MINIREVIEW

Prolactin and Growth Hormone in the Regulation of the Immune System (43286B)

RICHARD R. GALA[1]
Department of Physiology, Wayne State University School of Medicine, Detroit, Michigan 48201

Abstract. **Evidence implicating prolactin (PRL) and growth hormone (GH) in the regulation of the immune system has been reviewed. Hypophysectomized animals have deficiencies in both cell-mediated and humoral immunological functions and either PRL or GH corrects these deficiencies. Animals administered bromocryptine, a drug that specifically blocks PRL release, have impaired immune responses similar to hypophysectomized animals, and again both PRL and GH correct these deficiencies. Genetically dwarf animals, which lack both PRL and GH, are also immunocompromised, and once again PRL and GH can correct the deficiencies. In dwarf animals, however, fewer studies have examined PRL actions. In growth-deficient children, immune function is not dramatically altered and basal secretion of GH has been reported. Very few clinical studies have examined whether PRL secretion is also deficient, and this may explain why a clear loss in immune function is not evident in growth-deficient children. In a number of species, including man, both PRL and GH stimulate thymic function and increase the secretion of thymulin, a thymic hormone. No studies, however, have reported on the effects of PRL and GH on other thymic hormones. A number of studies have reported *in vitro* effects of PRL and GH on cells involved with immunity, and the presence of high-affinity PRL and GH receptors have been observed on a number of these cells. The action of GH on the proliferative response of cells involved with immunity *in vitro* appears to be mediated by the production of insulin-like growth factor I. The effect of PRL on insulin-like growth factor I production by these cells has not been examined. One of the most consistent findings from *in vitro* studies is that prolactin antisera blocked a number of immune reactions. This led to the discovery that cells involved with immunity appear capable of producing PRL and GH, but the physiological significance of these observations have not been explored. There is a great need to identify the cell types responding to PRL and GH and this should be a goal of future investigations. There is also a need for investigators to be aware that both PRL and GH are involved in the regulation of the immune system and to design experiments to elucidate where each functions in the maturation cascade of cells involved with immunity. From the evidence available, it is apparent that PRL and GH have an important function in the immune system and future investigations should be directed toward elucidating their site(s) of action.**

[P.S.E.B.M. 1991, Vol 198]

It is becoming more and more apparent that the endocrine system plays a significant role in the regulation of the immune system. Many years ago, it was observed that adrenal cortical secretions suppress the function of the immune system. Synthetic glucocorticoids have been developed and used for the treatment of autoimmune diseases and tissue transplantation (1). In addition, a number of autoimmune diseases, such as systemic lupus erythematosus, Hashimoto's thyroiditis, and rheumatoid arthritis, to name but a few, are more prevalent in women than in men, suggesting a sex hormone modulation of the immune system (2). The immune system also influences the endocrine system, since individuals lacking a thymus

[1] To whom requests for reprints should be addressed at Department of Physiology, Wayne State University School of Medicine, Detroit, MI 48201.

0037-9727/91/1981-0513$3.00/0

have a number of endocrine imbalances, especially of those hormones involved in reproduction (3, 4). Stress, whether induced by disease or emotional or physical conditions, activates the endocrine system and modulates the immune system (5). The major hormones of stress involved in immunomodulation are glucocorticoids, prolactin (PRL), and growth hormone (GH; 1, 6, 7). While glucocorticoids are well-known to suppress the immune system, PRL and GH are believed to be involved in stimulating it (8, 9). The involvement of anterior pituitary hormones with the immune system had its beginnings from observations in hypophysectomized animals and in animals and humans with deficiencies in anterior pituitary hormones (10). The purpose of this review is to examine the literature implicating PRL and GH in immunocompetence to determine whether they are indeed significant factors in immune regulation and to indicate areas of future investigation.

Anterior Pituitary Hypofunction

Animal Studies. One of the earliest known indications that pituitary hormones regulate the immune system stems from P. E. Smith's (11) original observations that in hypophysectomized (hypox) rats, the thymus gland is atrophic. This initial observation was confirmed by others (12) and was extended to include other alterations in immune function. Hypophysectomized rats and mice were shown to exhibit decreased antibody response (13, 14), a prolongation of graft survival (15), a decrease in lymphocyte proliferation to dinitrochlorobenzene (16), a reduction in spleen natural killer (NK) cell activity (17, 18), and an inability to develop adjuvant arthritis (19). In addition, hypox rats exposed to sublethal irradiation were defective in the recovery of leukocyte count, antibody formation, and skin allograft rejection (20). Nagy and Berczi (21) observed marked decreases in antibody production to sheep red blood cells (RBC), skin contact sensitivity to dinitrochlorobenzene, and adjuvant arthritis, as well as an increase in skin allograft survival, in the hypox rat, thus confirming earlier observations. The above responses represent defects in both humoral and cell-mediated immunity in the hypox animal.

Other evidence implicating anterior pituitary hormones in the regulation of immunity came from studies using dwarf animals. The Snell (also known as Snell-Bagg) and the Ames mouse strains have a recessive gene (Snell, *dw*; Ames, *df*) that, when homozygous, produces the dwarf phenotype. The primary defect of these mice is that no acidophils can be identified in the anterior pituitary (22). It is commonly believed that these animals are completely deficient in GH (23), but in fact they also lack PRL (24). Early studies with the Snell strain of dwarf mouse showed the thymus and peripheral lymphoid organs to be atrophied and there was a cellular depletion of the bone marrow (25, 26). Immunological defects include a depressed primary (IgM), but not secondary (IgG), antibody response to sheep RBC, a decrease in graft versus host (GVH) reactivity, a decrease in the number of splenic T and B lymphocytes, and a prolonged survival of skin grafts (27, 28). Studies of the Ames dwarf mouse resulted in similar observations: involution of the thymus and lymphopenia of peripheral lymphoid tissue, a delay in production of IgM and IgG antibodies to sheep RBC, and a decrease in GVH reactivity of spleen cells (29). There also exists a strain of dwarf dogs. The offspring of inbred Weimaraner dogs have retarded growth, a small thymus, an absence of a thymic cortex, and a deficiency in lymphocytic response to phytohemagglutinin (PHA), whereas antibody titers to heat-killed *Brucella abortus* were normal (30, 31). Although basal plasma GH was normal, clonidine-induced GH release was markedly decreased; the status of other pituitary hormones was not examined (30).

A selective PRL deficiency can be induced by the administration of a potent dopaminergic D_2-stimulating drug 2-bromo-α-ergokryptin (CB-154; 32). The administration of CB-154 to rats on the day of kidney allografts did not alter survival; however, CB-154 administered with a dose of cyclosporine that by itself had no effect resulted in 100% of the animals (5 of 5) accepting the allograft (33). These investigators further reported that CB-154 alone could prevent the GVH reaction, as evidenced by lymph node weight, and that CB-154 and cyclosporine together had an additive effect on preventing the response. Other workers noted that CB-154 administered 5 days before immunization and continued for the duration of the experiment decreased the incidence of experimental autoimmune uveitis in the Lewis rat and lowered antibody titers (34). Low-dose cyclosporine combined with CB-154 induced a greater degree of suppression of both parameters than when either drug was given separately. A subsequent report indicated that the severity of established collagen-induced arthritis in mice was reduced by 50% after the injection of CB-154 (35). Examining adjuvant-induced arthritis in rats, Neidhart (36) reported that CB-154 administered 3 days before adjuvant injection induced a 70% reduction in hind-limb swelling. He further observed that injection of the Freund's complete adjuvant increased plasma PRL by 150% and increased ornithine decarboxylase activity (an indication of proliferation) in the bone marrow, thymus, spleen, and lymph nodes; CB-154 administration prevented all these responses. Bromocryptine administration to mice has also been reported to decrease antibody production to sheep RBC (37).

Thus, a number of animal models indicate that pituitary hypofunction can compromise the immune system.

Clinical Studies. To my knowledge, there have been no published studies in primates (monkey or human) in which the immune system has been examined after hypophysectomy. It is hoped that this void will soon be alleviated, since hypophysectomy is being performed routinely by a number of clinical investigative teams. A number of clinical studies, however, have examined the immune system in situations in which pituitary dwarfism was the major clinical finding.

Pituitary dwarf children were reported to have a normal proportion of peripheral 9.6^+ T cells, an increase in B cells, no change in $CD4^+$ T helper cells (but an increase in $CD8^+$ cytotoxic T suppressor cells, resulting in a lower CD4 to CD8 ratio), a decrease in NK cells (null cells), a subnormal response in the mixed lymphocyte reaction, a slightly higher suppressor cell activity after concanavalin A (Con A) stimulation, and no alteration in the PHA proliferation response (38). Other investigators found that dwarf children in their studies had normal IgM, IgA, and IgG levels, normal PHA responses, normal T and E rosette formation, and normal delayed hypersensitivity skin tests (cell-mediated immunity) to a variety of agents (39). Still others found normal proportions of B, T helper, and T suppressor cells, but a significant depression in PHA-induced lymphocyte proliferation, in their populations of dwarf children when compared with normal children (40, 41). Kiess and co-workers (42, 43) reported no change in the proportion of T helper and suppressor cells, B cells, and monocytes identified by monoclonal cell markers, but a decrease in the number and activity of NK cells. A similar decrease in NK cell activity in GH-impaired women and GH-deficient children has been reported by others (44–46). In all of these studies, a complete evaluation of pituitary hormones was not performed (in no case was PRL evaluated), and in those studies in which GH values were reported, basal levels were usually within the normal range, but provocative tests were subnormal. In one group, a hypothalamic origin of dwarfism was confirmed when the sample population did not respond to provocative GH tests, but did respond to GH-releasing factor (42, 43). In all but one report (39), there was little constant indication of immunological malfunction, except for a decrease in NK cell number and/or function. A number of the above investigators reported no increased incidence of infections in their patient population (39, 40).

The clinical studies to date do not offer strong support for a pituitary involvement in immune function; however, there is a great need for clinical studies in which the hypopituitary patient population is carefully selected and evaluated for anterior pituitary function, i.e., both GH and PRL levels after provocative tests.

Hormone Replacement in Anterior Pituitary Hypofunction

Animal Studies. Hypophysectomy in rodents results in a marked suppression of immune function. Berczi *et al.* (47) reported that anterior pituitary transplantation to the kidney capsule restored the production of IgG and IgM antibodies when hypox rats were injected with sheep RBC (humoral immunity). The transplanted pituitary produced large amounts of PRL, while all other pituitary hormones underwent a marked decrease in secretion (48). The administration of 40 μg/day of bovine PRL considerably improved the response in hypox rats, while the response to 100 μg/day was similar to that of intact animals (47). Bovine GH ranging between 24 and 120 μg/day gave a partial improvement in antibody production, a response noted earlier (49), and ACTH administration suppressed the response in anterior pituitary-transplanted and PRL- and GH-injected animals (47). Subsequent work (50) indicated that either anterior pituitary transplants or the daily injection of 40 μg of bovine PRL could markedly correct the adjuvant arthritis response in male and female hypox rats (humoral immunity). It was further observed that the administration of CB-154, a potent suppressor of PRL release (32), to intact animals suppressed the adjuvant arthritis response comparable to that observed in hypox animals. An additional report indicated the CB-154 was as effective as hypophysectomy in blocking contact sensitivity induced by dinitrochlorobenzene (cellular immunity) and that either anterior pituitary grafts or 40 μg of bovine PRL completely reversed the blockade (51). A subsequent report evaluated the specificity of PRL in the induction of contact sensitivity in the hypox rat and found that 40 μg of bovine GH was as effective as PRL. It was further observed that 40 μg of ACTH, human chorionic gonadotropin, thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) either alone or in combination, did not alter the response of the hypox rat (52). With evidence that GH was as effective as PRL in reestablishing contact sensitivity in hypox animals, Berczi and co-workers reevaluated the specificity of PRL on other immune responses. Antibody formation to sheep RBC and the development of contact sensitivity in response to dinitrochlorobenzene were restored in hypox rats by the injection of 40 μg/day of rat PRL or GH, bovine PRL or GH, human GH, or placental lactogen (53). In a subsequent paper, adjuvant arthritis in hypox rats or CB-154-injected intact rats was restored with 100–200 μg/kg of either bovine PRL or GH, while ACTH had no effect alone and, when given together with PRL and GH, it inhibited their action (54). The anemia, leukopenia, and thrombocytopenia observed for hypox rats were corrected by anterior pituitary transplants or 40 μg/day of either bovine PRL or GH (55). It was further

shown that a specific antiserum to rat PRL partially blocked the effect of anterior pituitary transplants, but not bovine PRL or GH, in correcting bone marrow function in hypox animals.

The decrease in NK cells in hypox mice was partially prevented by the injection of 100 μg/day of ovine GH; no other hormones were examined (17). Macrophages isolated from the peritoneal cavity of hypox rats showed a marked decrease in tumor necrosis factor α (TNF-α) production, and the exogenous administration of 96 μg/day of rat GH or 48 μg/day of porcine GH partially (54%) restored production (56). Edwards *et al.* (56) further showed that an antiserum to TNF-α administered to hypox rats along with GH could block macrophage cytotoxicity, suggesting that the *in vivo*, induced GH stimulation of macrophage cytotoxicity was due to the production of TNF-α.

Mice administered CB-154 had a suppressed GVH reaction as evidenced by spleen weights, and a prolactin-releasing drug, Sandoz 25-240, returned the response to control values (57). Bromocryptine administration to mice blocked the tumoricidal effects of macrophages during infection with *Mycobacterium bovis* and *Listeria monocytogenes*, and 100–200 μg of ovine PRL corrected the response (58). Bernton *et al.* (58) further demonstrated that the suppressed Con A-, PHA-, and lipopolysaccharide (LPS)-induced proliferation of splenocytes from CB-154-injected mice could be partially restored by the injection of 20 μg of mouse PRL or 100 μg of ovine PRL. They (58) further reported that the suppressed production of γ-interferon by splenocytes from CB-154-treated animals was completely restored by administration of 100 μg of ovine PRL. Neither study (57, 58) examined the effect of GH administration.

These studies indicated that PRL and GH isolated from a number of species were capable of restoring both humoral and cellular immune responses in hypox animals. In addition, the studies indicated that CB-154 was capable of blocking immune responses comparable to that of hypophysectomy and that immune responses could be restored by either PRL or GH when both were examined.

Studies in dwarf animals also provided evidence of pituitary hormone involvement with immunity. In the Snell dwarf mouse, either 100 μg/day of bovine GH or 2.5 μg/day of thyroxine were observed to increase thymus and spleen weights, to restore the histological structure of the thymus and spleen, and to increase antibody production to sheep RBC similar to that of the normal mouse (59). In a subsequent publication, Fabris *et al.* (60) extended their observations and noted that either 250 μg of bovine GH or PRL or 2.5 μg of thyroxine were equally effective in correcting the deficiency in peripheral lymphocytes, in antibody production, and in skin rejection in the Snell dwarf mouse. In addition, the effects of GH administration were not observed if the animals had been thymectomized (PRL was not examined), suggesting that GH acts through the thymus. Fabris *et al.* (60) further suggested that thyroxine may act by stimulating endogenous GH production and synergizing with it in the immune system. This does not seem possible, because the Snell dwarf mouse pituitary does not produce GH unless the cells involved with immunity produce GH (see Prolactin and Growth Hormone Production by Cells Involved with Immunity). The thyroxine issue in the dwarf mouse is still not resolved. In the Weimaraner dwarf dog, the injection of 100 μg/kg of bovine GH resulted in clinical improvement in the wasting syndrome and a marked increase in the thickness and cellularity of the cortex of the thymus, but no consistent blastogenic response to PHA, Con A, or pokeweed mitogen was observed (31).

Studies with dwarf animals provide some evidence that PRL and GH can improve immunological deficiencies, but addition studies with these animal models are greatly needed. The lack of an effect of GH in thymectomized mice (60) and of PRL and GH in the nude rat, a rat strain that lacks a thymus (61), suggests that the thymus may be one site of action of these hormones.

Clinical Studies. In GH-deficient children, most investigators indicated that some GH could be detected in the serum of children, but that the increase induced by provocative tests was considerably below normal. In all cases, human (h) GH administration improved the growth characteristics of their sample population. Although the PHA response in hGH deficient children was in the normal range, the administration of hGH for 9 to 12 months resulted in a significant increase in response (39). T and E rosette levels, immunoglobulin concentration, and hypersensitivity to skin tests were not altered by GH therapy. Human growth hormone obtained from natural sources (anterior pituitary extraction) when given to growth-deficient children for 12 to 16 months resulted in a decrease in the ratio of $CD4^+$ helper to $CD8^+$ cytoxic/suppressor T cells and in the PHA proliferative response (40). The decrease in the T cell ratio was related to both an increase in $CD8^+$ T cells and a decrease in $CD8^+$ T cells. Naturally derived hGH may contain the Creutzfeldt-Jakob virus (62), and what effect this virus has on immune response is unknown. Rapaport *et al.* (41), again using naturally derived hGH, found a diminished response to PHA and a decrease in the percentage of $CD19^+$ B cells in both GH-deficient and normal children. Kiess and coworkers found a decrease in NK cell activity in their population of GH-deficient children, and 3 weeks of GH-releasing hormone and/or 6 weeks of recombinant hGH administration did not alter the activity of these cells (43). The administration of biosynthetic hGH to

GH-impaired women for 10 to 17 days (44) and to GH-deficient children for 3 months to 3 years (45, 46) was reported to significantly increase NK cell activity. Neither hGH nor insulin-like growth factor I (IGF-I) had any effect on NK cell activity when added *in vitro* (46). In addition, Matsura *et al.* (46) reported an increase in lymphocyte blastogenesis to PHA and Con A and an increase in NK activity after only 14 days of biosynthetic hGH administration (46). Thus, it appears that hGH is capable of increasing the depressed NK cell activity of GH-impaired individuals, but is not effective when added directly to cell cultures.

There have been no studies, to my knowledge, that have examined the effect of exogenous PRL administration on the immune system in a clinical setting. However, in four patients with hyperprolactinemia and normal ovarian function, Vidaller *et al.* (63) observed a decreased proliferative response of peripheral mononuclear cells when exposed to Con A, pokeweed mitogen, and PHA. These cells also had a decreased production of interleukin 2. The administration of CB-154 returned the responses to near normal levels. Others noted that some patients with hyperprolactinemia had chronic recurrent iridocyclitis autoimmune disease and that treatment with CB-154 prevented the recurrence of the disease (64). In both of these studies, plasma GH levels were not determined, and, in many incidences of hyperprolactinemia, elevated GH may also occur (65). In clinical conditions in which both PRL and GH secretion are elevated, the specificity of CB-154 to block PRL secretion is lost and both hormones are suppressed by the drug (66). Thus, it is difficult to ascribe the immunological changes observed in patients with hyperprolactinemia to prolactin.

Thymus and Its Secretions

One of the most consistent observations of pituitary hypofunction is a decrease in thymus weight and function. The thymus gland has been suspected for many years to have an endocrine function, and early studies indicated that extracts of the thymus could improve immune function in hypox and thymectomized animals (67–69). The improvement of immune functions by anterior pituitary hormones, however, did not occur in thymectomized animals and in nude animals that genetically lack a thymus (60, 61). Thus, it is of importance to determine the effect of PRL and GH on the secretions of the thymus.

A number of thymic factors have been described that influence immune function (70). Only a few of them have been isolated chemically and elucidated structurally. Thymopoietin (70), a polypeptide originally called thymin, has a mol wt of 5500 and consists of 49 amino acids. A peptide composed of amino acids 32 through 36 of thymopoietin has been synthesized. It has activity similar to native thymopoietin and is called thymopoietin pentapeptide. Thymopoietin pentapeptide, however, cannot restore thymus-dependent immunocompetence in neonatally thymectomized mice and appears to induce differentiation at the prethymocyte level.

Thymosin is another peptide system isolated from the thymus (71). Thymosin fraction 5, the end point of a purification process, contains 10 to 15 major components, and one active peptide isolated is called thymosin α_1. This peptide is an acidic molecule containing 28 amino acids with a mol wt of 3107. It has been synthesized by recombinant techniques. It is not a complete substitute for the thymus, but it acts on T cells to stimulate the production of a macrophage-inhibiting factor and it increases the production of antibody-forming cells, restores terminal deoxynucleotide transferase activity in bone marrow cells, and causes maturation of T cells that in turn produce lymphokines. There is no species specificity in its response; it is found in the circulation of species ranging from the chicken to the human and is absent in circulation in individuals lacking a thymus.

Another peptide found in thymosin fraction 5 is thymulin (72). It was originally isolated and chemically elucidated from pig serum using the rosette assay and was called serum thymic factor. It consists of nine amino acids, has a mol wt of 922, and has been synthesized by recombinant techniques. It exists in both a biologically active and inactive form. The active molecule contains zinc and zinc is an absolute requirement for biological activity. Thymulin has no species specificity in its action and is found in the circulation of a wide range of species, provided the thymus gland is present. It is synthesized by thymic epithelial cells. Thymulin induces Thy-1 and Lyt-2 (CD8) antigens on the surface of mouse lymphocytes. In addition, it stimulates terminal deoxynucleotide transferase activity in bone marrow cells, enhances T cell-mediated cytotoxicity and delayed-type hypersensitivity to dinitrofluorobenzene in thymectomized mice, delays allogenic skin graft rejection, and stimulates interleukin (IL) 2 production by thymocytes or nude mouse spleen cells. At low doses it appears to have a helper effect on the immune system, whereas at high doses it appears to have a suppressor effect.

Effect of Pituitary Hormones on Thymic Secretions

Evidence for an effect of PRL and GH on thymic hormone secretion is not extensive at present. An early study indicated that bovine GH, but not LH or TSH, administered to hypox rats could induce DNA synthesis in the cortical and medullary regions of the thymus (49). Goff and associates (73) reported that the administration of bovine GH to dogs improved the morphological characteristics of the thymus and increased plasma thymulin levels in both middle-aged and old

dogs. In a subsequent study, these investigators attempted to chronically increase thymulin secretion by feeding clonidine, a GH secretogogue, and although they noted an increase in lymphocyte blastogenesis to standard mitogens, neither plasma GH nor thymulin was increased at the end of the 30-day trial (74). In an extensive investigation, Dardenne and colleagues (75) examined the influence of PRL on thymulin secretion. They reported that 50 or 100 μg/day of ovine PRL given to intact, but not thymectomized, mice markedly increased circulating thymulin within 2 days and induced an increase in thymulin-containing cells in the thymus when examined 2 weeks after injection. They further noted that the decrease in plasma thymulin in aged and Snell dwarf mice noted previously (76, 77) was increased to normal adult levels after 20 days of 100 μg of ovine PRL administration per day. Bromocryptine administration significantly decreased plasma thymulin and 100 μg of ovine PRL returned the level to control values. In human and murine thymus epithelial cell lines, hPRL stimulated thymulin production and thymic cell proliferation in a dose-dependent manner and the response was blocked by the addition of a specific PRL antiserum. In addition, Dardenne and colleagues reported that hGH (which has PRL activity inherent in its molecule), but not rat or bovine GH, administration could stimulate thymulin production and cell proliferation, thus verifying the responses as specific for PRL. They further reported that specific PRL receptors were present on thymic epithelial cells, although no data were presented for this statement. This extensive investigation established that PRL could specifically stimulate the secretion of thymulin. A subsequent clinical investigation reported that plasma thymulin was increased in patients with hyperprolactinemia and/or acromegaly and that the level of plasma thymulin was correlated with the level of IGF-I and not with the level of GH or PRL (78). They also noted that IGF-I could directly stimulate thymulin production from thymic epithelial cell lines. Mocchegiani *et al.* (79) reported recently that plasma thymulin levels were decreased in GH-deficient boys and that a single injection of hGH increased plasma thymulin levels to near normal values 48 hr after administration. Both basal and thyrotropin-releasing hormone-stimulated plasma TSH and PRL levels were normal, confirming a specific GH deficiency in their subjects. Furthermore, they confirmed that plasma thymulin levels were correlated with plasma IGF-I levels and not with plasma GH, PRL, or thyroid hormone levels. The influence of PRL and GH on the secretion of other thymic hormones, to my knowledge, has not been examined and indicates an area of much needed careful investigation.

Direct Actions of Pituitary Hormones on Cells Involved with Immunity

Much evidence exists that PRL and GH have effects on the immune system, but what is the evidence that they directly effect immune cell function? There are a number of reports indicating that cells involved with immunity have GH and PRL receptors.

Growth Hormone Receptors. An initial report indicated that lymphocytes in culture have high-affinity receptors for hGH and that ovine PRL and human placenta lactogen at high levels (10–50 μg/ml) could partially displace hGH (80). It was also observed that bovine, porcine, and rat GH, as well as bovine TSH, had no effect. Others observed high-affinity receptors to bovine GH on lymphocytes isolated from calf and mouse thymus and lymph nodes, and that bovine PRL (2 μg/ml) had no effect in displacing GH binding (81). This investigator further calculated approximately 10,000–20,000 GH-binding sites/cell. Lymphocytes isolated from human peripheral blood also showed high-affinity hGH binding that was partially displaced by 50 μg/ml of bovine and ovine GH; lactogenic hormones were not evaluated (82). A lymphocyte cell line, IM-9, which was derived from the bone marrow cells of a patient with chronic myelogenous leukemia (a B cell line), also has been shown to have high-affinity receptors for hGH that could not be displaced by ovine, porcine, and bovine GH (1 μg/ml); again, lactogenic hormones were not examined (83). Lesniak *et al.* (83) calculated that the IM-9 B cell line had 4,000 GH-binding sites/cell. Kiess and Butenandt (84) isolated peripheral mononuclear cells from human blood and observed that freshly isolated cells had low binding activity to hGH, but if allowed to condition for 8 to 24 hr at 20°C in a Tris buffer, the binding greatly increased. The binding of hGH to conditioned cells was of high affinity (10^{-9} *M*), but ovine PRL at a level of 200 ng/ml could displace about 50% of the binding activity of hGH. Kiess and Butenandt calculated that their conditioned cells had 7,000 hGH-binding sites/cell. Others observed that lymphocytes isolated from growth-deficient children had low initial binding to hGH, but 2 ½ hr after hGH treatment, a 4-fold increase in binding sites was evident (85). Thus, a number of investigators reported that lymphocytes had high-affinity GH-binding sites and that PRL at high concentrations could partially displace GH.

Prolactin Receptors. Efforts by Berczi and co-workers (53) to identify PRL-binding sites on lymphocytes isolated from rat thymus, spleen, and lymph nodes were negative and supported the immunocytochemical studies of others (86). Russell and co-workers (87), however, isolated monocytes and T and B lymphocytes from human blood and showed high-affinity specific binding to rat PRL (87). They further indicated that 10^{-6} *M* ovine GH, insulin, or epidermal growth factor did not alter PRL binding. T and B lymphocytes had a comparable number of PRL-binding sites, which they calculated to be 360 per cell, while binding sites on monocytes were one third that of lymphocytes. In a

subsequent study, Russell *et al.* (88) isolated T and B lymphocytes from the human spleen and reported the presence of high-affinity PRL-binding sites, again using rat PRL. High-affinity PRL-binding sites were also observed on peripheral monocytes and on four cell lines involved with immunity of human and mouse origin. Others confirmed the presence of high-affinity PRL-binding sites on human peripheral lymphocytes using hPRL and also showed similar receptors on erythrocytes (89). Ovine PRL and hGH were equally able to displace hPRL binding, whereas ovine GH was much less effective; insulin and rat FSH had no effect. There appears to be no published data that support specific PRL receptors on normal lymphoid cells from rats or mice; however, a tumor lymphoid cell line, Nb2, which was cloned from a rat lymphoma, has high-affinity PRL receptors (90, 91). Shiu and co-workers (92) identified high-affinity PRL receptors on Nb2 lymphoma cells using hPRL and showed that ovine PRL, hGH, and human placental lactogen were equally effective in displacing hPRL from the receptor; ovine GH, hLH, and bovine insulin had no effect. They calculated that there are approximately 12,000 PRL-binding sites/cell.

Direct Prolactin Effects. Although the detection of specific receptors for PRL on normal cells involved with immunity in rats and mice has not been reported, there are some reports suggesting that PRL has biochemical effects on these cells *in vitro*. Russell and coworkers (87) were the first to show that PRL could stimulate cells involved with immunity *in vitro* when they observed that rat PRL at 10^{-10} *M* was capable of increasing ornithine decarboxylase activity in human peripheral white blood cells. They further showed, using Nb2 lymphoma cells, that ornithine decarboxylase activity and thymidine incorporation were markedly increased when low doses of ovine PRL (10 ng/ml) were added to the culture medium (93). Others, on the other hand, observed a suppression of the incorporation of thymidine in the mouse mixed lymphocyte reaction when PRL from a number of species was added to the medium; only rat PRL at high levels (0.2–1 μg/ml) stimulated the reaction (57). Natural killer cells, morphologically defined as large granular lymphocytes (CD16), were isolated from human blood and cultured in serum-supplemented medium containing PRL (species not reported; 94). The cytotoxic activity of these cells was increased with 12 and 25 ng/ml of PRL, whereas higher levels (50–200 ng/ml) were not effective. Cell proliferation was initiated only with 50 ng/ml. When the NK cells were not separated from other mononuclear blood cells, no effect of PRL was observed, suggesting a suppressor action in mixed cell cultures. Splenocytes and thymocytes isolated from 1- to 6-week-old chickens and cultured in serum-free medium incorporated [^{3}H]thymidine when exposed to 2.4 and 24 ng/ml of bovine PRL for 66 hr (95). The proliferative response of mouse spleen cells cultured in Hanks' balanced salt solution and exposed to Con A, but not LPS, was significantly potentiated by 0.2 to 200 ng/ml of bovine PRL (37), although a dose-response curve was not evident and PRL alone gave no response. Spangelo *et al.* (37) stated that an initial experiment with mouse PRL gave similar results, but they showed no data to support this statement.

Except for Nb2 cells, it has been difficult to consistently demonstrate PRL effects on immune function *in vitro*. In studies designed to evaluate the *in vitro* effects of PRL on mouse and rat lymphocyte proliferation in either serum-supplemented or serum-free medium, little to no effects were observed (96). A recent report, however, observed that if lymphocytes were isolated from the spleens or lymph nodes of ovariectomized rats, high levels of rat PRL (0.3–5 μg/ml) could induce proliferation, whereas rat GH could not (97). The addition of IL-2 and PRL to the culture medium markedly increased the proliferative response above either peptide alone. Splenocytes isolated from intact male or female animals or thymocytes from ovariectomized animals were unresponsive to rat PRL, but splenocytes from female rats obtained during the diestrus phase of the estrous cycle were responsive to PRL at a high concentration (1 μg/ml). Mukherjee *et al.* (97) suggested that PRL induced IL-2 receptor expression in their cultured splenocytes, which they verified using a monoclonal antibody (OX39) for the IL-2 receptor and flow cytometric analysis. In addition, they also reported an increase in $CD5^+$ and $CD8^+$ T cell subsets, but not in $CD4^+$. This extensive publication indicated that the key to observing a PRL response with cells involved with immunity *in vitro* is the removal of estrogen from the animals; however, the high level of homologous PRL (1 μg/ml) required to obtain responses in the ovariectomized animals opens to question the exact physiological relevance of these observations.

Direct Growth Hormone Effects. The evidence that cells involved with immunity have specific receptors for GH is supported by biochemical data from *in vitro* studies. When nucleated bone marrow cells from the mouse and humans were cultured in medium supplemented with 30% fetal calf serum and colony-forming factor (erythropoietin), 50–100 ng of bovine GH (in mouse cultures) or 25–100 ng of hGH (in human cultures) significantly stimulated erythroid colony formation (98). No effect of GH was observed in the absence of erythropoietin. Porcine PRL added to mouse cultures (at 50–500 ng/ml) with erythropoietin suppressed colony formation. In a subsequent study, Golde *et al.* (99) examined Friend virus-infected human erythroleukemia cells without adding erythropoietin to medium supplemented with 0.5% bovine serum albumin and reported that as little as 0.1 ng/ml of hGH was able

to stimulate colony formation. Ovine PRL (25–100 ng/ml) and bovine GH were also able to stimulate colony formation, but the sensitivity and magnitude of response were much lower than those observed for hGH. Examining colony formation of human peripheral blood mononuclear cells (containing 79% T cells and 8% B cells) in fetal calf serum-supplemented medium. Golde and co-workers (100) reported that 100 ng/ml of hGH, but not bovine GH, gave positive stimulation. Ovine PRL (100 ng/ml) was as effective as 100 ng/ml of hGH, but when a dose response was examined, hGH proved to be more sensitive. Using a lymphoblastic cell line (MO), they observed no significant effect of ovine PRL (200 ng/ml), whereas 50–100 ng/ml hGH stimulated colony formation. Other investigators using mouse splenic cells examined the generation of cytotoxic T lymphocytes in serum-free medium and observed that 12 μg/ml of porcine GH generated significant cell lysis, provided it was present in the medium from the beginning of culture (101). This observation suggested to the authors that GH influences the differentiation of a cytotoxic lymphocyte precursor. Snow *et al.* (101) further noted that as little as 12 ng/ml of porcine GH could induce specific cell lysis. Granulocytes isolated from the peripheral blood of human pituitary dwarfs had an increase in cellular tetrazolium reductase activity after being exposed to 100 ng/ml of hGH *in vitro* (102). In a subsequent publication, Rovensky *et al.* (103) isolated human polymorphonuclear leukocytes from the blood of normal and pituitary dwarfs and again observed an increase in cellular content of lysosomal enzymes, but a decrease in release was observed when hGH was added to serum-free medium at levels from 2.5 ng/ml to 25 μg/ml. Others reported that mononuclear phagocytes (macrophages) isolated from porcine blood and lung responded with a 2-fold increase in superoxide anion production to both natural and recombinant porcine GH (50–100 ng/ml) when added to medium supplemented with fetal serum (104). Superoxide anions are responsible for the intracellular killing of pathogenic microbes. In addition, it was observed that an antiserum to porcine GH blocked the response. These latter two reports (103, 104) appear to contradict each other for a reason that is not apparent at this time; however, in one report, serum was present in the culture medium (104), whereas it was absent in the other report (103).

A number of GH actions are not mediated directly, but act through the stimulation of IGF-I production. When human bone marrow mononuclear cells were cultured in medium containing granulocyte/macrophage colony-stimulating factor, the addition of IGF-I (6–60 ng/ml) or recombinant hGH (150–250 ng/ml) significantly enhanced myeloid colony formation (105). No colonies grew in the absence of colony-stimulating factor. In the presence of colony-stimulating factor, hGH and IGF-I stimulated colony growth in the presence and absence of serum supplement. The addition of an antiserum to the IGF-I receptor blocked the response to both hGH and IGF-I. Merchow *et al.* (105) further observed a decrease in immature granulocytes (myelocytes) and an increase in mature granulocytes when either IGF-I or hGH was added. The effect of hGH, but not of IGF-I, was lost when marrow accessory cells (adherent cells) were removed from the culture system. Other investigators examined several virus-transformed human T lymphoblast cell lines with and without fetal calf serum supplement and observed that hGH at a level of 50–100 ng/ml and IGF-I at a level of 10–15 ng/ml stimulated colony growth (106). The addition of monoclonal antibodies to IGF-I blocked the response to both GH and IGF-I; however, attempts to demonstrate increased IGF-I production (by radioimmunoassay) when hGH was added to the culture system were unsuccessful.

Thus, it appears that GH action on cells involved with immunity, as in other systems, may be mediated in part by IGF-I. A number of *in vitro* reports indicated that PRL at higher levels had effects similar to those of GH. Since it appears that GH action may be mediated by the local production of IGF-I, it is of interest to note that Friesen and his co-workers (107) reported that ovine PRL administered to hypox rats increased hepatic IGF-I mRNA 15-fold and increased serum IGF-I levels by 65%. Whether PRL has a similar action on the immune system is unknown at present.

Prolactin and Growth Hormone Production by Cells Involved with Immunity

The inability of a number of investigators to demonstrate *in vitro* effects of PRL and GH on cells involved with immunity led them to examine whether the cells themselves could produce these hormones.

Prolactin Production from Normal Cells. Hartmann *et al.* (96) observed that although PRL could not stimulate cell proliferation, antiserum to PRL blocked the proliferative response of Con A, PHA, LPS, IL-2, and IL-4 on a number of T and B cell lines, mouse splenocytes, and human peripheral mononuclear cells. They further demonstrated that polyclonal antibodies generated to PRL from a number of species were active in blocking proliferation and that the potencies of these antibodies did not correlate with their ability to bind PRL. Antisera to human and rat GH, human LH, FSH, and placental lactogen had no effect. The effect of PRL antisera was observed in both serum-supplemented and serum-free medium, suggesting that lymphoid cells may be producing a PRL-like molecule. Hiestand and co-workers (57) also had difficulty in obtaining an *in vitro* PRL response in rat and mouse mixed lymphocyte reactions. Using specific rat PRL and GH RNA probes, they identified the presence of PRL and GH RNA in

the lymphocyte cytoplasms of both species by dot blots after stimulation with Con A. An analysis of the electrophoretically fractionated poly(A) RNA showed that the hybridizing RNA species were larger than the corresponding precursor and mature RNA species from the pituitary. Other investigators stimulated mouse splenocytes with Con A in serum-free medium and observed an increase in PRL bioactivity in the medium using the Nb2 lymphoma cell assay (108). Montgomery *et al.* (108) further noted that antiserum to rat PRL eliminated the stimulation of Nb2 cell proliferation by Con A supernatants and that rat PRL antiserum also eliminated the Con A proliferative response of murine splenocytes. Dot blot analysis of Con A supernatants stained positive with rat PRL antiserum. In mouse splenic cells cultured in serum-free medium, PRL was identified by immunocytochemistry using polyclonal and monoclonal PRL antibodies in 37% of the cells, and, after Con A (but not LPS) stimulation, the percentage of cells containing PRL increased to 87% (109). Other investigators reported that Con A-stimulated, but not resting, rat splenocytes secreted a molecule that induced Nb2 cells to proliferate and this response could be blocked by an antiserum to rat PRL (110). Since Nb2 lymphoma cells can also respond to IL-2 (111–113), they absorbed out IL-2 using CTLL-2 cells (these cells have specific receptors for IL-2) and reported that the proliferative response was not due to IL-2. They further reported that Con A-stimulated human peripheral blood mononuclear cells also secrete molecules that induce the proliferation of Nb2 cells, and that the response could be partially blocked by antisera to either hPRL or hGH, which suggests that both PRL and GH are secreted by human mononuclear cells. Recently, Montgomery and co-workers (114) identified the PRL-like substance produced by normal mouse thymocytes and splenocytes *in vitro* when stimulated by Con A. Cell lysates were evaluated by Western blot analysis and 35- and 33-kDa bands were identified in resting cells using two different rat PRL antisera and a mouse PRL antiserum. Stimulation by Con A induced a 22-kDa band in cell lysates and increased the concentration of the 35- and 33-kDa bands. Culture medium contained only the 22-kDa component. The addition of [^{35}S]methionine to the culture medium resulted in the recovery of radioactivity in the 22-kDa component from cell lysates and culture medium after Con A stimulation, but not in the 35- and 33-kDa components. This latter finding was perplexing to Montgomery and co-workers (114) and they suggested that the production of larger PRL components may be regulated differently than the smaller PRL component.

Growth Hormone Production from Normal Cells Involved with Immunity. In an extensive report, Weigent *et al.* (115) examined the production of GH from rat and human cells involved with immunity in serum-free medium. Using immunocytochemistry, mRNA production, *de novo* synthesis, antibody affinity chromatography, radioimmunoassay, and bioassay, they showed that resting mononuclear leukocytes isolated from a number of sources (spleen, thymus, bone marrow, and peripheral blood) were capable of synthesizing and releasing GH. In one experiment in which they isolated leukocyte-derived immunoreactive hGH by affinity chromatography, they reported that hGH antiserum, but not hPRL antiserum, could block the Nb2 proliferative response, supporting the specificity of the GH bioassay. It is unfortunate, however, that this extensive and careful study did not also examine whether PRL was produced along with GH as has been reported by others using human peripheral blood mononuclear cells cultured in medium supplemented with fetal calf serum. Hattori *et al.* (116), using a specific and sensitive hGH ELISA assay, confirmed that normal human monocytes released small amounts of GH in culture. They further observed that when the cells were stimulated with PHA or pokeweed mitogen, but not LPS, the amount of immunoreactive hGH detected in the medium increased 2- to 5-fold. The addition of 50–100 pg/ml of hGH to the culture system resulted in a further 4-fold increase in GH release when the cells were stimulated by PHA.

Prolactin Production from Malignant Cells and T and B Cell Lines. The above studies indicate that normal lymphocytes are capable of synthesizing and releasing PRL and GH when stimulated. There are other studies examining lymphoid cell lines and malignant lymphoid cells that also support the production of PRL by cells involved with immunity. Hatfill *et al.* (117) reported that 57% of the patient with acute myeloid leukemia had elevated levels of serum PRL and that leukemic blast cells isolated from the blood of these patients contained PRL in their cellular lysates, as determined by direct immunoblot assay. They suggested that the elevated serum PRL may be due to the release of PRL from these cells. It is unfortunate that they did not determine whether these cells could actually release PRL *in vitro*, because others have reported the presence of intracellular PRL in a large number of malignant cell lines, but the cells were unable to release the hormone into the medium (118). The synthesis and secretion of PRL by a human B lymphoblastoid cell line (IM-9-P) were demonstrated using gene expression, bioactivity, immunological reactivity, and immunoelectrophoresis; however, the authors believed that in this case, the secretion of PRL reflects abnormal expression of the PRL gene by a nonpituitary cell type (119). They further noted that the lymphoblast-derived PRL mRNA was approximately 150 bases longer than that produced by the human pituitary, as determined by Northern blot analysis, and that continuous culturing for 7 months resulted in the loss of PRL-producing

capabilities. Cleveinger *et al.* (120) examined the proliferation of a murine T helper lymphocyte clonal line, L2, to IL-2 in serum-free medium and reported that PRL antiserum blocked the response. The synthesis of PRL or its mRNA was not observed as a result of IL-2 stimulation, but PRL was detected intracellularly. The detected prolactin was of bovine origin and Clevenger *et al.* (120) showed that it was sequestered from the fetal calf serum during prior culture. However, IL-2 stimulated a 7-fold increase in PRL receptor and a 2-fold increase in the mRNA for the PRL receptor. The authors suggested that in the L2 cell line, IL-2 stimulated the induction of PRL receptors and the release of sequestered PRL from the cell. The released PRL then bound to the receptor and was internalized and transported to the nucleus to initiate the proliferative response. The importance of the export of intracellular PRL in initiating the proliferative response was clearly demonstrated by Davis and Linzer (121) using Nb2 cells and genetic constructs for secreted and nonsecreted mouse PRL. They showed that if the gene construct allowed only for the intracellular synthesis of PRL, but not its release, then the cells did not proliferate unless PRL was added to the medium. If, however, the gene construct allowed for both synthesis and export of PRL, then the cell proliferated autonomously and could be blocked by the addition of a specific antiserum for mouse PRL. In a subsequent paper, Clevenger *et al.* (122) demonstrated nuclear translocation of PRL using immunofluorescence and electron microscopy in IL-2-stimulated L2 cells and Con A-stimulated murine splenocytes. The response could be blocked by PRL antiserum added to the medium.

Conclusions and Comments

It is apparent from the above discussion that the anterior pituitary plays a major positive role in the regulation of the immune system. Studies with hypox and dwarf animals suggest that both PRL and GH are capable of returning immunocompetence to these animal models, but only a handful of studies have examined both hormones under identical experimental conditions. In many cases, investigators have ignored the wealth of literature regarding one of the hormones in trying to prove that the hormone they are championing has an effect on the immune system. In some cases, specificity of the response of GH is demonstrated, while PRL is not responsive. The opposite situation has also been reported. The result is a great deal of confusion and the confusion does not appear to be resolvable at this time. Both PRL and GH are important in the regulation of the immune system, but the responsive cell type and site of action in the cascading process of cell maturation must be clarified in the future.

Much of the work done to date has not identified the cell type responding to the PRL and GH. The wealth of monoclonal antibodies available for cell surface determinants should allow a distinction to be made. The Nb2 cell line is very sensitive to PRL-like hormones and was cloned from a rat lymphoma. Is this just a tumor cell that happens to respond to PRL or does it represent a true transitory lymphoid cell type that happened to get "stuck" and to not be able to progress to the next stage? An examination of the surface antigens indicated that the Nb2 cell is of thymic origin, is positive for the W3/25 HLK monoclonal antibody, which indicates that it is a T helper cell, and is positive for the OX8-HL monoclonal antibody, which identifies it as a cytotoxic/suppressor cell (123). These two cell surface antigens are usually not present in the same cell. In addition the Nb2 cell is negative for terminal deoxynucleotidyl transferase, which indicates that these cells have completed an early phase of thymic development. Thus, the Nb2 cell is a thymocyte at an intermediate stage of differentiation. It would appear important then that a thymocyte with similar characteristics be isolated from the normal thymus and a determination be made as to whether it responds to PRL. Mukherjee *et al.* (97) attempted to identify the cell type responsive to PRL when they observed that PRL added *in vitro* to rat splenic cells obtained from ovariectomized animals increased the proportions of CD8 (cytotoxic/suppressor) and CD5 (helper-like) cells in culture, but did not alter the proportion of CD4 (helper) cells. A number of studies indicated that NK cell activity appeared to be stimulated by GH, but other studies reported that PRL, under different experimental conditions, had a similar effect. Thus, a resolution of the hormonal activity responsible for NK activity cannot be determined at present. Future investigations in identifying cell surface antigens of responsive cells would help to focus on the immune cell type responsive to PRL and GH.

Both PRL and GH stimulate the thymic epithelial cell to increase the production of thymulin and to proliferate. No data are available, however, to indicate whether other thymic hormones (i.e., thymosin) can also be stimulated by these hormones. The thymic epithelial cell has been identified as the source of thymulin, thymosin, and thymopoietin (124), and it appears that the same cell produces all of these hormones. Perhaps PRL and GH have a differential effect on stimulating one thymic hormone over another. The recent report of the administration of recombinant hGH to older people (125) with an improvement in some aging parameters may stimulate additional investigations of GH involvement with the immune system. In animal studies, the immune function of aged animals is improved by providing a combination of GH and PRL (61). Similar studies with PRL, or preferably in conjunction with GH in clinical studies, may prove to be equally rewarding, with the possible discovery that

PRL may be more beneficial and have fewer side effects than those observed for GH.

Another area that has been neglected is the effects of PRL and GH on the early development of the immune system. Russell *et al.* (126) have administered PRL antiserum to neonatal female mice (Day 1) and have observed an early decrease (Day 14) in the proportion of Thy 1.2^+ and $L3T4^+$ ($CD4^+$) cells in the thymus, while a later increase (Day 32) in these cell types occurred in the spleen. A decrease in spleen B cell numbers was also noted in PRL antiserum-injected animals. The long-term significance of these changes on the immune system of the adult is unknown. Grosvenor and colleagues (127) have identified high concentrations of PRL in rat milk, and this PRL is absorbed from the gastrointestinal tract into the circulation of the pups. Recent investigations by Grosvenor's group have shown that if the level of PRL in the milk is experimentally decreased, then the offspring have a disrupted PRL neuroregulation as adults (128). Would the loss of milk PRL also disrupt the immune system of these offspring? Information of this nature would greatly help investigators understand the function of PRL in the early development of the immune system. The human fetus is bathed in amniotic fluid, which is high in PRL (129). The fetus is also believed to consume large amounts of amniotic fluid (130). No physiological function has been ascribed to PRL in the amniotic fluid. Is is possible that the PRL in amniotic fluid could find its way into the circulation of the fetus by way of the gastrointestinal tract and stimulate the early development of the immune system? An action on the immune system would explain why high concentrations of PRL are found in the milk of rats (and other species) and in the amniotic fluid.

During sleep in men and women, large amounts of GH and PRL are released into circulation. The secretion of GH is greatest during early sleep and is tightly coupled to slow wave sleep (131), whereas the largest amount of PRL release occurs in the latter two thirds of the sleep period and is associated with rapid eye movement sleep (132). These increases in GH and PRL have no known physiological function. Is it possible that these increases in GH and PRL are important in maintaining normal immune function? Recent experiments by Moldofsky *et al.* (133) indicated that there were dramatic increases in plasma interleukin 1 levels during sleep that were related to the onset of slow wave sleep, a time when large amounts of GH are released. Interleukin 1 is an initiator of the immune cascade. Increases in plasma IL-2 followed those in IL-1 and were associated with rapid eye movement sleep, a time when plasma PRL levels normally increase. Natural killer cell activity was decreased coincident with plasma IL-2 increases. Additional investigations of this nature may help to elucidate the physiological significance of the sleep-induced increases in GH and PRL, as well as the importance of these hormones in the immune system.

Although there appears to be conflicting evidence, it also appears that PRL and GH can act directly on cells involved with immunity. In some cases, GH appears to stimulate the production of IGF-I by these cells, and IGF-I initiates the proliferative response. In other cases, the cells appear to be able to synthesize and secrete GH- and PRL-like molecules that are released and initiate proliferative and secretory events. If the cells involved with immunity can produce GH- and PRL-like molecules, why don't they rescue the animal from the insult of hypophysectomy? The physiological significance, if any, of the apparent production of GH- and PRL-like molecules by these cells requires elucidation by careful investigation.

The evidence to date indicates that PRL and GH are important regulators of the immune system. The task ahead is to identify where in the immune system they function.

Note added in proof. Some of the confusion dealing with PRL and GH actions on the immune system stem from the use of hGH. Human GH has inherent in its molecular structure prolactin activity to which no known physiologic function has been ascribed. The action of hGH on the immune system, therefore, cannot be assigned to the GH activity of the GH molecule unless the immune system being examined fails to respond to hPRL and/or responds only to other mammalian GH (ovine, mouse, etc.) that lack PRL activity.

The author expresses his appreciation to Dr. David M. Lawson of the Department of Physiology and Dr. Yu-Chi M. Kong of the Department of Immunology and Microbiology at Wayne State University for reviewing the manuscript and offering helpful suggestions for improving it.

1. Boland EW. Clinical comparison of the newer anti-inflammatory corticosteroids. Ann Rheum Dis **21**:176–186, 1962.
2. Shoenfeld Y, Isenberg D. Chapter 6, Hormonal components and autoimmune diseases. The Mosaic of Autoimmunity. Research Monographs in Immunology. Amsterdam: Elsevier, Vol **12**: p230, 1989.
3. Piantanelli L, Fabris N. Hypopituitary dwarf and athymic nude mice and the study of the relationships among thymus, hormones and aging. Birth Defects **14**:315–333, 1978.
4. Michael SD. Interactions of the thymus and the ovary. In: Greenwald GS, Terranova PF, Eds. Factors Regulating Ovarian Function. New York: Raven Press, p445, 1983.
5. Weiss JM, Sundar SK, Becker KJ. Stress-induced immunosuppression and immunoenhancement: Cellular immune changes and mechanisms. In: Goetzl EJ, Spector NH, Eds. Neuroimmune Networks: Physiology and Diseases. New York: A. R. Liss, p193, 1989.
6. Gala RR. The physiology and mechanisms of the stress-induced changes in prolactin secretion in the rat. Life Sci **46**:1407–1420, 1990.

7. Brown GM, Seggie JA, Chambers JW, Ettigi PG. Psychoendocrinology and growth hormone: A review. Psychoneuroendocrinology **3**:131–153, 1978.
8. Berczi I, Nagy E. Prolactin and other lactogenic hormones. In: Berczi I, Ed. Pituitary Function and Immunology. Boca Raton, FL: CRC Press, p168, 1986.
9. Kelley KW. Growth hormone, lymphocytes and macrophages. Biochem Pharmacol **38**:705–713, 1989.
10. Berczi I. Pituitary malfunction and immune abnormalities. In: Berczi I, Ed. Pituitary Function and Immunity. Boca Raton, FL: CRC Press, p41, 1986.
11. Smith PE. Effect of hypophysectomy on the involution of the thymus in the rat. Anat Rec **47**:119–129, 1930.
12. Comsa J. Hormone interactions of the thymus. In: Luckey TD, Ed. Thymic Hormones. Baltimore: University Park Press, p59, 1973.
13. Lunkin PM. Action of hypophysectomy on antibody formation in the rat. Acta Pathol Microbiol Scand **48**:351–355, 1960.
14. Enerback L, Lundin PM, Mellgren J. Pituitary hormones elaborated during stress. Action on lymphoid tissues, serum proteins and antibody titers. Acta Pathol Microbiol Scand [Suppl] **144**:141–144, 1961.
15. Comsa J, Leonhardt H, Schwarz JA. Influence of the thymus-corticotropin-growth hormone interaction on the rejection of skin allografts in the rat. Ann NY Acad Sci **249**:387–401, 1975.
16. Prentice ED, Lipscomb H, Metcalf WK, Sharp JG. Effects of hypophysectomy on DNCB-induced contact sensitivity in rats. Scand J Immunol **5**:955–961, 1976.
17. Saxena QB, Saxena RK, Adler WH. Regulation of natural killer activity in vivo. III: Effect of hypophysectomy and growth hormone treatment on the natural killer activity of the mouse spleen cell population. Int Arch Allergy Appl Immunol **67**:169–174, 1982.
18. Cross RJ, Markesbery WR, Brooks WH, Roszman TL. Hypothalamic-immune interactions. Neuromodulation of natural killer activity by lesions of the anterior hypothalamus. Immunology **51**:399–405, 1984.
19. Toivanen P, Siikala H, Laiko P, Paavilainer T. Suppression of adjuvant arthritis by estrone in adrenalectomized and ovariectomized rats. Experientia **23**:560–561, 1967.
20. Duquesnoy RJ, Mariani T, Good RA. Effect of hypophysectomy on immunological recovery after sublethal irradiation of adult rats. Proc Soc Exp Biol Med **131**:1176–1178, 1969.
21. Nagy E, Berczi I. Immunodeficiency in hypophysectomized rats. Acta Endocrinol **89**:530–537, 1978.
22. Bartke A. Histology of the anterior hypophysis, thyroid and gonads of two types of dwarf mice. Anat Rec **149**:225–236, 1964.
23. Lewis UJ. Growth hormone in normal and dwarf mice. Mem Soc Endocrinol **15**:179–191, 1967.
24. Barkley MS, Bartke A, Gross DS, Sinha YN. Prolactin status of hereditary dwarf mice. Endocrinology **110**:2088–2096, 1982.
25. Baroni C. Thymus, peripheral lymphoid tissues and immunological responses of the pituitary dwarf mouse. Experientia **23**:282–283, 1967.
26. Baroni C, Fabis N, Bertoli G. Age dependency of the primary immune response in hereditary pituitary dwarf and normal Snell-Bagg mouse. Experientia **23**:1059–1061, 1967.
27. Fabris N, Pierpaoli W, Sorkin E. Hormones and the immunological capacity. III: The immunodeficiency disease of the hypopituitary Snell-Bagg dwarf mouse. Clin Exp Immunol **9**:209–225, 1971.
28. Duquesnoy RJ, Kalpaktsoglou PK, Good RA. Immunological studies on the Snell-Bagg pituitary dwarf mouse. Proc Soc Exp Biol Med **133**:201–206, 1970.
29. Duquesnoy RJ. Immunodeficiency of the thymus-dependent system of the Ames dwarf mouse. J Immunol **108**:1578–1590, 1972.
30. Roth JA, Lomax LG, Alszuler N, Hampshire J, Laeberle ML, Shelton M, Draper DD, Ledet AE. Thymic abnormalities and growth hormone deficiency. Am J Vet Res **41**:1257–1262, 1980.
31. Roth JA, Laeberle ML, Grier RL, Hopper JG, Spiegel HE, McAllister HA. Improvement in clinical condition and thymus morphologic features associated with growth hormone treatment of immunodeficient dogs. Am J Vet Res **45**:1151–1155, 1984.
32. Parkes D. Drug therapy: Bromocriptine. N Engl J Med **301**:873–880, 1979.
33. Hiestand PC, Gale JM, Mekler P. Soft immunosuppression by inhibition of prolactin release: Synergism with cyclosporine in kidney allograft survival and in the localized graft-versus-host reaction. Transplant Proc **18**:870–872, 1986.
34. Palestine AG, Muellenberg-Coulombre CG, Kim MK, Gelato MC, Mussenblatt RB. Bromocriptine and low dose cyclosporine in the treatment of experimental autoimmune uveitis in the rat. J Clin Invest **79**:1078–1081, 1987.
35. Whyte A, Williams RO. Bromocriptine suppresses postpartum exacerbation of collagen-induced arthritis. Arthritis Rheum **31**:927–928, 1988.
36. Neidhart M. Bromocriptine microcapsules inhibit ornithine decarboxylase activity induced by Freund's complete adjuvant in lymphoid tissues of male rats. Endocrinology **125**:2846–2852, 1989.
37. Spangelo BL, Hall NRS, Ross PC, Goldstein AL. Stimulation of in vivo antibody production and concanavalin-A-induced mouse spleen cell mitogenesis by prolactin. Immunopharmacology **14**:11–20, 1987.
38. Gupta S, Fikrig SM, Noval MS. Immunological studies in patients with isolated growth hormone deficiency. Clin Exp Immunol **54**:87–90, 1983.
39. Abbassi V, Bellanti JA. Humoral and cell-mediated immunity in growth hormone-deficient children: Effect of therapy with human growth hormone. Pediatr Res **19**:299–301, 1985.
40. Rapaport R, Oleske J, Ahdich H, Solomon S, Delfaus C, Denny T. Suppression of immune function in growth hormone-deficient children during treatment with human growth hormone. J Pediatr **109**:434–439, 1986.
41. Rapaport R, Oleske J, Ahdieh H, Skuza K, Holland BK, Passannante MR, Denny T. Effects of human growth hormone on immune functions: In vitro studies on cells of normal and growth hormone-deficient children. Life Sci **41**:2319–2324, 1987.
42. Kiess W, Doerr H, Eisl E, Butenandt O, Belohradsky BH. Lymphocyte subsets and natural-killer activity in growth hormone deficiency. N Engl J Med **314**:321, 1986.
43. Kiess W, Malozowski S, Gelato M, Butenandt O, Doerr H, Crisp B, Eisl E, Maluish A, Belohradsky BH. Lymphocyte subset distribution and natural killer activity in growth hormone deficiency before and during short-term treatment with growth hormone releasing hormone. Clin Immunol Immunopathol **48**:85–94, 1988.
44. Crist DM, Peake GT, Mackinnon LT, Sibbitt WL Jr, Kraner JC. Exogenous growth hormone treatment alters body composition and increases natural killer cell activity in women with impaired endogenous growth hormone secretion. Metabolism **36**:1115–1117, 1987.
45. Bozzola M, Cisternino M, Larizza D, Maghnie M, Morelta A, Valtorta A, Schimpff RM, Severi F. Correspondence. Metabolism **38**:193–194, 1989.
46. Matsuura M, Kikkawa Y, Kitagawa T, Tanaka S. Modulation of immunological abnormalities of growth hormone-deficient children by growth hormone treatment. Acta Paediatr Jpn **31**:53–57, 1989.

47. Berczi I, Nagy E, Kovacs K, Horvath E. Regulation of humoral immunity in rats by pituitary hormones. Acta Endocrinol **98**:506–513, 1981.
48. Adler RA. The anterior pituitary-grafted rat: A valid model of chronic hyperprolactinemia. Endocr Rev **7**:302–313, 1986.
49. Pandian MR, Talwar GP. Effect of growth hormone on the metabolism of thymus and on the immune response against sheep erythrocytes. J Exp Med **134**:1095–1113, 1971.
50. Berczi I, Nagy E. A possible role of prolactin in adjuvant arthritis. Arthritis Rheum **25**:591–594, 1982.
51. Nagy E, Berczi I. Prolactin and contact sensitivity. Allergy **36**:429–431, 1981.
52. Berczi I, Nagy E, Asa SL, Kovacs K. Pituitary hormones and contact sensitivity in rats. Allergy **38**:325–330, 1983.
53. Nagy E, Berczi I, Friesen HG. Regulation of immunity in rats by lactogenic and growth hormones. Acta Endocrinol **102**:351–357, 1983.
54. Berczi I, Nagy E, Asa SL, Kovacs K. The influence of pituitary hormones in adjuvant arthritis. Arthritis Rheum **27**:682–688, 1984.
55. Nagy E, Berczi I. Pituitary dependence of bone marrow function. Br J Haematol **71**:457–462, 1989.
56. Edwards CK III, Lorence RM, Dunham DM, Arkins S, Yunger LM, Greager JA, Walter RJ, Dantzer R, Kelley KW. Hypophysectomy inhibits the synthesis of tumor necrosis factor α by rat macrophages: Partial restoration by exogenous growth hormone or interferon beta. Endocrinology **128**:989–996, 1991.
57. Hiestand PC, Mekler P, Nordmann R, Grieder A, Permmongkol C. Prolactin as a modulator of lymphocyte responsiveness provides a possible mechanism for cyclosporine. Proc Natl Acad Sci USA **83**:2599–2603, 1986.
58. Bernton EW, Meltzer MS, Holaday JW. Suppression of macrophage activation and T-lymphocyte function in hypoprolactinemic mice. Science **239**:401–404, 1988.
59. Pierpaoli W, Baroni C, Fabris N, Sorkin E. Hormones and immunological capacity. II: Reconstitution of antibody production in hormonally deficient mice by somatotropic hormone, thyrotropic hormone and thyroxine. Immunology **16**:217–230, 1969.
60. Fabris N, Pierpaoli W, Sorkin E. Hormones and the immunological capacity. IV: Restorative effects of developmental hormones of lymphocytes on the immunodeficiency syndrome of the dwarf mouse. Clin Exp Immunol **9**:227–240, 1971.
61. Davila DR, Brief S, Simon J, Hammer RE, Brinster RL, Kelley KW. Role of growth hormone in regulating T-dependent immune events in aged, nude and transgenic rodents. J Neurosci Res **18**:108–116, 1987.
62. Powell-Jackson J, Kennedy P, Whitcombe EM. Creutzfeldt-Jakob disease after administration of human growth hormone. Lancet **5**:260–262, 1985.
63. Vidaller A, Llorente L, Larrea F, Mendez JP, Alcocer-Varela J, Alarcon-Segavia D. T-cell dysregulation in patients with hyperprolactinemia: Effect of bromocriptine treatment. Clin Immunol Immunopathol **38**:337–343, 1986.
64. Hedner LP, Bynke G. Endogenous iridocyclitis relieved during treatment with bromocriptine. Am J Ophthalmol **100**:618–619, 1985.
65. Daughday WH. The anterior pituitary. In: Wilson JD, Foster DW, Eds. Textbook of Endocrinology, 7th ed. Philadelphia: W. B. Saunders, p568, 1982.
66. Lancranjan I. The medical treatment of prolactin and growth hormone-secreting pituitary tumors. Acta Neurochir [Suppl] **47**:71–85, 1990.
67. Goldstein AL, White A. Thymosin and other thymic hormones. Their nature and roles in the thymic dependency of immunological phenomena. Contemp Top Immunobiol **2**:339–350, 1973.
68. Comsa J, Loenhardt H, Ozminski K. Hormonal influences on the secretion of the thymus. Thymus **1**:81–93, 1979.
69. Dardenne M, Bach JF. Thymic hormones. In: Kendall MD, Ed. The Thymus Gland. New York: Academic Press, p113, 1981.
70. Cardarelli NF. Thymic hormones: An introduction. In: Cardarelli NF, Ed. The Thymus in Health and Senescence. Boca Raton, FL: CRC Press, p161, 1989.
71. Cardarelli NF. Thymosin. In: Cardarelli NF, Ed. The Thymus in Health and Senescence. Boca Raton, FL: CRC Press, p199, 1989.
72. Pleau JM, Dardenne M, Bach JF. Thymulin: Biochemistry, biology and pharmacology. In: Cardarelli NF, Ed. The Thymus in Health and Senescence. Boca Raton, FL: CRC Press, p207, 1989.
73. Goff BL, Roth JA, Arp LH, Incefy GS. Growth hormone treatment stimulates thymulin production in aged dogs. Clin Exp Immunol **68**:580–587, 1987.
74. Morrison WB, Goff BL, Stewart-Brown B, Incefy GS, Arp LH, Roth JA. Orally administered clonidine as a secretogogue of growth hormone and as a thymotropic agent in dogs of various ages. Am J Vet Res **51**:65–70, 1990.
75. Dardenne M, Savino W, Gagnerault MC, Itoh T, Bach JF. Neuroendocrine control of thymic hormonal production. I: Prolactin stimulates in vivo and in vitro the production of thymulin by human and murine thymic epithelial cells. Endocrinology **125**:3–12, 1989.
76. Bach JF, Dardenne M. Studies on thymus products. II: Demonstration and characterization of a circulating thymic hormone. Immunology **25**:353–366, 1973.
77. Pelletier M, Montplaisir S, Dardenne M, Bach JF. Thymic hormone activity and spontaneous autoimmunity in dwarf mice and their littermates. Immunology **30**:783–788, 1976.
78. Timsit J, Safieh B, Gagnerault MC, Savino W, Lubetzk J, Bach JF, Dardenne M. Augmentation des taux circulants de thymuline au cours de l'hyperprolactinemi et de l'acromegalie. C R Acad Sci [II] **310**:7–13, 1990.
79. Mocchegiani E, Paolucci P, Balsamo A, Cacciari E, Fabris N. Influence of growth hormone on thymic endocrine activity in humans. Horm Res **33**:248–255, 1990.
80. Lesniak MA, Roth J, Gorden P, Gavin JR III. Human growth hormone radioreceptor assay using cultured human lymphocytes. Nat New Biol **241**:20–22, 1973.
81. Arrenbrecht S. Specific binding of growth hormone to thymocytes. Nature **252**:255–257, 1974.
82. Eshet R, Manheimer S, Chobsieng P, Laron Z. Human growth hormone receptors in human circulating lymphocytes. Horm Metab Res **7**:352–353, 1975.
83. Lesniak MA, Gorden P, Roth J, Gavin JR III. Binding of ^{125}I-human growth hormone to specific receptors in human cultured lymphocytes. J Biol Chem **249**:1661–1667, 1974.
84. Kiess W, Butenandt O. Specific growth hormone receptors on human peripheral mononuclear cells: Reexpression, identification and characterization. J Clin Endocrinol Metab **60**:740–746, 1985.
85. Stewart C, Clejan S, Fugler L, Cheruvanky T, Collipp PJ. Growth hormone receptors in lymphocytes of growth hormone-deficient children. Arch Biochem Biophys **220**:309–313, 1983.
86. Dube D, Kelley PA, Pelletier G. Comparative localization of prolactin binding sites in different rat tissues by immunohistochemistry, radioautography and radioreceptor assay. Mol Cell Endocrinol **18**:109–122, 1980.
87. Russell DH, Matrisian L, Kibler R, Larson DF, Poulos B, Magun BE. Prolactin receptors on human lymphocytes and their modulation by cyclosporine. Biochem Biophys Res Commun **121**:899–906, 1984.
88. Russell DH, Kibler R, Matrisian L, Larson DF, Poulos B,

Magun BE. Prolactin receptors on human T and B lymphocytes: Antagonism of prolactin binding by cyclosporine. J Immunol **134**:3027–3031, 1985.
89. Bellussi G, Muccioli G, Ghe C, DiCarlo R. Prolactin binding sites in human erythrocytes and lymphocytes. Life Sci **41**:951–959, 1987.
90. Noble RL, Beer CT, Gout PW. Evidence in vivo and in vitro of a role for the pituitary in the growth of malignant lymphomas in Nb rats. Cancer Res **40**:2437–2440, 1980.
91. Gout PW, Beer CT, Noble RL. Prolactin-stimulated growth of cell cultures established from malignant Nb rat lymphomas. Cancer Res **40**:2433–2436, 1980.
92. Shiu RPC, Elsholtz HP, Tanaka T, Friesen HG, Gout PW, Beer CT, Noble RL. Receptor-mediated mitogenic action of prolactin in a rat lymphoma cell line. Endocrinology **113**:159–165, 1983.
93. Russell DH, Buckley AR, Montgomery DW, Larson NA, Gout PW, Beer CT, Putnam CW, Zukoski CF, Kibler R. Prolactin-dependent mitogenesis in Nb_2 lymphoma cells: Effects of immunosuppressive cyclopeptides. J Immunol **138**:276–284, 1987.
94. Matera L, Cesano A, Muccioli G, Veglia F. Modulatory effect of prolactin on the DNA synthesis rate and NK activity of large grandular lymphocytes. Int J Neurosci **51**:265–267, 1990.
95. Skwarlo-Sonta K. Mitogenic effect of prolactin on chicken lymphocytes in vitro. Immunol Lett **24**:171–178, 1990.
96. Hartmann DP, Holaway JW, Bernton EW. Inhibition of lymphocyte proliferation by antibodies to prolactin. FASEB J **3**:2194–2202, 1989.
97. Mukherjee P, Mastro AM, Hymer WC. Prolactin induction of interleukin-2 receptors on rat splenic lymphocytes. Endocrinology **126**:88–94, 1990.
98. Golde DW, Bersch N. Growth hormone: Species specific stimulation of erythropoiesis in vitro. Science **196**:1112–1113, 1977.
99. Golde DW, Bersch N, Li CH. Growth hormone modulation of murine erythroleukemia cell growth in vitro. Proc Natl Acad Sci USA **75**:3437–3439, 1978.
100. Mercola KE, Cline MJ, Golde DW. Growth hormone stimulation of normal and leukemic human T-lymphocyte proliferation in vitro. Blood **58**:337–340, 1981.
101. Snow EC, Feldbush TL, Oaks JA. The effect of growth hormone and insulin upon MLC responses and the generation of cytotoxic lymphocytes. J Immunol **126**:161–164, 1981.
102. Rovensky J, Vigas M, Lokaj J, Cuncik P, Lukac P, Takac A. Effect of growth hormone on the metabolic activity of phagocytes of peripheral blood in pituitary dwarfs and acromegaly. Endocrinol Exp **16**:129–134, 1982.
103. Rovensky J, Ferencikova J, Vigas M, Lukac P. Effect of growth hormone on the activity of some lysomal enzymes in neutrophilic polymorphonuclear leukocytes of hypopituitary dwarf. Int J Tissue React **7**:153–159, 1985.
104. Edwards CK III, Ghiasuddin SM, Schepper JM, Yunger LM, Kelley KW. A newly defined property of somatotropin: Priming of macrophages for production of superoxide anion. Science **239**:764–771, 1988.
105. Merchow S, Tatarsky I, Hochberg Z. Enhancement of human granulopoiesis in vitro by biosynthetic insulin-like growth factor I/somatomedin C and human growth hormone. J Clin Invest **81**:791–797, 1988.
106. Geffner ME, Bersch N, Lippe BM, Rosenfeld RG, Hintz RL, Golde DW. Growth hormone mediates the growth of T-lymphoblast cell lines via locally generated insulin-like growth factor-I. J Clin Endocrinol Metab **71**:464–469, 1990.
107. Murphy LJ, Tachibana K, Friesen HG. Stimulation of hepatic insulin-like growth factor-I gene expression by ovine prolactin: Evidence for intrinsic somatogenic activity in the rat. Endocrinology **122**:2027–2033, 1988.
108. Montgomery DW, Zukoski CF, Shah NG, Buckley AR, Pacholczk T, Russell DH. Concanavalin A-stimulated murine splenocytes produce a factor with prolactin-like bioactivity and immunoreactivity. Biochem Biophys Res Commun **145**:692–698, 1987.
109. Kenner JR, Smith PF, Bernton EW, Hartmann D, Holaday JW. Murine splenic lymphocytes demonstrate Con A-inducible prolactin-like immunoreactivity as determined by immunocytochemistry (ICC). Soc Neurosci Abstr **14**:756, 1988.
110. Roz DM, Kelley KM. Con A-activated rat splenocytes and human peripheral blood mononuclear cells secrete bioactive prolactin and somatotropin-like molecules. FASEB J **2**:A1640, 1988.
111. Moy JA, Lawson DM. Serum specifically potentiates the mitogenic response of Nb_2 lymphoma cells to rat prolactin. Endocrinology **123**:1314–1319, 1988.
112. Rayhel EJ, Fields TJ, Albright JW, Diamantstein T, Hughes JP. Interleukin-2 and a lactogen regulate proliferation and protein phosphorylation in Nb_2 cells. Biochem J **249**:333–338, 1988.
113. Croze F, Walker A, Friesen HG. Stimulation of growth of Nb_2 lymphoma cells by interleukin-2 in serum-free and serum containing media. Mol Cell Endocrinol **55**:253–259, 1988.
114. Montgomery DW, LaFevre JA, Ulrich ED, Adamson CR, Zukoshi CF. Identification of prolactin-like proteins synthesized by normal murine lymphocytes. Endocrinology **127**:2601–2603, 1990.
115. Weigent DA, Baxter JB, Wear WE, Smith LR, Bost KL, Blalock JE. Production of immunoreactive growth hormone by mononuclear leukocytes. FASEB J **2**:2812–2818, 1988.
116. Hattori N, Shimatsu A, Sugita M, Kumagai S, Imura H. Immunoreactive growth hormone (GH) secreted by human lymphocytes: Augmented release by exogenous GH. Biochem Biophys Res Commun **168**:396–401, 1990.
117. Hatfill SJ, Kirby R, Hanley M, Rybicki E, Bohm L. Hyperprolactinemia in acute myeloid leukemia and indication of ectopic expression of human prolactin in blast cells of a patient of subtype M4. Leuk Res **14**:57–62, 1990.
118. Rosen SW, Weintraub BD, Aaronson SA. Nonrandom-ectopic protein production by malignant cells: Direct evidence in vitro, J Clin Endocrinol Metab **50**:834–841, 1980.
119. DiMattia GE, Gellersen B, Bohnet HG, Friesen HG. A human β-lymphoblastoid cell line produces prolactin. Endocrinology **122**:2508–2517, 1988.
120. Clevenger CV, Russell DH, Appasamy PM, Prystowsky MB. Regulation of interleukin 2-driven T-lymphocyte proliferation by prolactin. Proc Natl Acad Sci USA **87**:6460–6464, 1990.
121. Davis JA, Linzer DH. Autocrine stimulation of Nb_2 cell proliferation by secreted, but not intracellular prolactin. Mol Endocrinol **2**:740–746, 1988.
122. Clevenger CV, Sillman AL, Prystowsky MB. Interleukin-2 driven nuclear translocation of prolactin in cloned T-lymphocytes. Endocrinology **127**:3151–3159, 1990.
123. Fleming WH, Pettigrew NM, Matusik RJ, Friesen HG. Thymic origin of the prolactin-dependent Nb_2 lymphoma cell line. Cancer Res **42**:3138–3141, 1982.
124. Savino W, Dardenne M. Thymic hormone containing cells. VI: Immunohistologic evidence for the simultaneous presence of thymulin, thymopoietin and thymosin α1 in normal and pathological human thymuses. Eur J Immunol **14**:987–991, 1984.
125. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Schlenker RA, Cohn L, Rudman IW, Mattson DE. Effects of human growth hormone in men over 60 years of age. N Engl J Med **323**:1–6, 1990.
126. Russell DH, Mills KT, Talamantes FT, Bern HA. Neonatal administration of prolactin antiserum alters the developmental pattern of T- and B-lymphocytes in the thymus and spleen of BALB/C female mice. Proc Natl Acad Sci USA **85**:7404–7407, 1988.
127. Grosvenor CE, Whitworth NS. Accumulation of prolactin by

maternal milk and its transfer to circulation of neonatal rat—A review. Endocrinol Exp **17**:271–281, 1983.
128. Shah GV, Shyr SW, Grosvenor CE, Crowley WR. Hyperprolactinemia after neonatal prolactin (PRL) deficiency in rats: Evidence for altered anterior pituitary regulation of PRL secretion. Endocrinology **122**:1883–1889, 1988.
129. Andersen JR, Decidual prolactin. Studies of decidual and amniotic prolactin in normal and pathological human pregnancy. Dan Med Bull **37**:154–165, 1990.
130. Mestretta CM, Bradley RM. Taste and swallowing in utero. Br Med Bull **31**:80–84, 1975.
131. Takahashi Y, Kipnis DM, Daughaday WH. Growth hormone secretion during sleep. J Clin Invest **47**:2079–2090, 1968.
132. Franz AG. Prolactin. N Engl J Med **298**:201–207, 1978.
133. Moldofsky H, Lue FA, Eisen J, Keystone E, Gorczynski RM. The relationship of interleukin-1 and immune functions to sleep in humans. Psychosom Med **45**:309–318, 1986.