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SEX STEROID REGULATION OF AUTOIMMUNITY

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Summary—The immune response of males and females is not identical but instead has been shown to be dimorphic in its nature, with females generally demonstrating a greater overall response than males. This dimorphism extends to both the humoral and cell mediated systems and appears to be mechanistically based on the differences in type and concentration of sex steroids in males vs females. Furthermore, growth hormone and prolactin secretions which are different in males and females may also be partly responsible for the observed dimorphism. Because autoimmune disease results from a pathological perturbation of normal immune function, it follows that expression of these diseases will also demonstrate a dimorphic pattern. Examples of this autoimmune dimorphism include (but are not limited to) lupus, rheumatoid arthritis and multiple sclerosis with the two former more prevalent in females than males and the latter more severe during pregnancy. To explain autoimmune dimorphism it therefore becomes necessary firstly to describe the cellular and hormonal interactions found in normal immune regulation and thereafter extrapolate these to autoimmune phenomena.

IMMUNITY AND HOMEOSTASIS

Maintenance of an internal steady state, although the external environment continues to fluctuate, defines classic homeostasis. The development of the cell membrane was probably the initial event that allowed the primeval cell to regulate its internal environment. Multicelled organisms which functioned as a single unit advanced homeostatic regulation still further because they must have found it necessary to develop more complex regulatory mechanisms. Thus, two levels of homeostatic controls were superimposed, the older inter-cellular relationships now overlayed by the newer extra-cellular (but still intra-organism) pathways. Linkage of these various life support systems through both positive feedforwards and negative feedbacks thus allowed exquisite control of intra-organism homeostasis.

Because such complex regulatory arrangements supply both intra and inter-system controls, it is not surprising to find them present in all systems within multicelled organisms. What is surprising is that it has taken so long for investigators to define these homeostatic regulatory pathways in the immune system. The older theories describing regulatory interactions during an immune response suggested that the presence of antigen stimulated both the specific and nonspecific arms of the immune system. Activation of phagocytic activity, complement and interferons accompanied by production of antibodies and stimulation of specific effector cells would then function in concert to inactivate, destroy and clear the antigen containing structures from the body. Removal of the antigen would then act to down regulate the system. Subsequently and more recently it was shown that other factors also must function to down regulate the system including the presence of suppressor lymphocytes to balance the action of the helper lymphocytes and idiotypic and anti-idiotypic networks to control the production of antibody. However, most recently we have come to realize that the communication between cells of the immune system at all levels during the response is far more complex and involves the production of factors such as monokines (from phagocytic cells such as macrophages) and lymphokines (from various subclasses of lymphocytes). Furthermore, these interactions are not restricted to the effector cells of the immune system alone but also extend to cells of other systems diverse from the immune system. Notably such interactions also involved communication between the endocrine and immune systems and most recently the nervous and immune systems.

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MAINTENANCE OF HOMEOSTASIS VIA COMMUNICATION BETWEEN THE IMMUNE AND ENDOCRINE SYSTEMS

An excellent example of interactions between the immune and endocrine systems designed to maintain homeostatis can be found in the lymphocyte/monocyte factor mediated (LMFM) axis [1] (see Fig. 1). Upon activation of effector helper lymphocytes and monocytes of the immune system by antigen both lymphokines such as glucocorticoid increasing factor and tumor necrosis factor [2] and monokines such as interleukin-1 (IL-1) are generated. These substances then exert a direct control at the level of the hypothalamus causing an increase in the release of corticotropin releasing hormone (CRH). CRH then stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH) which in turn then acts at the level of the adrenal glands to increase the levels of circulating glucocorticoid. Additionally ACTH may be directly released by activated lymphocytes [3] to stimulate glucocorticoid release at the adrenal gland. The increased levels of circulating glucocorticoid then directly down regulates effector T and B lymphocytes through glucocorticoid receptors and also decreases the release of thymic hormones from the reticuloepithelial cells of the thymus. Reduced levels of thymic hormones (such as thymulin) will also down regulate the effector lymphocytes while decreases in thymosins acting at the level of the hypothalamus–pituitary may reduce the release of the gonadotropin luteinizing hormone (LH) thereby decreasing the release of sex steroids from the gonads. It should also be noted that increases of CRH have also been reported to exert an inhibitory effect at the hypothalamus–pituitary which will also decrease the release of LH and reduce sex steroid release from the gonads [4]. This accounts for the observation that during stress, levels of circulating glucocorticoids increase but circulating sex steroids decrease. Reductions in sex steroids (estrogens, androgens) from the gonads then will, up regulate the release of thymic hormones, possibly act to restimulate effector lymphocytes and increase LH release from the pituitary, increasing sex steroid release which will then down regulate thymic hormones, etc. The overall effect would be for the system to experience repeated cycles of decreasing frequency of perturbations finally spiraling down to a new level of homeostasis. It should also be noted that in immature chickens the androgen dihydrotestosterone, has been reported to modulate the levels of glucocorticoid receptors in both the bursa and thymus [5], adding yet another possible level to these regulatory interactions. Thus it can be seen that upon activation of effector immune cells by antigen additional, complex regulatory pathways are set in motion that are designed to down regulate the system, preventing or limiting damage by over-zealous effector lymphocyte/monocyte activities.

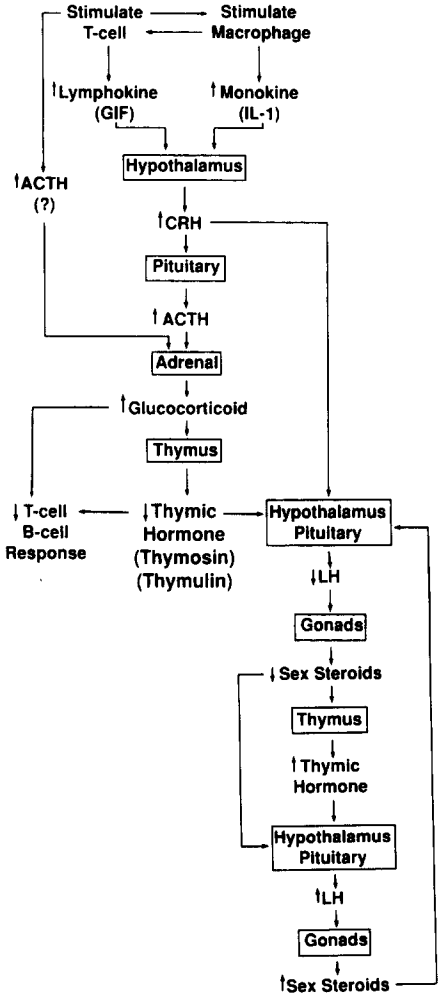

Fig. 1. LMFM axis. Interactions known or proposed to account for the down regulation of the immune response involving lymphokines and monokines elaborated during the immune response. These substances then recruit the HPAT and HPGT axes to continue this down regulation process. See text for details. Reprinted with permission from Ref. [1]

THE IMMUNOLOGICAL BASIS OF AUTOIMMUNITY

If effector lymphocyte/monocyte action is not limited by protective regulatory pathways, then these cells will either directly or indirectly

mistakenly attack innocent bystander cells, disrupting the tissue structure and leading to autoimmune disease. Direct attack includes the release of biologically active agents (enzymes, toxic cytokines, etc.) from the monocytes or cytotoxic lymphokines from the T-lymphocytes, while indirect attack may be mediated through antibodies released from B-lymphocytes or activation of the complement or kinin systems. It therefore follows that to properly understand the phenomena of autoimmunity one must understand the regulatory pathways designed to limit effector cell function.

A variety of factors have been identified that are both directly and indirectly responsible for the inappropriate activation of immune effector cells. In a recent paper by Sinha *et al.* [6] the authors succinctly list six genetic, immunologic and environmental factors believed to be involved in the breakdown of self tolerance leading to autoimmunity (see Table 1).

1. A major histocompatibility complex (MHC) susceptibility allele must be present on a precursor clone cell which is capable of binding and presenting target cell self antigen or foreign antigen that will stimulate blastogenic transformation and initiate the autoimmune process. This will allow for the selection of antiself T-cells involved in the autoimmune responses.
2. For autoimmune disease to be expressed it is necessary for classes of T-cells to be present which are antiself reactive. For such T-cells to be generated this specificity must be encoded in the germline and, for the phenotypic MHC molecule expression, there must also be the correct T-cell receptor (TCR) gene rearrangement which is a somatic event. The subsequent MHC molecular expression then leads to positive or negative selection of particular subclasses of T-cells within the microenvironment of the thymus. However, to effectively allow full expression of the autoimmune potential of these antiself T-cells, mechanisms that assure the generation and maintenance of peripheral tolerance must also be abrogated. While a full understanding of such regulatory mechanisms await further study, the function of antigen-specific T-suppressor cells that block the effects of the antiself reactive T-cells is thought to be of importance since such suppressor cells would promote clonal anergy of the antiself T-cells [7].
3. The MHC allele must bind to the target antigen and then present it to the antiself reactive T-cells initiating blastogenesis. Such initiating antigens may be autoantigens derived from inter-cellular or cell surface molecules and this process may require ectopic expression of certain class II molecules on nonlymphoid cells [8].
4. This process may require local production of lymphokines to activate the self-reactive T-cells [9].
5. The possible involvement of other non-MHC loci such as immunoglobin genes may exacerbate the disease.
6. Environmental triggers, for example microbial components or toxins can produce tissue damage and release sequestered self antigen from privileged inter-cellular immunological pools. Furthermore, local inflammation may stimulate lymphokine release resulting in the expression of ectopic class II molecules. Finally, cross-reactivity may take place because microbial antigen may be similar to self antigen. Such cross-reactive tissue destruction once initiated continues to be self activating because sequestered self antigen continues to be released by this tissue destruction.

Table 1. Genetic, immunologic and environmental factors involved in the breakdown of self-tolerance

1. Presence of an MHC susceptibility allele that is able:
   (i) to bind and present target self antigen;
   (ii) to select for antiself T-cells.
2. Existence of self-reactive T-cells based on:
   (i) germline V, D, J and constant (C) region elements;
   (ii) somatic rearrangement;
   (iii) positive and negative selection in thymus;
   (iv) escape from tolerance induction in the periphery.
3. Exposure of self antigens to immune system based on:
   (i) release of antigens from sequestered sites;
   (ii) ectopic expression of class II molecules on nonlymphoid cells.
4. Lymphokines and other constimulatory signals necessary to activate self-reactive T-cells (absence may lead to peripheral tolerance by clonal anergy).
5. NonMHC loci (mostly unidentified, although TCR and immunoglobulin genes have been linked to disease in some cases).
6. Environmental trigger (microbial or toxin) due to:
   (i) inflammation leading to lymphokine release and ectopic class II expression;
   (ii) molecular mimicry.

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THE DIMORPHIC EXPRESSION OF AUTOIMMUNE DISEASES

Interestingly, one finds that while MHC class II—associated autoimmune diseases (systemic lupus erythematosis, hyperthyroidism,

etc) show a highly specific female predominance, those diseases associated with MHC class I (ankylosing spondylitis, Reiter's syndrome) demonstrate a male predominance [10]. Such dimorphic phenotypic expression of the disease process is fascinating given the observation that in females the immune response is generally more active than in males except during pregnancy when cell mediated immunity is significantly reduced [1, 11, 12]. We will return to this point, but first it may prove useful to review information on those autoimmune diseases that demonstrate dimorphism. An excellent example of the dimorphic expression of autoimmunity can be found in Hashimoto's disease which is a chronic form of thyroiditis characterized by goiter with lymphocyte infiltration that progresses towards thyroid hypofunction [13]. This disease is four times more commonly found in women than in men and is four times more common in whites than in blacks. In an English study thyroid cytoplasmic antibodies were also found in 10.3% women but only in 2.7% men and while frequencies did not increase with age in men, there was a marked increase in women over 45 years of age [14]. Furthermore, in women it has also been reported that 3–6 months after the birth of a child, exacerbations in Hashimoto's disease as well as Grave's disease may take place, supporting a connection between abrupt changes in levels of circulating sex hormones and onset or reappearance of autoimmune dysfunction.

Two other excellent examples of autoimmune diseases that are more prevalent in women than men are rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). RA is manifested as an inflammatory disorder in the joints, but which may also be seen extensively in many other organs and tissues. For the disease to be expressed both a genetic component and environmental factors (such as infectious agents) are believed to be necessary. While several forms of RA have been identified with children the disease is classically observed in adults, the frequency increasing after age 30 and the female/male ratio is 3:1 [15]. Furthermore, the fact that experimental arthropathy in animals is sexually mediated [16] along with the observation that patients taking oral contraceptives demonstrated an apparent improvement [11, 16, 17] suggests that sex steroids act to modulate RA.

In SLE the disease ratio of women to men is 9:1 with alterations in estrogen metabolism frequently seen in female patients [18]. In the NZB/NZW F1 SLE mouse model females normally develop this disease after puberty and die, but will survive if treated with the androgen dihydrotestosterone, while males will die if castrated prepubertally and treated with estrogen [18]. Here we again find an apparent link between circulating levels of sex steroids and the onset and course of an autoimmune disease. However, while treatment of experimental animals with sex steroids may alter the disease process in such autoimmune models as mouse lupus, the clinical use of sex steroids in humans has not proved as effective.

One autoimmune disease whose course can be effected by treatment with the androgen danazol is idiopathic thrombocytopenic purpura [19]. The active variety of this disease in children is frequently found to follow a viral infection with a duration of 1 to 2 months. While the female/male ratio for this acute form in children is 1:1 in the chronic form found in the adult (which may last 30 years) the female/male ratio is 4:1 [20]. Another autoimmune disease which may in the future be treatable with androgen is Sjogren's syndrome. Here 90% of the patients are females and the disease presents as a chronic inflammation of the lachrymal and salivary glands [21]. Sullivan *et al.* [22] working with the MLR/lpr mouse model has demonstrated that androgen implantation can reduce the lymphocyte infiltrate in the lachrymal glands and prevent destruction of this tissue and subsequent dry eye.

A number of other autoimmune diseases also appear to depend on a sexual basis for their expression. These include (but are not limited to) diseases of the liver and islets of the pancreas. For example, in autoimmune chronic active hepatitis the female/male sex ratio is 8:1, with two peaks of expression, in young women age 10–30 and in older women 50–70 [23]. Sex differences in the incidence of hepatitis B infection have also been reported, with the incidence of the carrier state greater in males post infection than in females, as is the presence of chronic liver disease associated with the virus [18]. A linkage between alcoholic hepatitis, associated with a possible progression to hepatic fibrosis and cirrhosis has also been suggested [18]. Here the fibrogenesis has been linked to lymphocyte cytokine production [23, 24] and associated with increased T-lymphocyte infiltration [25] and specialized liver macrophage (Kupffer cell) activation [26]. The prevalence of injury is found predominantly in males

(3.3:1.0) [27] which parallels the higher prevalence of heavy alcohol intake in the males [28]. However, the prognosis for females suffering from this disease is far worse than it is for males with liver failures occurring at 2.5 times that seen in males. Interestingly androgenic anabolic steroid therapy has produced an improvement in these patients [29–31], possibly because it may function to reduce the autoimmune component of the disease. However, these androgens are also known to stimulate protein synthesis within the liver and thus to repair cellular damage. Possibly they may improve liver function by acting through both mechanisms simultaneously [18].

Regarding the autoimmune interactions associated with diabetes mellitus, the increase in the incidence of both organ specific and nonspecific antibodies in Type I Diabetes (and to a lesser extent Type II) most certainly involves a genetic HLA component. However, while in humans there is no apparent difference in the sex ratio between males and females, the occurrence of this disease in the nonobese diabetic mouse (NOB) is sex-related, occurring with a much greater incidence in females than in males. In this mouse model the disease develops spontaneously and is associated with lymphocytic infiltration in the pancreatic islets, thyroid gland, adrenal gland and testis, and castration increases the incidence in males and decreases it in females. These results further lend credence to a link between gonadal steroids and autoimmunity and clearly suggest that estrogens stimulate the onset and course of this disease while androgens are inhibitory [32].

THE DEVELOPMENT OF THE SELF-TOLERANT STATE

Development of autoimmune disease results from the breakdown of the self-tolerant mechanisms. Therefore, before we proceed further it may prove helpful to review those processes that are thought to lead to the self-tolerant state. In very early life (in rodents a few days after birth, in humans in the last months before birth) exposure to antigens produces tolerance rather than immunity because specific clones of T and possibly also B cells are specifically susceptible to inactivation at this time. This tolerant state is then maintained by several immune mechanisms involving the presence of specific classes of T-suppressor cells that inhibit the function of T-helper cells as well as B-cells [33]. Since an antibody response requires T/B cooperation, tolerance in either cell population will result in overall tolerance. However, if only B-cells are tolerant then T-cells may still mount a cell-mediated immune response. In general, immature lymphoid cells are more easily tolerized than are mature cells, T-cells are more easily tolerized than are B-cells, the duration of T-cell tolerance is longer than is B-cell tolerance, and both the dosage and method of antigen presentation are critical factors in the development of tolerance. Methods of generating B-cell tolerance include; clonal deletion, clonal abortion, clonal exhaustion and antibody forming cell (AFC) blockade, while methods of generating T-cell tolerance include clonal abortion [34].

PROPOSED HORMONAL MECHANISMS TO EXPLAIN THE DIMORPHIC EXPRESSION OF AUTOIMMUNE DISEASES

Since a large majority of autoimmune diseases are dimorphically expressed it is of great interest to define those mechanisms responsible. Although many of the regulatory interactions that can account for this sexual dimorphism still remain to be characterized, it would seem that they depend on a genetic and hormonal component. Furthermore, these two components must function together both in early development and later in the adult. Regarding the hormonal component we, along with a multitude of other investigators, have demonstrated that hormones elaborated from the gonads, adrenals, thymus, pineal and anterior pituitary as well as the thyroid and pancreas, all play a part in the complex regulatory axes involved in endocrine–immune regulation. For a complete overview of these various axes the reader may also wish to consult Fig. 2. In addition to the complex pathways outlined in this figure recent results also suggest that an age dependent thymic factor is inhibitory on human chorionic gonadotropin (HCG) which results in inhibition of steroidogenesis in rat ovarian cells [35], and also inhibits HCG binding to rat testes cells [36]. Because this factor is present in extracts of 14 day thymi but declines with increasing age this suggests a further level of negative feedback possibly also involved with puberty. The fact that gonadal steroids are intimately involved in these regulatory pathways outlined in Fig. 2 may account for the observation reported by Sinha *et al.* [6] that "many autoimmune diseases have a peak

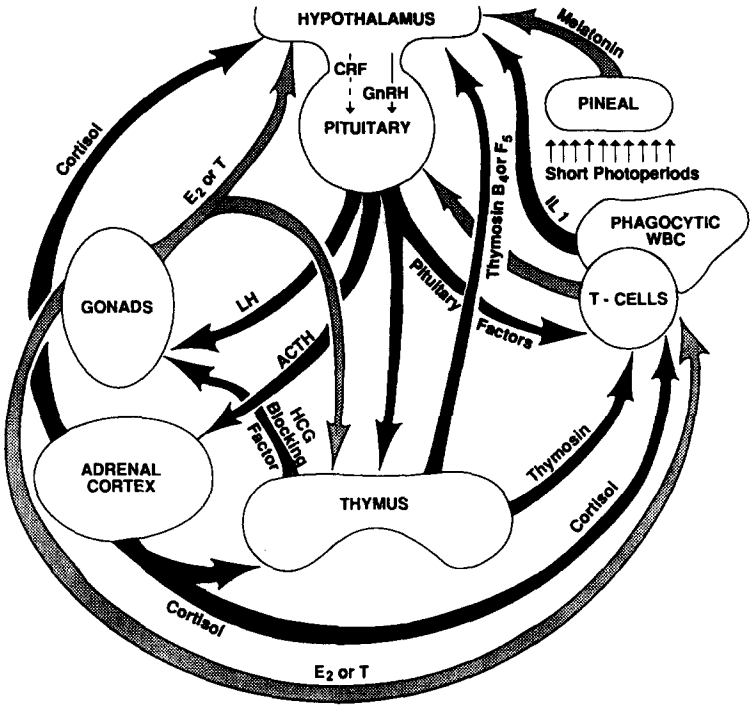

Fig. 2. Regulatory axes. Interactions of the HPAT axis, the HPGT axis and the LMFM axis involved in the regulation of immune effector cells. See text for details. This modified diagram is reprinted with permission from Ref. [1]

incidence at or shortly after puberty, often with a second peak in the forties and fifties", since circulating levels of gonadal steroids rise at puberty and fall again in the forties and fifties at menopause. Given our primary hypothesis that the maintenance of immune function is a homeostatic process, then such major changes in levels of hormones at puberty and menopause may significantly alter the regulatory mechanisms involved in maintaining this homeostasis. Thus, the outcome in susceptible individuals, (those possessing the six prerequisites described above) would consist of major alterations in the clinical expression of autoimmune disease.

It is also of importance to mention that significant depression in the cell mediated immune response takes place in females during pregnancy [1, 11, 12, 18] and which can be directly attributed to the elevation in the levels of circulating estrogen and progesterone. This decrease in cell mediated immunity in the pregnant female can be linked to an increased incidence of certain diseases during pregnancy but can also account for the improvement in autoimmune diseases (such as lupus and arthritis) during this period [11, 12, 18]. It also explains why termination of pregnancy increases the frequency of autoimmune clinical symptoms; undoubtedly resulting from the fall in circulating levels of steroids and the increase in cell mediated immunity. Given the observation that in nonpregnant female the immune response is more active than in the male we can ask what is the benefit of such a system where the response fluctuates with circulating steroid levels? It has been suggested by Rheins [37] that for an adult female to effectively overcome the stress of nurturing offspring she must be better prepared to meet the challenges of her environment. To do so a greater immune response is present in the nonpregnant female [1]. As expected, this greater immune response develops at the time of puberty because this is the beginning of her child-bearing years. However, during pregnancy to prevent graft rejection of the paternal (and therefore antigenic) foreign tissue component of the fetus, elevated levels of estrogen and progesterone now function to depress the cell mediated immune response [1]. After termination of pregnancy the increased immune response returns to allow the female to meet the stress of effectively rearing the offspring. While this system appears to work well in most cases, if regulatory pertubations occur, this would lead to adverse autoimmune responses.

In Figs 3 and 4 we outline our proposed mechanisms involved in generation of the

normal dimorphic immune response [1, 38]. As can be seen for the female, elevations in estrogen and prolactin and basal growth hormone secretion result in increased activity of T-helper cells concurrently with decreased activity of T-suppressor cells. The outcome is an elevation of both the cell mediated and humoral immune responses. Thymic hormones regulated by estrogen are also effected. The opposite effect is observed in the male where low levels of estrogen, increased levels of androgen, reduced prolactin and pulsatile growth hormone secretion increase T-suppressor function and reduce T-helper cell function. Thus, in the male both the cell mediated and humoral immune system is less active than in the female. In the male the androgen, dihydrotestosterone, may also reduce secretion of interleukin-2 (IL-2) a lymphokine that acts to stimulate the maturation and activity of other lymphocytes [1, 38]. Most recently further support for the increased production of the lymphokine, interferon, by NK-like spleen cells in the female mouse after stimulus by viral infective agents has been reported by Bigley [39–42]. Based on the premise that the immune response in normal females is greater than in males, it is not unexpected that autoimmune diseases are more commonly expressed in females than in males.

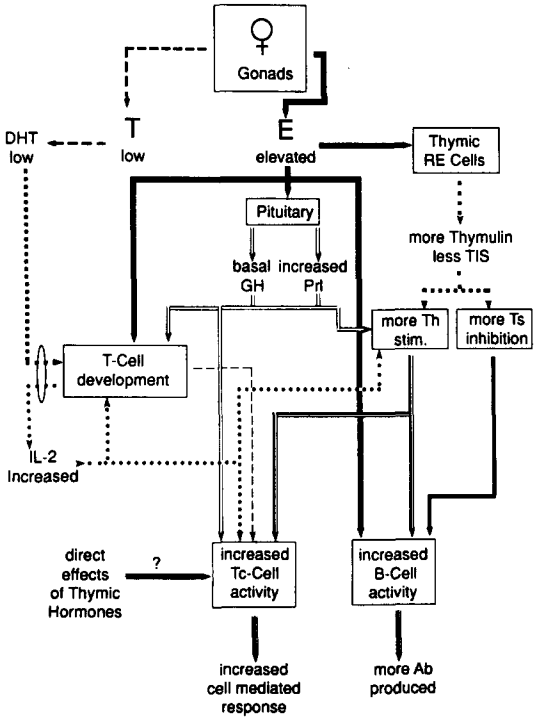

Fig. 3. Immunoendocrine regulatory pathways involved in the generation of the female dimorphic immune response. See text for details. Reprinted with permission from Ref. [1]

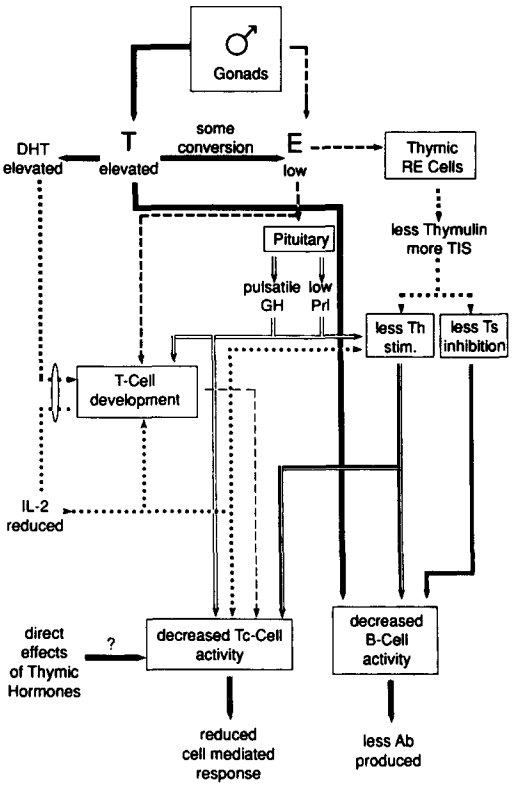

Fig. 4. Immunoendocrine regulatory pathways involved in the generation of the male dimorphic immune response. See text for details. Reprinted with permission from Ref. [1]

We have suggested [1] that in the female the immune system responds to a greater degree than it does in the male because first, the antigen response threshold is set lower than in the male, and second once the response is mounted the duration is longer and the levels of product (such as antibody) are greater. The longer duration of the response may be based on less sensitive feedback mechanisms, but this is as yet only a conjecture and still requires corroborating research. However, some information relating to this set point can be gleaned from studies on the immunoregulatory responses elicited by a stress stimulus. As can be seen (Fig. 5) the initial response is to elevate CRH, thereby stimulating those regulatory pathways controlled by ACTH and glucocorticoid [the hypothalamic–pituitary–adrenal (HPA) axis and hypothalamic–pituitary–adrenal–thymic (HPAT) axis], while inhibiting those regulatory pathways controlled by LH and sex steroids [the hypothalamic–pituitary–gonadal (HPG) axis and hypothalamic–pituitary–gonadal–thymic (HPGT) axis]. The immediate outcome at the level of the effector lymphocytes would be inhibition and destruction through increased release of glucocorticoid,

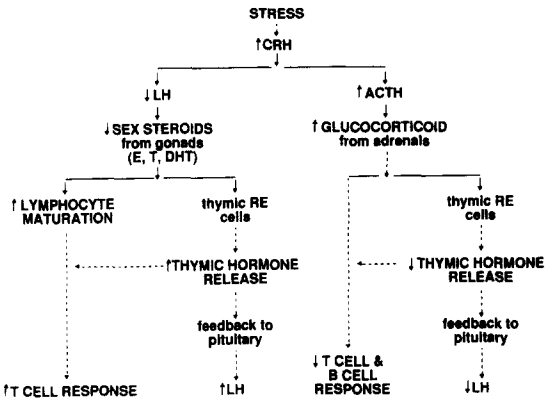

Fig. 5. Immunoendocrine regulatory pathways involved in the initial response to stress. Reprinted with permission from Ref. [1]

followed by increased maturation of precursor lymphocytes in the microenvironment of the bone marrow, spleen and thymus because of the withdrawal of sex steroids (Fig. 6). Over time these precursors would then replace the effector lymphocytes inhibited and destroyed. Hours to days after the initial stressor there is then a rebound in the levels of sex steroids which would then act to reestablish the original homeostasis [43]. Thus, both rates of initial stimulation and of the rebound play a role in immune regulation but the dynamics remain to be clarified. We are however convinced that the expression of these dynamics are based, at least in part, on immunological sexual dimorphism.

What factors (other than those discussed above) might play a role in the development of autoimmune disease and how might sex steroid hormones impinge on this process? To attempt to answer this question let us return once again to Table 1 and the list of 6 prerequisite factors that result in the breakdown of self-tolerance but let us now discuss their possible hormonal regulation. Since the development of self-tolerance is dependent on several mechanisms, it follows that steroid hormones could exert a significant effect on this process at more than one point. Clearly, for an individual to be susceptible to an autoimmune disease they must possess the appropriate HLA genotype. However, expression of the necessary phenotypic antigenic or receptor structures on the surface of the reacting target or effector cells may also require appropriate development within the microenvironment of the thymus or bone marrow. Such developmental processes are known to be under the control of a variety of hormones (Fig. 7) including sex steroid hormones [1, 38]. For example, androgens have been implicated in diverse regulatory activities including immunosuppression via specific subsets of T-suppressor cells [44], while androgens [45] and estrogens [46, 47] might act at the level of the thymus to regulate the secretion of inhibitory and excitatory immunomodulators. Furthermore, later stages (Fig. 8) in the activation of effector lymphocytes by antigen, including the formation of T-helper and T-suppressor lymphocytes, and the inter-regulation of these cell types with other effector cells such as T-cytotoxic lymphocytes and B-lymphocytes are also known to be under the control of various hormones including sex steroids.

The loss of T-suppressor cells may be one very important step in the development of autoimmune disease. In the BB mouse model, for example, "insulinitis" can be passively induced by transfer of lymphocytes from newly diabetic rats into athymic nude mice, or X-irradiated BB rats [32], while this autoimmune disease can be prevented by allogenic bone marrow transplantation from syngeneic nondiabetic rats. Transplantation is not effective if the cells transferred have been depleted of T-cells, suggesting that the appearance of the disease in the BB rat is due to the loss of T-suppressor cells capable of regulating tolerance to self antigen. Loss or abnormal function associated with T-suppressor

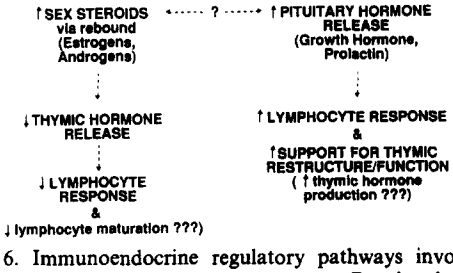

Fig. 6. Immunoendocrine regulatory pathways involved in the compensatory response to stress. Reprinted with permission from Ref. [43].

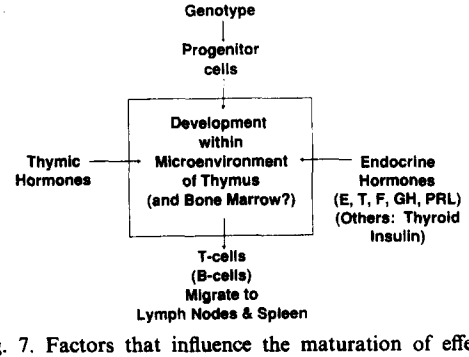

Fig. 7. Factors that influence the maturation of effector lymphocytes in the microenvironment of the thymus and bone marrow. Reprinted with permission from Ref. [38].

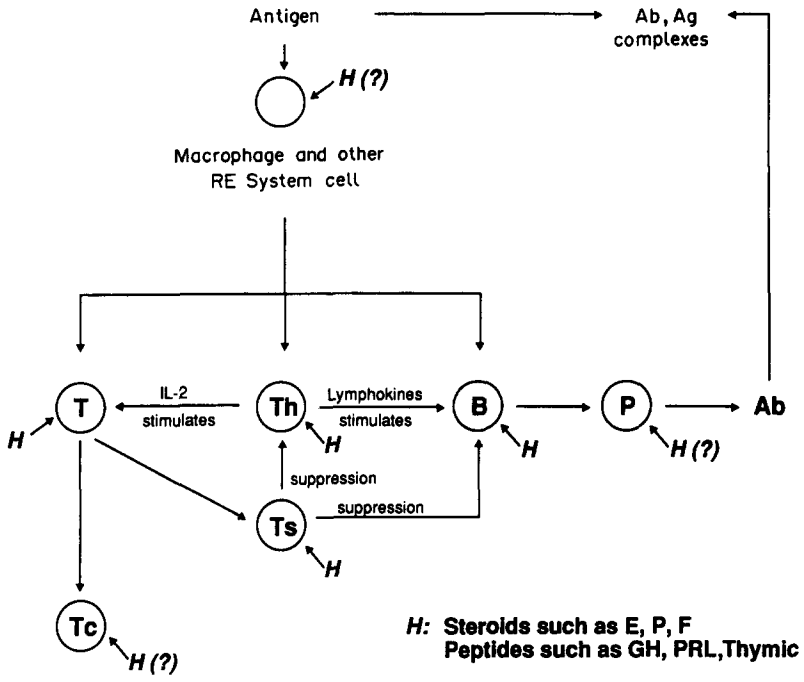

Fig. 8. Steps involved in the activation of effector lymphocytes after antigen stimulation. As can be seen, hormones are effective in exerting a modifying effect at each stage in the process.

cells has also been identified as a possible cause of autoimmune inflammatory bowel disease (IBD). Here both B and T-cells within the mucosal lymphoid tissue are mounting inappropriate antigenic responses to bacterial antigens. Patients with early IBD have T-suppressor cells resulting from autologous interactions between autoreactive T-cells and activated B-cells. However, late in the course of the disease there is a decrease in T-suppressor activity leading to the belief that IBD results from an underlying disorder of mucosal immunoregulation. It is possible that the primary initiating event is the inability to generate antigen-specific suppressor T-cells that normally turn off the response to a particular antigen [48].

Since both the early stages in cell development and the later stages of cellular activation allow opportunities for clonal deletion or clonal anergy leading to tolerance, it follows that inappropriate regulation during these stages may result in the breakdown of self-tolerance [1] (Fig. 9). Corroborating evidence to support this hypothesis can be found in the work of Ahmed [49] who proposed that sex steroids function at the levels of stem cells, pre-T and pre-B lymphocytes, and can also regulate adult T-cells and monocytes. Furthermore, Gulino has found that fetal thymus tissue [50] and large immature thymocytes [51] both contain receptors for estrogen. The obvious conclusion must be that sex steroids are involved in one or more stages of lymphocyte maturation in the microenvironment.

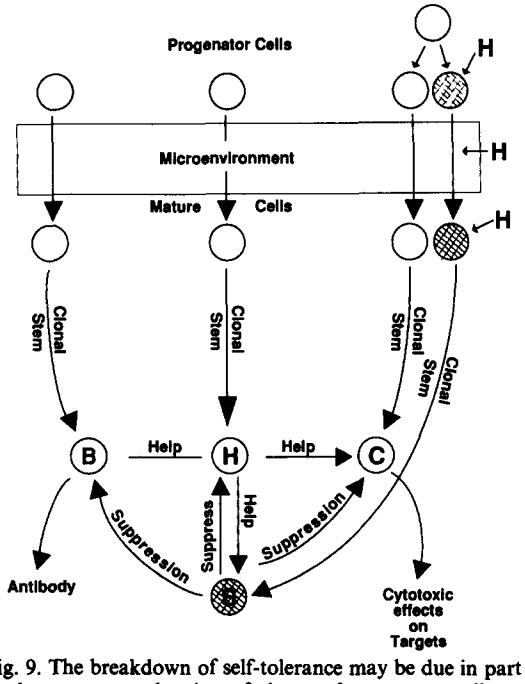

Fig. 9. The breakdown of self-tolerance may be due in part to the anergy or abortion of clones of suppressor cells or other effector lymphocytes. Here it can be seen that if hormones exert their effect on susceptible lymphocyte percursors during development then the absence of a particular hormonally susceptible clone may lead to the inability to down regulate other effector lymphocytes resulting in autoimmunity.

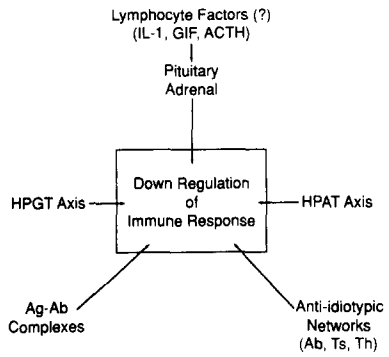

Fig. 10. A variety of factors are known or have been implicated in down regulation of the immune response. These include factors elaborated by lymphocytes, the HPGT and HPAT axes, the antiidiotypic networks (Jern hypothesis) and the generation of antibody–antigen complexes.

Sex hormone regulation of lymphokines may also promote changes in the clone populations or responses. For example Kovacs [52] has demonstrated that treatment of maturing thymocytes with the androgen dihydrotestosterone reduces their production of IL-2, although others have reported it to be increased [53], while Bigley [39–42] has demonstrated a sexual dimorphism in the production of Interferon. Earlier we alluded to the possibility that negative feedback mechanisms may be altered leading to abnormalities in immune regulation and disease. Pathways known or suspected of providing such down regulation (Fig. 10) include the HPGT axis and the HPAT axes (Fig. 2), LMFM axis (Figs 1 and 2), and idiotypic/anti-idiotypic networks (Figs 8 and 10). For example, Lahita [16] has proposed that the presence of rheumatoid factor (RF) quantitatively the major autoantibody present in the serum of patients with RA, appears due to a perturbation of idiotypic/anti-idiotypic network controlling RF production. This theory is supported by the presence of various anti-RF-idiotypes identified in both RA serum of experimental animals and in humans.

CONCLUSION

The function of the immune system is to mount an effective response against foreign antigen containing cells and substances, thereby keeping the body free of infection. Blalock [3] has suggested that the immune system is another sensory system that responds to antigenic stimulation by mounting an immune response. The transmission of information to the immune system is accomplished through neurological and endocrine factors which act as further stimuli for leukocytes. Since these regulators function both by negative feedback and positive feedforward circuits designed to maintain a homeostatic environment, inappropriate regulatory feedback mechanisms undoubtedly are responsible in part for autoimmune disorders. Generation of active autoimmune disease requires a variety of switches at the genetic, cellular and systemic levels, but the final outcome is a perturbation of normal homeostasis.

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