1990). Other experiments demonstrated that direct injection of growth hormone also increased lectin-induced proliferative responses of splenocytes in aged rats (Davila et al., 1987) and restored the

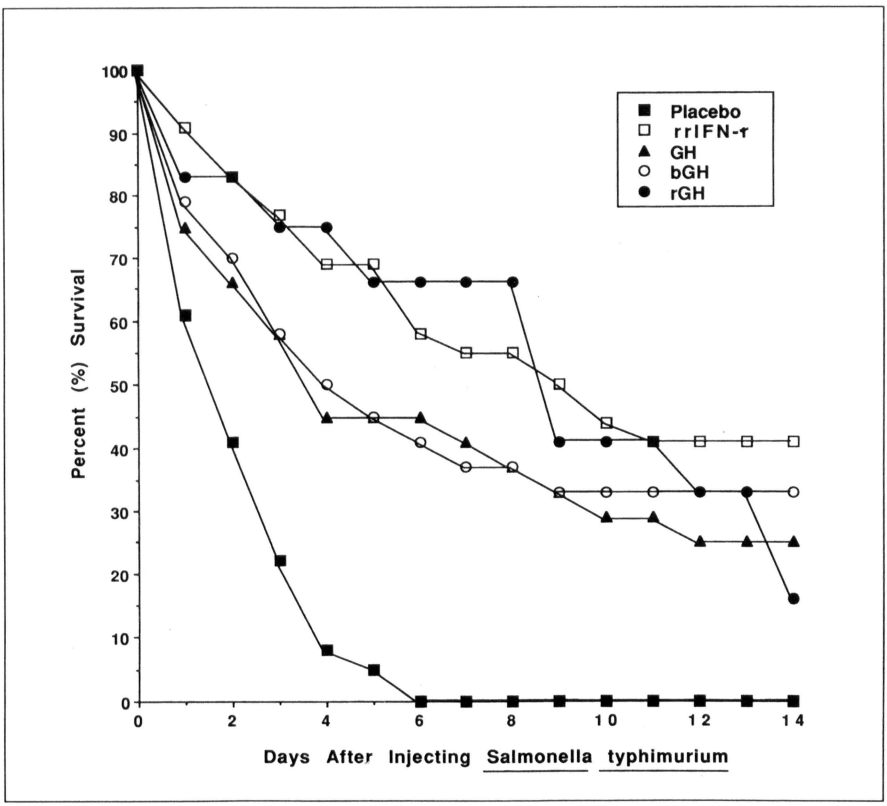


**Fig. 1. Daily injections of the macrophage-activating factor, recombinant rat interferon-γ (rrIFN-γ), pituitary-derived porcine growth hormone (GH), pituitary-derived bovine growth hormone (bGH) or recombinant porcine growth hormone (rGH) significantly increase survival of hypophysectomized rats following challenge with Salmonella typhimurium. (from Edwards et al., 1991a)**

synthesis of macrophage-derived tumor necrosis factor-α in hypophysectomized rats (Edwards et al., 1991b). These data established that the thymic atrophy and reduction in T cell responses that occurs as a normal consequence of aging are not irreversible events. Furthermore, these data suggested a potential functional role for growth hormone and prolactin as immunomodulators in aged, immunosuppressed animals.

In other experiments with young transgenic mice that carried the rat metallothionein-growth hormone gene, we also found augmented lectin-induced proliferation of splenocytes when compared to nontransgenic, littermate control mice (Davila et al., 1987). This growth hormone-augmenting activity depended on the presence of a thymus gland, because $GH_3$ cells did not affect lymphoid cell responses in nude rats.

One can ask what is the relevance of this research to the animal sciences since most livestock producers do not maintain their livestock to old age. However, the implication that growth hormone affects functional activities of lymphoid cells of rodents could have important consequences in livestock production. Growth hormone augments milk production in dairy cattle and improves growth rate and carcass quality in pigs and beef cattle. A number of large commercial companies have produced recombinant bovine and porcine growth hormone with the intent of selling it for future use in domestic livestock in the United States if they are approved by the Food and Drug Administration. It is therefore important to determine whether growth hormone affects animal health positively or negatively. We are actively studying the possibility that growth hormone affects the immune systems of domestic animals, and we have already identified both macrophages (Edwards et al., 1988; 1992a,b) and neutrophils (Fu et al., 1991) as targets for growth hormone action in pigs. In humans, growth hormone acts via binding to the prolactin rather than the growth hormone receptor (Fu et al., 1992). Furthermore, because growth hormone causes thymic growth and augments T cell proliferation in aged, immunosuppressed subjects, the fact that growth hormone and prolactin have been shown to prevent stress-induced thymic atrophy and certain suppressed T cell responses in stressed animals is also of interest (Kelley and Dantzer, 1991). The role of the somatolactogenic gene family in the entire area of immunoregulation is rapidly growing, as assessed by a recent issue of a research journal devoted entirely to this concept (see Kelley et al., 1992 for a summary and Kelley et al., 1993 for immunoregulatory role of insulin-like growth factor-I).

# Communication systems within the immune and central nervous systems

It has been demonstrated that injection of antigen is sufficient to elevate plasma glucocorticoids (Besedovsky et al., 1975) and increase turnover rate of hypothalamic catecholamines (Besedovsky et al., 1977, 1983). The increase in plasma corticosterone is probably caused by release of IL-1 from macrophages (Besedovsky et al., 1986), or possibly by another product of activated lymphocytes (Besedovsky et al., 1985), which augment synthesis of ACTH from both transformed (Woloski et al., 1985) and normal (Bernton et al., 1987) pituitary cells. The fact that other early investigations did not confirm that IL-1 is effective in increasing ACTH release from normal pituitary cells in vitro (Uehara et al., 1987a,b; Berkenbosch et al., 1987; Sapolsky et al., 1987), but recombinant IL-1 is effective in augmenting glucocorticoids in vivo (Besedovsky et al., 1986), suggests that another intermediate is involved in this postulated physiologic control loop. It has now been clearly shown that IL-1 can act at the level of the brain to augment the release of corticotropin-

releasing factor (Berkenbosch et al., 1987, Sapolsky et al., 1987, Uehara et al., 1987b), which in turn elevates plasma levels of ACTH and glucocorticoids (Krymskay et al., 1987). These novel findings have been discussed by Bateman et al. (1989). More recent data also suggest that proinflammatory cytokines can indeed act at the level of the pituitary gland (Combronero et al., 1992; reviewed by Harbuz and Lightman, 1992). Indeed, IL-1 receptors exist in the brain as well as the adenohypophysis (Takao et al., 1990; Haour et al., 1991, Ban et al., 1991; Bristulf et al., 1991; Cunningham et al., 1992; Parnet et al., 1993). IL-1 is a very potent molecule with a broad diversity of biological activities, including the regulation of nerve growth factor synthesis (Lindholm et al., 1987).

# Hormone synthesis by leukocytes

In 1982, Eric Smith and coworkers published an article which indicated that virus-infected splenocytes can synthesize and secrete an ACTH-like molecule, suggesting the exciting possibility of a lymphoid-adrenal axis. These workers offered further evidence for this possibility by showing that a virus infection elevated plasma glucocorticoids in hypophysectomized mice, which suggested that the leukocyte-derived ACTH was physiologically active in inducing the release and synthesis of adrenal corticosteroids. ACTH, as well as a number of other peptides, are derived from a large prohormone known as pro-opiomelanocortin (POMC). If this concept is true, one should be able to identify mRNA for ACTH in lymphoid cells infected with a virus, but not in control cells. To test this possibility, we isolated mRNA from murine splenocytes and hybridized it under high stringency conditions to a full-length cDNA for murine POMC (Westly et al., 1986). The positive control consisted of RNA from the ACTH-producing murine pituitary cell line, AtT-20. We detected positive hybridization with RNA isolated from pituitary and virus-infected lymphoid cells, but not from non-infected cells. Thus, it appears that splenocytes can be activated to express the POMC gene. If this mRNA is translated, processed and secreted by these cells, the possibility exists that all peptides derived from POMC, such as ACTH, MSH and β-endorphin, can be secreted by activated lymphoid cells. At least some POMC-derived peptides are secreted, as demonstrated by the finding that endotoxin stimulates lymphoid cells to synthesize and secrete authentic ACTH (residues 1-25; Smith et al., 1990). This leukocyte-derived POMC product is also regulated by corticotropin-releasing factor and arginine vasopression (Smith et al., 1986). The role of these POMC peptides in modulating lymphoid cell function is only beginning to be explored. Results by Dunn et al. (1987) have shown that virus infection elevates plasma corticosterone in normal mice but not in hypophysectomized mice, thus questioning the physiological significance of a lymphoid-adrenal axis. We favor the view that POMC peptides derived from cells of the immune system function to alter local

responses of regional lymphocytes, as supported by several recent findings.

It now appears that many of the peptides that were once thought to be secreted by only the neuroendocrine system can also be synthesized by cells of the immune system. For example, although several reports have suggested that prolactin is synthesized by murine leukocytes, neither the prolactin gene nor its product had been reported in human leukocytes. We used RT-PCR technology to search for prolactin gene transcripts in human peripheral blood mononuclear cells (Sabharwal et al., 1992). Synthetic oligomers consisting of 21 nucleotides were constructed that span exons 3 and 5 of the human prolactin gene. These primers amplify a 276 bp fragment that is digested by Ras 1 into two fragments of 116 and 160 bp. As shown in Figure 2A, appropriate size prolactin PCR products of 276 bp were generated from both human placenta and mononuclear cell RNA (lanes 3-6). The results also showed that two fragments of correct size were generated with the Rsa 1-digested PCR products (lanes 7-10). Southern blotting revealed that these cDNAs hybridized to a full-length human prolactin cDNA (Figure 2B). Other experiments by our collaborators at Ohio State University demonstrated that the prolactin protein was synthesized and secreted by human peripheral blood lymphocytes (Sabharwal et al., 1992).

Other hormones may also be produced by cells of the immune system, such as human chorionic gonadotropin, preproenkephalin, oxytocin, growth hormone and insulin-like growth factor-I (reviewed by Westly et al., 1987; Weigent and Blalock, 1987; Franklin and Kelley, 1988; Weigent et al., 1988; Kelley, 1989). Unpublished data from our laboratory using RT-PCR, solution hybridization-RNase protection assays and cloning and sequencing of the PCR cDNAs indicates that murine macrophages express bonafide transcripts for insulin-like growth factor-I (Arkins, University of Illinois Ph.D. dissertation, 1992). These cytokine-like hormones may modulate functional activities of lymphoid cells in three different ways: (a) autocrine mechanisms in which the hormones are intermediates within the same cell, (b) paracrine effects where the hormones affect nearby lymphoid cells and (c) endocrine effects mediated by the hormones acting at distant targets, such as the hypophysis. These possibilities are only now beginning to be understood.

# Cytokines as messenger molecules in health and disease

The concept that was originally suggested by Jerne (1974) and subsequently expanded by Blalock (1984a,b) was that products from leukocytes (now known as cytokines) can act as messengers to inform the brain that a foreign agent has entered the body. The pathogens that activate leukocytes cannot be recognized by the other classic sensory systems, such as those for sight, taste, touch, smell or sound. As such, these peptides might form

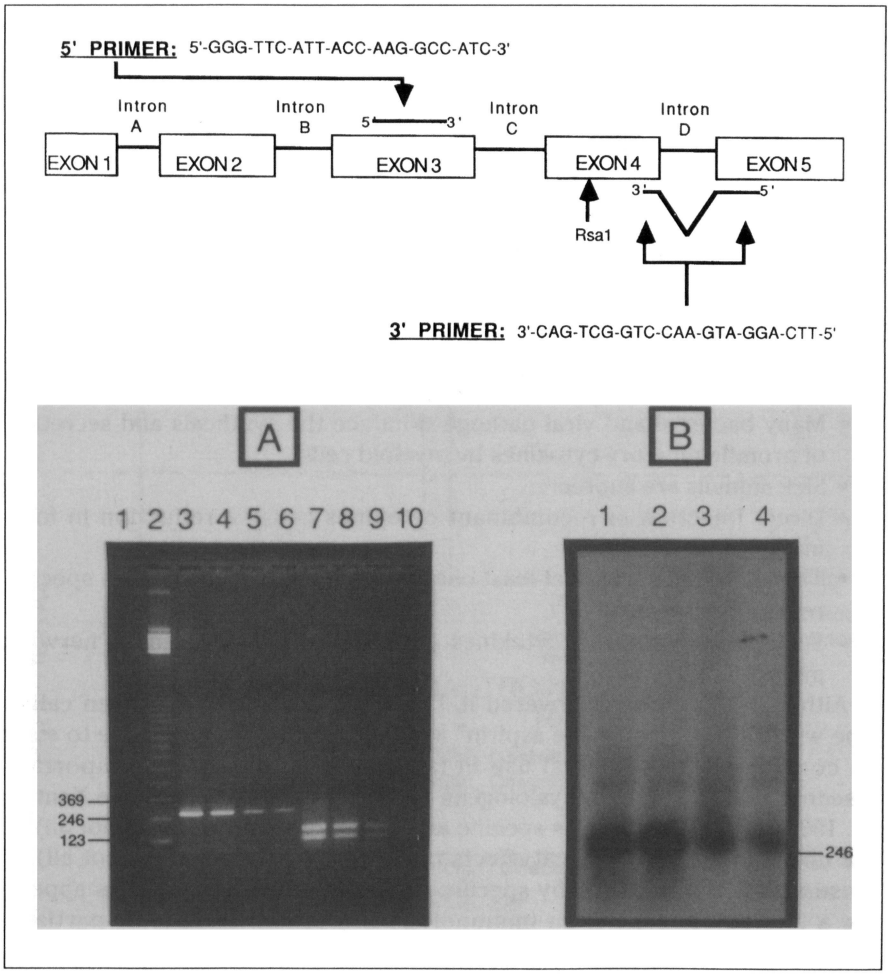


**Fig. 2 Human leukocytes express transcripts for prolactin, as assessed by polymerase chain reaction-amplified cDNA and visualized by both ethidium bromide staining (Fig. 2A) and Southern blotting (Fig. 2B). Lane 1, no cDNA template; lane 2, 123-bp molecular size marker; lane 3, placenta; lane 4, PBMCs from donor 1; lane 5, PBMCs from donor 2; lane 6, PBMCs (donor 2) stimulated with con A for 48 hr; lanes 7-10, Rsa I digestion of the PCR-amplified cDNA shown in lanes 3-6, respectively. (B) Southern blot of PCR-amplified prolactin products hybridized with a random-primer-labeled prolactin cDNA. Lane 1, placenta; lane 2, PBMCs from donor 1; lane 3, PBMCs from donor 2; lane 4, PBMCs (donor 2) stimulated with Con A for 48 hr. (from Sabharwal et al., 1992)**

part of a physiologic loop between the immune system and the brain. After induction of an immune response by antigen, leukocytes transmit signals not only to the many components of the immune system but also to the brain

and neuroendocrine organs. The signals involve cytokines and possibly classical hormonal proteins elaborated and released by immune cells. Within the central nervous system, these cytokines are probably responsible for the classic symptoms of sickness, including anorexia, somnia, fever, lack of motivation and general malaise (Dantzer and Kelley, 1989; Kent et al., 1992a). These "immunotransmitters" represent the afferent part of long-loop feedbacks regulating the immunologic apparatus via the hypothalamic-pituitary complex and the sympathetic branch of the autonomic nervous system.

The control of feed intake has long been studied by animal scientists because of its important role in controlling animal productivity, regardless of whether the animal of interest is a growing pig or a lactating dairy cow. The following facts offer strong support for an immunological mechanism at least partially determining why sick animals do not eat and therefore do not grow:

- Many bacterial and viral pathogens induce the synthesis and secretion of proinflammatory cytokines by myeloid cells
- Sick animals are anorectic
- Direct injection of recombinant cytokines cause a reduction in food intake
- The anorectic effect of at least one cytokine can be blocked be a specific receptor antagonist
- Specific receptors for cytokines are found within the central nervous system

Although the newly-discovered IL-1 receptor antagonist has been called "the world's most expensive aspirin" and is currently too expensive to even be considered for practical use in farm animals, it offers an important research tool to immunophysiologists and neuroscientists (e.g., see Kent et al., 1992a). The fact that this specific antagonist blocks many (but not all) of the non-specific physiological effects of IL-1, and that many (but not all) of these effects are mediated by specific receptors in the brain, makes appealing a unified concept of an immunological mechanism at least partially explaining why sick animals do not eat adequately (Figure 3). The fact that many of these cytokines, such as IL-1 and tumor necrosis factor-$\alpha$, directly and indirectly affect both glucose homeostasis, increase net protein oxidation, increase muscle proteolysis, elevate nitrogen excretion and increase net hepatic anabolism, offers further compelling evidence that helps to explain why sick animals do not grow (reviewed by Bistrian et al., 1992). Indeed, it is likely that cytokines, which are currently viewed as the major regulators of immune system activity, also regulate physiological processes such as food intake in healthy, non-infected animals as well as sick animals (Kennedy and Jones, 1991; Morganti-Kossmann et al., 1992). All of these hypotheses have been tested and generally found to be true in species such as mice, rats, rabbits and even humans. However, validating these concepts in domestic animals is only beginning, but all of these ideas have recently been shown to be true for the domestic chicken (Johnson et al., 1993 a,b). It is our task as scientists to design critical experiments to try to understand

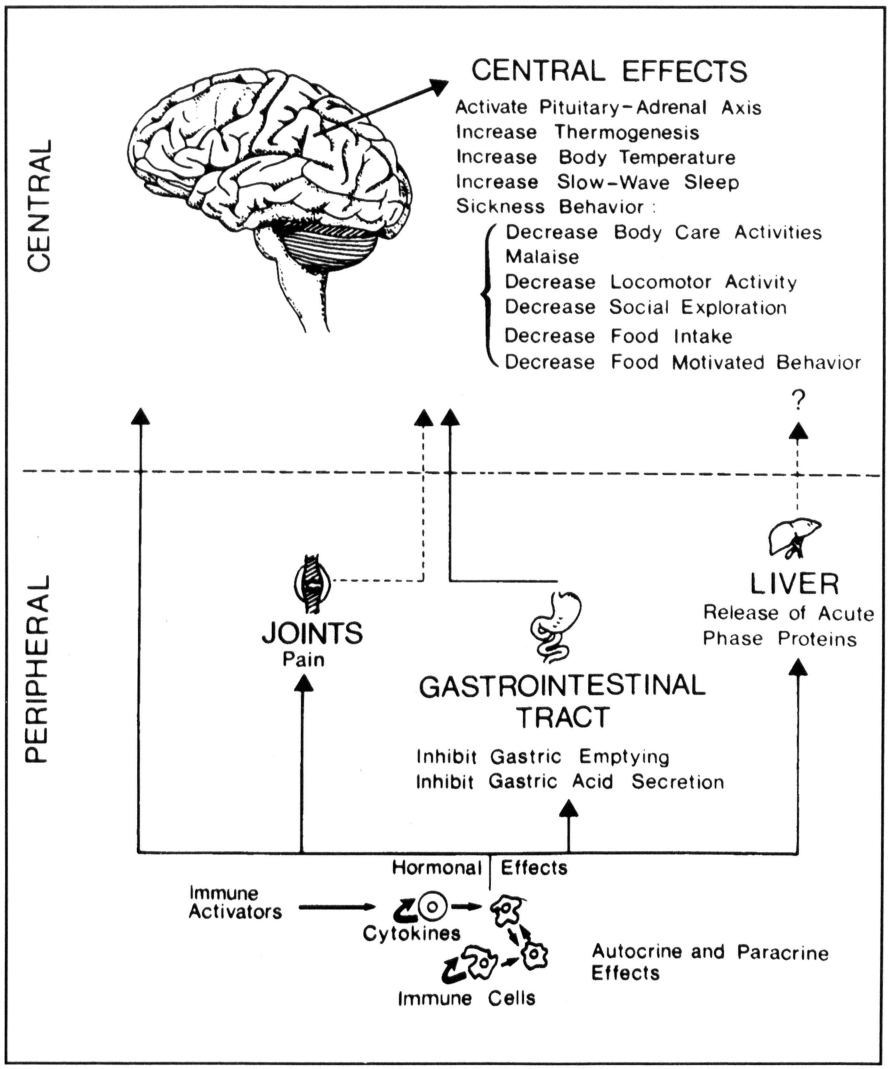


**Fig. 3. Cytokines reduce feed intake and cause many other physiological effects by interacting with specific receptors which are located in both the periphery and within the central nervous system. Central effects may be mediated by cytokines that originate outside the central nervous system or by cytokines that are synthesized by specific cells with the brain (e.g., microglia and neurons). (from Kent et al., 1992b)**

nature's way of integrating signals between the immune and central nervous systems in order for animals to maintain homeostasis in both normal and stressful situations.

# Conclusion

Our original concept, which is now supported by a large amount of experimental data, was that adverse stimuli that are encountered by livestock during their production affects susceptibility to infectious diseases by altering functional activities of cells within the immune system. Data have been presented to support the postulate that changes in lymphoid cell activities are caused by hormones that are secreted in response to acute stressors, such as glucocorticoids, catecholamines and β-endorphin. The implication of these findings has recently been expanded by development of the idea that some hormones suppress while other hormones augment T cell responses. Indeed, some classic, growth-promoting pituitary hormones are synthesized by lymphoid cells. Furthermore, certain cytokines that are produced by leukocytes are responsible for the classic signs of sickness in animals, including the economically-important trait of reduced food consumption.

These findings suggest that there is an intricate and important communication network between the immune and central nervous systems. As advances are made on the fundamental understanding of cells within both of these systems, a clearer picture will emerge on regulation of this communication network. Before such progress can be applied to animal production, much more must be learned about the fundamental immunology of domestic animals. Advances that have already been made in understanding cross-talk between the immune and endocrine systems have provided a new and fascinating picture, as well as a more realistic view, of the complex physiological regulatory networks that animals use to maintain homeostasis.

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## Memberships

American Association of Immunologists, American Association for the Advancement of Science, American Association of Veterinary Immunologists, Society for Leukocyte Biology, International Society of Neuroimmunomodulation, Society for Experimental Biology and Medicine, American Society of Animal Science

## Other Activities

NIH Ad Hoc Reviewer Neurology (1987); Experimental Immunology (1988); Allergy and Immunology (1991); Biological and Clinical Aging (1992); NIH Site Visit Team for NIA at Cornell Medical College (1990) and NYU Medical Center (1992); NIMH Psychopathology and Clinical Biology Review Committee (1988); USDA Competitive Biotechnology Grants Study Section 1986, 1987; Program Manager in 1988; Advisory Committee for 8th International Congress of Immunology, Budapest, Hungary (1992); Interdepartmental Immunology Seminar Series at UIUC (Chairman, 1986-); Major Professor for 26 M.S. and Ph.D. students; Editorial Boards (*Progress in NeuroEndocrinImmunology* (1988-1992); *Brain, Behavior and Immunity* (1990-1993);

*Animal Biotechnology* (1989-)).

## Publications:

Author and/or Co-author of 101 articles in peer-reviewed journals, 30 book chapters, 2 bulletins and technical reports, 16 proceedings of presented papers, 25 extension publications, and 117 abstracts.

## Representative Recent Peer-Reviewed Publications:


Parnet, P., D.L. Brunke, E. Goujon, J. D. Mainard, A. Biragyn, S. Arkins, R. Dantzer, K. W. Kelley, 1993. Molecular identification of two types of IL-1 receptors in the murine pituitary gland. *J. Neuroendocrinology*:(In Press).

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