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GENERAL REVIEW

EFFECTS OF GENDER AND SEX STEROIDS ON THE IMMUNE RESPONSE

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Summary—Elevated immune responses and the higher incidence of autoimmune diseases in female (compared to male) humans and animals have been known for a long time. However, the scientific interest in this interrelationship has been limited both amongst immunologists and endocrinologists. It is mainly in the last ten years that investigations in this area have been intensifying. A number of fairly recent review articles confirm the increased interest in various aspects of this "interdiscipline" [1–4]. In the present paper we should like to make a new assessment of the state of knowledge. We shall firstly discuss heteroimmune response differences between males and females in humans, rodents and birds and then the roles of gender and sex hormones in autoimmune disease in various species. The general conclusions are the following. Gender and sex hormones have a clear effect on various hetero- and auto-immune responses but the mechanisms of action are still unknown; starting from sex hormones, steroids can be devised which have favourable effects on immune processes but lack undesirable hormonal effects; such hormonomimetics should be, in principle, applicable for the treatment of autoimmune disease.

INFLUENCE OF GENDER AND SEX HORMONES ON HETEROIMMUNE RESPONSES IN HUMANS

Scientific knowledge regarding the influence of gender and sex hormones on the immune response in humans is on the one hand considerable but on the other hand disappointingly incoherent.

(For physiological sex hormone levels see Table 1 and Fig. 1).

(1) Females have higher immunoglobulin levels than males [5] and mount higher antibody (Ab) responses to *E. coli* [6], and the microorganisms causing measles [7], rubella [8], brucella [5] and hepatitis B [9].

(2) Females seem to have decreased cell-mediated immunity (CMI) responses compared to males [10] but this does not correlate with the reputedly reduced incidence of tumours and a better resistance against viral and parasitic infections [3].

(3) The sex predisposition to allergy changes at about the age of 15 (when in males testosterone and in females oestrogen levels increase) from males to females [11, 12].

(4) During pregnancy mitogenic [13, 14] and CMI responses [14, 15] are found to be decreased while skin homografts survive longer than in non-pregnant women [16]; natural killer (NK) cell activity is reported to be suppressed in negative correlation with oestrogen levels [17]; killer (K) cell levels are significantly decreased during pregnancy and significantly increased 1 month post partum [18]. Although the sex hormone status is profoundly changed during pregnancy it is not certain that this is the (only) reason for changes in immune reactivity.

(5) Receptors for 17β-oestradiol (E2) have been identified in lymphoid cells [19], CD8 positive (T-cells [20, 21], mononuclear cells in peripheral blood [20] and thymic cells [19, 22, 23]. Androgen receptors have been demonstrated in human thymus [24, 25]; they are claimed to be absent in peripheral blood cells [20].

(6) E2 in physiological doses (see Table 1) and the anti-oestrogens tamoxifen and FC-1157a stimulate pokeweed mitogen (PWM)-induced Ig synthesis of B-lymphocytes [26–28]. Testosterone (Te) in physiological doses (see Table 1) inhibits Ig synthesis [28] or has no effect [26], probably depending on the

Abbreviations: AA, adjuvant arthritis; AAb(s), autoantibody(ies); Ab(s), antibody(ies); CD, cluster of differentiation; CIA, collagen type II induced arthritis; CMI, cell-mediated immunity; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; E2, 17β-oestradiol; ESR, erythrocyte sedimentation rate; HI, humoral immunity; IDDM, insulin-dependent diabetes mellitus; Ig(s), immunoglobulin(s); IL, interleukin; MS, multiple sclerosis; ND, nandrolone decanoate; NK, natural killer; OC(s), oral contraceptive(s); PBMs, peripheral blood monocytes; PHA, phytohaemagglutinin; PWM, pokeweed mitogen; RA, rheumatoid arthritis; (S)LE, (systemic) lupus erythematosus; SS, Sjögren's syndrome; Te, testosterone.

Table 1. Plasma levels of sex hormones (nmol/l) in various species

Species	Hormone	Males	Females Di-oestrus[A]	Females pro-oestrus[B]	Pregnancy
Human	Progesterone	0.8[h]	0.3[c]	1–3[c]	300–1000[c]
	Oestradiol	0.1[h]	0.2[c]	1–2[c]	130[c]
	Testosterone	12–18[g]	0.1–1.2[c]	0.1–1.2[c]	—
Mouse	Progesterone	12[d]	10[d]	50[j]	150[i]
	Oestradiol	<0.003[d]	0.07[j]	0.13[j]	0.05–0.10[j]
	Testosterone	20[d]	0.6[d]	—	1.5[i]
Rat	Progesterone	—	50[e]	30[f]	250[f]
	Oestradiol	0.1[a]	0.03–0.05[b]	0.08–0.17[b]	0.15[b]–1.9[j]
	Testosterone	3–12[d]	0.12–0.18[b]	0.3–0.6[b]	1.2[b]

In humans: [A]di-oestrus = early follicular; [B]pro-oestrus = follicular phase. —: no data found.
[a–j]: Refs [276–285] respectively.

dose of PWM used [28]. E2 and dihydrotestosterone (DHT) in supraphysiological doses have an inhibitory effect on phytohaemagglutinin (PHA)-stimulated lymphocyte proliferation [29, 30].

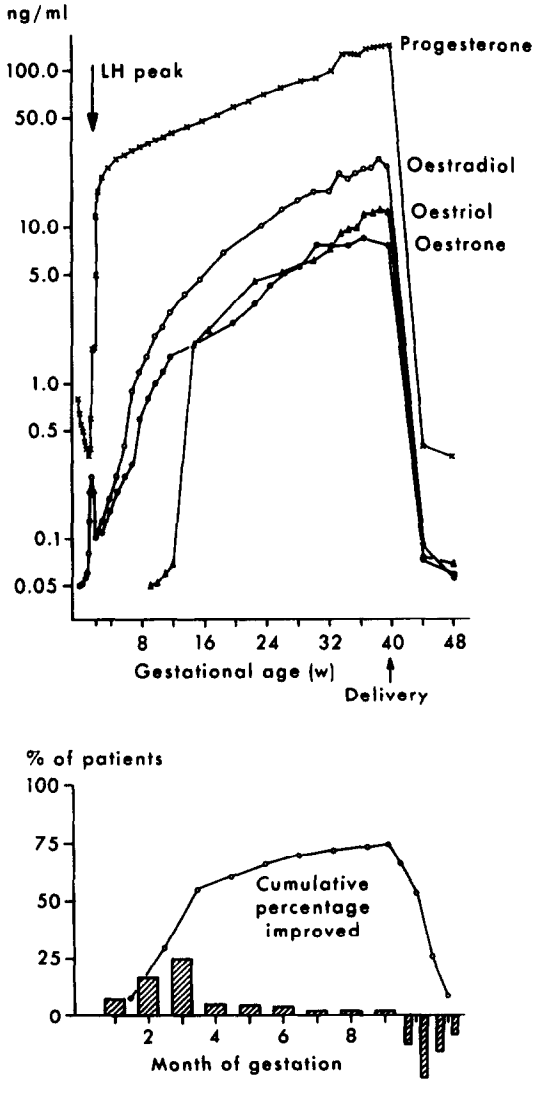

Fig. 1. Effects of plasma steroid levels during pregnancy on clinical manifestations of rheumatoid arthritis.

(7) Administration of human chorionic gonadotrophin to five prepubertal boys with incomplete descent of one testis causes a rise in Te to normal levels together with a significant decrease in the CD4/CD8 ratio [31].

(8) Progesterone increases the production of immunosuppressive factors by proliferative endometrial tissue (as determined by their effect on mixed lymphocyte reaction and PHA-induced proliferation); the higher inhibitory activity of secretory endometrium could not be significantly changed by progesterone [32]. Severe premenstrual exacerbations of asthma can be diminished by progesterone [33]. *In vitro* the progestagen lynestrenol stimulates active T rosetting, leukocyte adherence inhibition and phagocytosis by monocytes [34].

(9) E2 in physiological concentration increases granulocyte-macrophage colony formation from peripheral blood monocytes (PMBs) [35, 36].

(10) NK cell activity is decreased during the periovulatory period [37]. Tamoxifen stimulates human NK cell activity *in vitro* [38]. NK cell activity is also depressed during pregnancy (see above).

(11) Women taking oral contraceptives (OCs) containing progestagen and oestrogen have been reported to show a somewhat reduced *in vitro* PHA stimulation of lymphocytes but an increased skin reactivity to dinitrochlorobenzene; medroxyprogesterone acetate produces a similar increase [39]. More modern, low-dose combination OCs have no significant effects on Ig levels, *in vitro* Ig production [40, 41], mitogen-induced proliferation [42] or levels of leukocyte subsets [43].

(12) Interleukin-1 (IL-1) production by human monocytes *in vitro* is stimulated by 10^{-9} and inhibited by $>10^{-7}$ mol/l progesterone; E2 in concentrations of 10^{-10}–10^{-9} stimulates and concentrations of $>10^{-8}$ mol/l inhibits IL-1 production [44]. The menopause is accompanied by a significant rise in IL-1 release from monocytes; this rise is reversed in women treated with oestrogen/medroxyprogesterone acetate [45].

INFLUENCE OF GENDER AND SEX HORMONES ON THE HETEROIMMUNE RESPONSE IN RODENTS

The findings in humans have been confirmed and expanded by many studies in animals [1, 2, 46–49].

(1) Female rodents of various species have—compared to males—higher IgM, IgG and IgA levels and are able to mount higher Ab responses of various Ig classes to a variety of T-dependent and T-independent antigens [49, 50]. Female rodents have been reported to have lower [10] and higher CMI responses [48, 51, 52]. Females show a higher resistance to tumours and parasites (reviewed in [1, 3]).

(2) Castration of male rodents induces rises in Ig levels, HI and CMI responses and in weights of thymus, spleen and lymph nodes; in the latter two, cells in the T-dependent area are increased [1, 48–50]. In mature female rodents gonadectomy does not significantly change HI responses, whereas it increases CMI responses and thymus weight. The increase in thymic weight after neonatal or adult castration is the result of a delay in the physiological involution of the thymus and of hypertrophy of cortical and medullary glucocorticoid-sensitive thymocytes and reticuloendothelial cells [1, 53]. Recent data with genetically hypogonadal mice (F1 hybrids between the inbred strains C3H/HeH and 101/H) show interesting differences between castrated animals [54]. The splenocyte count in normal males was about 72×10^6 while in normal females and hypogonadal males and females it was between 110 and 120×10^6. Thymus weights and thymocyte counts in males were higher in hypogonadal animals while in females they were lower. In particular this latter point differs from results obtained with ovariectomized females.

(3) Treatment of intact and castrated male or female rodents with high or even physiological doses of E2 increases Ab responses—mainly of the IgM-type [55]—to various T-dependent and T-independent antigens [10, 56]. Supraphysiological doses of E2 decrease the CMI responses [2, 48, 57]. Cyclic exposure has a stronger effect on Ab formation than chronic exposure; it does not lead to thymic atrophy [58]. Tamoxifen inhibits both the Ab response and CMI [59]. In ovariectomized rats (near) physiological doses of E2 increase IgA, IgG and specific Ab (to sheep erythrocytes) levels in uterine secretions while E2 decreases levels in the vagina [60]. The non-steroidal oestrogen diethylstilbestrol has a suppressing effect on various immune responses; see [61] and cited literature.

(4) Treatment with supraphysiological doses of Te or DHT decreases HI and CMI responses [1, 10, 62] and thymic weight [1, 53, 63, 64]. The Te-induced immunosuppression is genetically regulated [65]. Mouse strains with high androgen responsiveness as measured in the seminal vesicles weight test show low immune responses [66].

(5) Receptors for sex hormones have been identified in thymic tissue in rodents [1, 67–69]. These receptors are probably localised in epithelial cells, although oestrogen receptors have also been found in lymphoid cells. The effects of E2 and Te on the immune reactions seem to be indirect [70–72].

(6) Macrophages from mature female rats produce more IL-1 than those from mature males or immature females; ovariectomy causes a reduction which can be reversed by E2 [73]. Physiological doses of oestrogens enhance and progestins inhibit the clearance of IgG-coated erythrocytes by guinea-pig splenic macrophages by affecting the Fc receptors in these cells; these activities do not correlate with the hormonal effects of the various analogues tested [74].

(7) Natural killer cell activity fluctuates during the oestrus cycle and during pregnancy in the mouse [75].

INFLUENCE OF GENDER AND SEX HORMONES ON THE HETEROIMMUNE RESPONSE IN BIRDS

The concept that sex hormones play a role in the regulation of the immune response is also supported by various findings in birds.

(1) The bursa of Fabricius attains its maximal weight in young animals and involutes at sexual maturity [76].

(2) Surgical removal of the testes increases the size of the bursa [76].

(3) Embryonally administered Te, nandrolone or mibolerone dose-dependently inhibits the growth of the bursa [77–83], whereas less pronounced or no effects are found on thymic weight [77, 79] or T-cell functions [80, 82]. Treatment with Te (esters), nandrolone or mibolerone tends to decrease total IgG levels, whereas IgM levels tend to be increased [80, 83, 84, 87]. In addition, complete or partial inability to mount specific Ab(s) to various antigens is observed [78, 80, 83–87]; specific Ab(s) are—when generated—of the IgM-type [80, 83, 87]. The inability to mount IgG Ab(s) seems not to be due to a lack of T-helper cell function but rather to an inability to switch from IgM-type responses to IgG-type responses [80, 87, 88].

An interesting pharmacological aspect is that the effects of steroids on bursa weight and Ab formation are not correlated with their androgenic or virilising properties; there is also no correlation with oestrogenic or progestational activities [87, 88].

(4) Receptors for oestrogens, androgens and progestagens have been identified in bursa tissue, most likely in the bursa epithelium [1, 89].

CONCLUDING REMARKS ON INFLUENCE OF GENDER AND SEX HORMONES ON THE HETEROIMMUNE RESPONSE

Although the picture of the influence of gender and sex hormones on normal cell-mediated and humoral immune responses is far from complete, much evidence suggests that physiological levels of oestrogens stimulate HI and CMI responses and that male hormones do the opposite. The presence of cytoplasmic receptors for oestrogens and androgens in lymphoid cells or in the thymic or bursal matrix may partly explain why these sex hormones are able to

modify structure and function of these organs and to interact with the immune system and regulate it. The exact mechanisms remain to be elucidated, but several possibilities may be put forward (cf. Ref. [28]):

(i) Oestrogens may have direct effects on B-cells [55], inhibit T-suppressor function [26] or facilitate T-helper maturation [93] and may influence macrophage maturation and function [35, 36, 73, 74];

(ii) Androgens may interfere with maturation processes of B-cells [1, 80, 85] and T-suppressor cells [91] from precursor B- and T-cells respectively or from bone marrow cells [92], the latter resulting in increased T-suppressor function [93].

EFFECTS OF GENDER AND SEX STEROIDS ON HUMAN AUTOIMMUNITY

Various observations in man support the concept that gender and sex hormones also influence autoimmune reactions. In view of the differences in origin and pathogenesis of various autoimmune diseases, it is dangerous to generalise; nevertheless, several observations suggest a more or less general pattern.

(1) A distinct female preponderance exists during the reproductive age in autoimmune diseases, e.g. 9:1 in systemic lupus erythematosus (SLE); 10:1 in Sjögren's syndrome (SS); 3:1 in rheumatoid arthritis (RA) overall but 7:1 during the first half of the fertile period; 2:1 in multiple sclerosis (MS) [10, 94–96].

(2) The female preponderance in SLE and RA is more pronounced during the reproductive age than before or after [12, 95, 97–99].

(3) Klinefelter's syndrome (with increased E2 and decreased Te levels) seems to increase the incidence of SLE [100] and RA [95] and to contribute to the pathology of RA [101] although conflicting evidence exists [102].

(4) Another indication that sex hormones influence autoimmune disease, but not necessarily in the same way, is pregnancy, where steadily increasing levels of oestrogens and progesterone are found (Fig. 1). Pregnancy is reported to reduce clinical symptoms in RA [103, 104] and MS [105], whereas in SLE exacerbations are observed mainly during the first trimester [106–111]. However, a recent study shows that T-suppressor function normalizes in SLE patients during pregnancy [112] and a prospective study [113] suggest that pregnancy has no effects on the symptoms of SLE. RA, MS and SLE may all deteriorate post partum [105, 112, 114]; in SLE this coincides with reduced T-suppressor cell function [112]. Clinical activity of Graves' and Hashimoto's disease and autoantibodies (AAbs) found in these conditions are reduced during pregnancy. Transient post partum thyroiditis is well-known: an incidence of 10–17% is reported; it recurs after subsequent pregnancies and sometimes progresses to permanent hypothyroidism [115]. In MS exacerbations were also found less frequently during pregnancy but they occurred more often 3 months post partum [116].

(5) Premenstrual flare-ups are frequently observed in SLE [95, 117] and RA [118, 119]. The statistical significance, however, is somewhat doubtful. In this context an interesting hypothesis is that menstruation is a steroid (oestrogen, progesterone)-regulated, cyclic autoimmune process [120].

(6) Abnormal production or metabolism of sex hormones has been reported in SLE and RA patients.

In SLE patients an increased 16α-hydroxylation of oestrogens leading to increased levels of 16α-hydroxyoestrone and oestriol is well documented [121–123]. 16α-Hydroxyoestrone binds to proteins [124] which supposedly leads to formation of Ab to oestrogen [125]. In addition, increased oxidation of Te at C17 is found in patients during "active" disease [126], resulting in low Te plasma levels [127]. Bermúdez *et al.* [128] reported a rise in androstenedione and decreases in Te, DHT and E2 levels in male SLE patients. In a later study [129] male SLE patients were found to have normal Te levels but decreased levels of androstenedione, dehydroepiandrosterone (DHEA) and DHEA sulphate; in female patients all four levels were lower than normal.

In female RA patients significantly reduced levels of dihydroandrosterone, etiocholanolone and DHEA (all 11-deoxy-17-ketosteroids, which are mainly androgenic/anabolic steroid hormone metabolites) are observed, whereas levels of 11-oxy-17-ketosteroids (mainly glucocorticoid hormone metabolites) are not significantly different from controls [99]. In postmenopausal RA patients both statistically increased [130] and decreased [131] androgen levels have been reported. In males suffering from RA significantly reduced levels of androgens or androgen metabolites are found [132–134]. Taken together these results suggest an abnormality of adrenal androgen synthesis or metabolism in RA which, based on the observation that the greatest relative deficiency occurred in DHEA secretion, may be localised in the 17,20-desmolase function [99]. Whether this is a primary predisposing or a secondary factor in RA remains to be investigated.

(7) Various epidemiological studies show a reduced incidence (about 50%) of RA in women using OCs containing an oestrogen and a progestin (e.g. Ref. [135]; however, not all studies report a statistically significant effect (e.g. Ref. [136]). A significantly reduced incidence of thyroid disease has also been reported [137]. Various studies [138–141] suggest that OCs induce LE cells and other symptoms associated with SLE in symptom-free women who had false positive syphilis tests or had previously suffered from rheumatic manifestations [142]. In contrast, extensive studies in healthy women taking OCs [12, 143] and a prospective controlled study [144] show no altered serology or rheumatic complaints.

According to several reports in the 1960s the severity of already manifest RA is reduced by OCs [145–147]; in addition, in some patients the

dose of glucocorticoids required to control the RA can be reduced when they receive concomitant OCs containing norethynodrel and mestranol [146]. In SLE patients the findings are different: OCs containing oestrogen and progestagen induce exacerbations [138, 142, 148]. These exacerbations are suppressed when OCs are discontinued [138] or when progestagen-only OCs are used [142, 149].

(8) Several early studies suggest favourable effects of Te or Te esters on RA [150–152], SLE [153] and SS [154, 155]. In a recent study five patients with Klinefelter's syndrome combined with SS (3 patients) or SLE (2 patients) treated with Te undecanoate (2 × 60 mg daily) showed clinical remission and normalization of various laboratory parameters: erythrocyte sedimentation rate (ESR), anti-nuclear antibodies, rheumatoid factor, complement and various clusters of differentiation CD3, CD4, CD8 and CD4/CD8 [156].

Various studies suggest that therapies which include nandrolone decanoate (ND) have some favourable effects on RA [157] and that ND counteracts catabolic changes induced by concomitant glucocorticoid therapy [158, 159].

In an epidemiological study on "non-contraceptive hormones" and RA in peri- and post-menopausal women [160] reduction of RA incidence was found amongst users of non-contraceptive hormones in particular oestrogens, and amongst previous OC users; the protective effects were especially visible in seropositive RA.

Danazol® has some favourable effects on SLE [161], discoid lupus [162] and idiopathic thrombocytopenia [163]. ND also has favourable effects in female SLE and SS patients [164, 165]. In a controlled trial of ND (50 mg once every 3 weeks) in 47 post-menopausal patients with RA no clinical improvement was seen except in the concurrent anaemia [166]. An earlier study in RA with stanozolol (2 × 5 mg/day) has shown a significant decrease in disease activity and ESR [167]. Tamoxifen has been shown, in a limited study, to have no favourable effects in SLE [168]. The anti-androgen cyproterone acetate suppressed exacerbations in SLE; this is explained by suppressed E2 levels [169].

(9) Male patients with autoimmune disease have an increased incidence of AAbs against the oestrogen receptor [170].

(10) Intraarticularly injected progesterone gives a highly significant inhibition of local inflammation [171]. This may be related to the inhibition of IL-1 production by monocytes [44].

The data presented in this section provide evidence that sex hormones are involved in and altered during the expression of autoimmune disease in humans, although their effects may vary from one disease to another. Androgens seem to "dampen" autoimmunity, whereas oestrogens may have a favourable effect in RA and thyroiditis but may be deleterious in SLE.

INFLUENCE OF GENDER AND SEX HORMONES ON SPONTANEOUS AUTOIMMUNE DISEASE IN ANIMALS

Several inbred strains of mice and rats exhibit a consistent incidence of autoimmune disease. Some of these animals models for autoimmune disease show an influence of gender and sex hormones; in others this influence is not apparent.

NZB mice

The autoimmune disease of NZB mice is characterized by the spontaneous development of autoimmune haemolytic anaemia, including production of anti-erythrocyte Abs, hypergammaglobulinaemia (Abs to e.g. dsDNA, ssDNA, retrovirus gp70), hypocomplementaemia (C5 deficiency), occasional lymphoproliferative disorders and mild immune complex-type glomerulonephritis, associated with positive LE tests [94, 172–176]. This seems to be a consequence of a defect in bone marrow cells, resulting in abnormal T- and B-cells [177, 178] with a hyperresponsiveness or a polyclonal B-cell activation [173]. In addition, thymic atrophy, myocardial infarction and brain-reactive Abs are found [179].

There is no marked sex difference with respect to the development of the autoimmune disease symptoms [172] and the median life span is 16 (female) and 17 (male) months respectively. Te has no effect on survival [180], but still seems to reduce autoantibody production. DHEA delays haemolytic anaemia and significantly decreases body weight [181]. ND prolongs survival and lowers anti-DNA levels [182].

NZB/NZW F1 hybrid mice (NZB/W)

The autoimmune disease of NZB/W mice is considered a relevant model, in particular for human SLE [172–175, 183]. These mice spontaneously develop AAbs to nucleic acids [dsDNA, ssDNA, RNA), retrovirus gp70 and erythrocytes, brain-reactive and natural thymocytotoxic AAbs, circulating immune complexes and hypergammaglobulinaemia. Important is the switch of IgM- to IgG-type AAbs which coincides with the development of overt immune complex disease [173, 174, 184–186]. Deposits of Ig(s), immune complexes and complement are frequently found in various organs; deposits in the kidneys, for example, result in glomerulonephritis. Thymic atrophy, a mild lymphoid hyperplasia and myocardial infarction are frequently observed [172, 187].

These hybrid mice also show large mononuclear cell infiltrations around the blood vessels and glandular ducts in submandibular and lacrimal glands, in which also destruction of glandular parenchyma, oedema and proliferation of ductal cells are observed. This sialoadenitis closely resembles SS in humans [188, 189]. The pathogenesis of lupus and

sialoadenitis is still unknown. Defects may be present in both B-cell and T-cell compartments.

The influence of gender and sex hormones on autoimmunity in NZB/W mice can be summarised as follows.

(a) Onset of murine lupus is earlier and the disease more severe in females than in males; median lifespan in females and males in 8.5 and 15 months respectively. Castration of male animals before puberty generates a disease pattern very similar to that in females; castration of female animals has no significant effects. Chronic treatment of intact females and orchidectomised or intact males with androgen postpones lupus and death, restores suppressor function and IL-2 production [185, 190–198] and delays the switch from IgM- to IgG-type AAbs, a phenomenon comparable to that found in the Te-induced inhibition of IgG-type Ab production in chickens [80, 81, 83–85, 87, 88]. DHEA also delays the autoimmune symptoms [196]. E2 in silastic implants was reported to accelerate autoimmune disease and death [185, 194]. Progesterone has no effect [194].

(b) Short-term administration of Te increases Lyt 2^+ (T suppressor/cytotoxic] cells and suppressor functions whereas E2 tends to reduce these parameters [200].

(c) Sex hormones modulate the clearance of IgG- and complement-coated autologous erythrocytes in NZB/W mice: E2 delays and DHT promotes clearance from the blood [201]. This is different from the reported enhancement of clearance by E2 found in guinea-pigs (cf. [74, 201]).

(d) Receptors for oestrogens and androgens have been demonstrated in thymic tissue extracts [194, 197].

(e) Also hormonomimetics have been investigated. The anti-oestrogen Nafoxidine® delays autoimmune phenomena [199]. Danazol is without effect [195] while ND is found to be active on both lupus and sialoadenitis even with concurrent corticosteroid treatment [202–205]. Another anabolic steroid, ethylestrenol, the progestagen lynestrenol, and a compound with weak androgenic, oestrogenic and progestational properties, tibolone, are found to be effective; another progestagen, desogestrel, however, is in comparable doses without effect [206, 207]. These results in NZB/W mice suggest that there is no correlation between intrinsic hormonal and autoimmunosuppressive activities; this is in line with the effects of various steroids on bursa weight and Ab formation in chickens [88].

BDF1 mice

Aging female (C57Bl/6NCrj × DBA/2NCrj)F1 = BDF1 mice develop sialoadenitis while significant inflammatory changes do not develop in the salivary gland of males [208].

Lpr/lpr mice

Autoimmune disease in MRL-lpr/lpr mice is characterised by severe early-onset subacute glomerulonephritis, AAb formation to DNA and retrovirus gp70, IgM- and IgG-rheumatoid factors, arteritis and arthritis, and is associated with massive lymphadenopathy and splenomegaly [173–176, 187, 209, 210]. The massive lymphoproliferation—which is not a common feature of human autoimmune disease—is induced by the lpr gene and consists mainly of one particular T-lymphocyte subpopulation (Thy^+, Lyl^+, $Ly2^-$, which are found on T-helper cells). Excessive T-help signals might explain the B-cell hyperreactivity [174, 175].

Male mice tend to survive slightly longer than females and show lower levels of AAbs against e.g. DNA [211]. Administration of Te or DHT to castrated male and female mice prolongs survival [212, 213] and restores the ability to produce IL-2 [197, 200]. We have found no improvement in morbidity and mortality by treatment with Te decanoate or ND (Verheul *et al.*, unpublished data). Danazol has a favourable effect in female but not in male MRL-lpr mice [214]. Manipulations which retard disease development such as splenectomy at 2-weeks of age [215], neonatal thymectomy [215] or cyclophosphamide treatment [216] tend to increase the difference in morbidity and mortality between males and females. The introduction of the lpr gene into mice with different genetic backgrounds induces different patterns of disease: either mice experience no autoimmune disease at all and die early from infiltrative pulmonary disease due to the excessive lymphoproliferation or they have severe autoimmune disease and die early as a consequence of immune complex glomerulonephritis [217–219]. The C57Bl/6-lpr/lpr mice show a distinct but limited sex difference in autoimmune disease; Te is autoimmunosuppressive [49]. Remarkably, F1 mice of this strain and MRL-lpr/lpr show a greater sex difference [49].

NOD mice

The Non-Obese Diabetic mouse strain developed by Makino *et al.* shows insulitis in almost all animals while hyperglycaemia and insulin-dependent diabetes mellitus (IDDM) develop in 80% of the females and 20% of the males [220]. Ovariectomy decreases and orchiectomy increases the incidence of IDDM in female and males respectively [220]. Bone marrow cells from NOD mice can transfer insulitis and diabetes to related non-diabetic mice [221]. T-cells are essential for diabetes to develop: introduction of the nude mouse gene in NOD mice prevents the development of diabetes; when these immunodeficient animals are reconstituted with T-lymphocytes from "normal" NOD mice diabetes reappears [222]; (monoclonal) Ab(s) against T-cells or T-cell populations (anti-Thy 1.2 and anti-L3T4) prevent diabetes [223, 224].

BB-diabetic rats

The BioBreeding (BB) rat is another model for

human IDDM [225]. The disease in the BB rat is characterized by infiltration of lymphocytes and macrophages into the islets of Langerhans in about 30–60% of the rats when they are 60–130-days old. In addition, lymphopenia, non-toxic goitre associated with circulating thyroid growth stimulating Igs and Abs to islet cell surface antigens or thyroglobulin are frequently observed [225–227]. IDDM in the BB rat is secondary to severe cellular abnormalities, probably as a consequence of a stem cell defect [228, 229]. No sex preponderance can be demonstrated in this model [225, 230] with respect to incidence, onset and severity. Castration and various sex hormones do not affect the development of IDDM [231, 232].

Obese Strain (OS) chickens

The OS chickens spontaneously develop an organ-specific autoimmune disease, namely a thyroiditis resembling human Hashimoto's disease with autoimmune destruction of thyroid tissue 4–8 weeks after hatching [233, 234]. During the selective inbreeding process for the autoimmune thyroiditis trait, incidence and severity of the thyroiditis were higher in female than in male animals [235]. The incidence is now 100% in both males and females. Removal of the bursa of Fabricius either by surgery or by treatment *in ovo* with Te prevents the development of thyroiditis [236]. Decline of thyroglobulin AAb(s) with age is found in males, but not in females [237]. Physiological levels of Te also prevent the development of thyroiditis [238, 239]. Te also lowers the levels of corticosteroid binding globulin which are abnormally high in OS chickens [239]. These data indicate that the autoimmune process in OS chickens may be influenced by sex hormones or their derivatives. *In ovo* treatment of OS chickens with various hormonomimetics also inhibits the development of autoimmune disease: e.g. nandrolone, lynestrenol, ethylestrenol and tibolone (data from Wick *et al.*, Innsbruck, Austria, in collaboration with us; partly published [240]).

INFLUENCE OF GENDER AND SEX HORMONES IN NON-SPONTANEOUS ANIMAL MODELS FOR AUTOIMMUNE DISEASE

Many animal models involving experimentally induced autoimmune diseases have been described without generating data on any influence of gender or sex hormones. Therefore, only models, in which this aspects has been investigated, are described below.

Collagen type II induced arthritis (CIA)

Immunization of a susceptible mouse strain, e.g. DBA/1, with type II collagen causes polyarthritis; remarkably, effects of gender, gonadectomy and sex hormones in this model are opposite to those found in human autoimmune disease and in various spontaneous models of autoimmune disease, e.g. in the NZB/W mouse model: male mice are more susceptible to CIA than female mice [241, 242]. Ovariectomy of females produces a disease pattern similar to that in males; orchidectomy of males does not change the disease pattern [241]; E2 in physiological doses protects ovariectomized females [243]. Pregnancy of mice with CIA causes a remission, while post partum an exacerbation has been reported [244, 245]; this is similar to clinical experience with pregnant patients with RA. However, whereas male mice are more susceptible to CIA, female humans are more susceptible to RA and other autoimmune diseases.

Adjuvant arthritis (AA)

Injection of complete Freund's adjuvant in susceptible rat strains causes polyarthritis with little difference between males and females [246]. Very high doses of oestrogens (4000 × the physiological level) diminish disease symptoms [247]. In male rats with AA Te levels are reduced [248, 249] whereas LH is raised [249].

The connection between these scattered data is difficult to see; a more systematic study in this animal model is lacking.

Experimental autoimmune thyroiditis

A quasi-spontaneous thyroiditis model is the thymectomized and sublethally irradiated rat [250, 251]. The rat develops thyroiditis without further manipulation. The incidence varies from 20–66% depending on the strain [252]. Females are preferentially and more severely affected than males; orchidectomy enhances thyroiditis while Te protects [252, 253].

Bacterial cell wall-induced arthritis

Systemic administration of bacterial cell wall preparations to certain strains of rats causes chronic erosive arthritis [254–256]. Particularly in the LEW/N rats the incidence and degree of arthritis are considerably higher in female than in male animals [256]. Orchidectomy of males produces a "female" disease pattern. E2 at a high dose [257] increases the incidence and severity of arthritis.

DISCUSSION

The influence of sex hormones on hetero- and auto-immune reactivity cannot be denied. In general terms androgens and progestagens seem to dampen immune responses while oestrogens show the opposite tendency. The mechanisms behind this influence are still unknown.

A remarkable feature is that the extent of the effects of gender or sex hormone can vary considerably: in human autoimmune diseases the ratio of the incidence between males and females varies from 1:1.5–1:9; in animal models the effects of gender and sex hormones on (auto)immune response may vary from negligible to very significant. Under the following circumstances "sex" differences in immune reac-

tivities in experimental animals are more easily demonstrable [49]:

(i) in F1 rather than inbred mouse strains;
(ii) in hormone-sensitive strains;
(iii) after only moderately strong antigenic challenge;
(iv) in immunologically manipulated animals.

The first two points emphasize the importance of genetic background. Inbred animal strains are likely to have more than one defect leading to the immune pathology which is aimed at during the inbreeding process. This genetic pressure towards the development of autoimmune disease may be lower in F_1 animals, so that autoimmune disease can be more easily controlled. This, however, is not always the case; in NZB/NZW F_1 mice autoimmune disease seems to be qualitatively modified rather than alleviated. The present inbred OS chicken shows an equally high incidence of thyroiditis in males and females whereas earlier in the breeding process males were less frequently affected than females [235]. Despite the lack of difference in incidence in the present breedings of the OS chicken the thyroiditis can still be suppressed with sex steroids [238–240].

Various mouse strains differ in their sensitivity to hormone action [258]. An influence of the MHC(H-2) locus on the amount of oestrogen receptor in the mouse uterus has been described [259]. If this were to be extended to a general notion of an H-2 controlled oestrogen sensitivity, this might also imply a genetic influence, e.g. on the oestrogen-enhanced clearance of Ab-coated cells by splenic macrophages [74] and on the protection from arthritis by oestrogen as described in mice immunized with collagen type II [243]. H-2-controlled androgen sensitivity in mice has been more extensively documented [65, 258, 260, 261]; here high and low androgen responders can be distinguished. Male high-androgen responding mice show low immune responses as compared to females of their own strain and to males of low-androgen responding strains [65, 66, 262]. In outbred animals and in humans MHC-controlled sensitivity to oestrogens and androgens may affect hetero- and autoimmune responses in different ways and to different degrees. This hypothesis is consistent with the concept of minor or background genes contributing to autoimmune diseases in inbred chickens [263] and mice [264, 270].

The third circumstance regarding the relationship between sex hormones and immune reaction mentioned above is the strength of the challenge. If, indeed, hormonal influence is based on a "minor" genetic trait it is logical that a strong immunogenic challenge is not or hardly affected by sex (hormones). This could perhaps explain why in various non-spontaneous autoimmune disease models sex (hormone) effects are lacking and why in F_1 animals sex influences can be more strongly expressed than in their parents.

The final circumstance is that of immune manipulation. An example is the MRL-lpr/lpr mice [49, 215]: splenectomy at 2-weeks of age, neonatal thymectomy, combinations of neonatal thymectomy with splenectomy of neonatal thymectomy with chronic treatment with polyclonal activators do not enlarge male/female differences in disease parameters; only in the combination thymectomy/splenectomy/polyclonal activator treatment does the male/female difference become statistically significant. In addition, immunosuppression by cyclophosphamide increases sexual dimorphism in the MRL-lpr mice [216]. Another example is chronic thyroiditis in thymectomised and sublethally irradiated rats which can be suppressed with Te [253]. It is conceivable that in humans a virus infection could be an example of an unintentional "immune manipulation" leading to autoimmune disease with its typical sexual dimorphism.

In the seventies Morton and Siegel [265–268] emphasized the primary role of the haemopoietic stem cell in autoimmune diathesis. They showed that transplantation of bone marrow cells from NZB mice to irradiated mice of a non-autoimmune, H-2 compatible strain conveys autoimmune disease; transplantation in the opposite direction protects NZB mice from autoimmune disease. The importance of the haemopoietic stem cell for autoimmune disease has been confirmed in various settings [177, 178, 269–271]. It would be interesting to repeat these experiments by using highly purified stem cells to determine whether the non-committed stem cell carries all information for the autoimmune derangement.

Androgens play a stimulatory role in haemopoiesis. They act on the pluripotent stem cell but also on committed granulocyte [272] and erythrocyte [273] precursors. According to Byron [274] it seems likely that the normal androgen receptor is not involved in this process. It is tempting to hypothesize that this stimulation by androgens plays a role in the favourable effects of androgens in autoimmune disease.

The favourable effects of androgens in autoimmune disease appears to be dissociable from the hormonal i.e. androgenic effects. In other words, steroids can be devised which still maintain the protective effect in autoimmune disease but have a decreased androgenic potency. Steroids with such profile could be an interesting therapeutic tool in human autoimmune disease [88]. A comparable dissociation has been suggested for oestrogens: enhancing effects on clearance of antibody-coated cells is, to some extent, dissociated from oestrogenic potency [74]. The above-mentioned dissociations from hormonal effects suggest that these steroids do not always work through the classical steroid receptors; this could be explained by the recent finding of new classes of steroid receptors [275].

In conclusion, gender and sex hormones have a

clear effect on various hetero- and auto-immune responses but the mechanisms of action are still unknown; starting from sex hormones, steroids can be devised which have favourable effects on immune processes but lack undesirable hormonal effects; such hormonomimetics should be, in principle, applicable for the treatment of autoimmune disease.

Note added in proof

Supplementary issue I (1989) of *Br. J. Rheumat.* contains the proceedings of the *International Workshop on Female Sex Hormones and Rheumatoid Arthritis*, held at Leiden, The Netherlands, 20–21 March 1989 with interesting new information.

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