LETTER TO THE EDITOR

MASI AT

Comments to: IMRICH R: *The role of neuroendocrine system in the pathogenesis of rheumatoid diseases. Endocrine Regul 36:95-106, 2002*

To the editor:

The concept promoted by collaborators and myself that rheumatoid arthritis (RA) seems to result from the accumulative effects of multiple determinants [e.g., genetic, neuroendocrine, behavioral (smoking), other somatic and environmental factors] during a long preclinical period has been recently reviewed in your Journal (IMRICH 2002). The concept is also important that risk factor profiles for RA may differ among subsets of susceptibles, i.e., premenopausal- vs postmenopausal-onset women and men. As was mentioned in the paper, and by the MASI collaborators, such knowledge may lead to possible approaches to primary prevention or modulation of RA risks.

One reason for this letter is to update on several additional studies by collaborators and myself, which reinforce the preceding concepts. Our paper (MASI et al. 2002), which was recently published, indicated independent laboratory confirmation of low serum dehydroepiandrosterone sulfate (DHEAS) levels many years prior to the onset of premenopausal RA.

Evidence for relative adrenal androgen deficiency (i.e., low serum DHEAS levels) prior to onset of RA in adolescent and younger women is now quite strong (see my discussion of the contrary HEIKKILLÄ et al 1998). Nevertheless, this hormone per se is not likely to be a pathogenetic factor for RA. Rather, it seems to be a *marker* for relative adrenal cortical and glucocorticoid (GC) insufficiency. This interpretation was summarized in Table 5 of my review article (MASI 2000).

Data supporting subtle GC dysfunction in younger female RA patients, and even many years before clinical onset, were summarized in the German literature (MASI et al 2000). As you know, the negative GC feedback control of the hypothalamic - pituitary - adrenal (HPA) axis tends to obscure detection of subtle degrees of insufficiency of this hormone, unlike the more reliable indicator of low serum levels of DHEAS, which has a much longer half-life than cortisol in the circulation.

If one proposes a concept that relative adrenal cortical glucocorticoid hypofunction may be a predisposing factor to RA in a minority of younger-onset women (estimated at about one-third), then the next question is how does one explain such a state? This area of human physiology is essentially unexplored. In fact, it is rarely mentioned in the literature.

In a detailed earlier review (MASI et al. 1996), collaborators and myself proposed an hypothesis regarding possible mechanisms operating in this challenging question. The occurrence of relative adrenal cortical and gonadal *trophic* (i.e., functioning cell capacities/mass) *hypocompetence* was hypothesized as a constitutional polymorphic variant. For women, subtle adrenal/gonadal *mass* hypocompetence would be clinically unnoticed. Such status could be the polar opposite of the polymorphic polycystic ovarian syndrome (PCOS), which, of course, is usually clinically evident. As you know, increased ovary (especially) and adrenal mass has been documented in PCOS as well as robust androgenic and glucocorticoid functions. Endocrinologists need to explore more critically the occurrence or non-occurrence of intrinsic adrenal/gonadal hypocompetence in younger women, as a possible polymorphic polar opposite to PCOS. Whether or not such polymorphisms might

be part of a population continuum, from *hypo* to *normal* to *hyper* competencies (cell capacities/mass) also remains to be investigated.

When our hypothesis of intrinsic adrenal and gonadal androgenic hypocompetence was proposed in 1996, it was believed to apply only to a minority subset of premenopausal-onset RA women. However, as shown in Table 1 of our article (Masi et al. 2002), low serum cortisol (<140 nmol/L) and *relatively* low serum total testosterone (<15 nmol/L) were significantly correlated in 18 pre-RA males, but not in 72 controls. In Table 7 of my review (Masi 2000), it has been noted that low serum cortisol *and* definitely low serum testosterone (<10 nmol/L) is a significant, independent long-term predictor of RA in men. However, this risk factor occurs in only a small minority (circa 10 %) of susceptible men.

Interestingly, in postmenopausal women, combined low serum cortisol (<140 nmol/L) *and* low total testosterone (<3.5 nmol/L) levels were also a significant predictor of RA. Among subjects having such assays, the combination occurred in 6 (33.3 percent) of 18 pre-RA women, 4 to 17 (mean 11) years *prior* to clinical onset at age 50 years or older. Among 61 control women matched for age at entry into this cohort study, the combination of low serum cortisol and testosterone was found in 6 (9.8 percent), odds ratio 4.58, 95 % confidence intervals 1.25, 16.69.

Varied profiles of presumably constitutional hypocompetences of adrenal glucocorticoids and/or gonadal androgens (i.e., low serum testosterone) have now been observed in our controlled prospective studies of females with premenopausal-and postmenopausal-onsets of RA and of males, albeit in minority subsets of each.

The physiopathogenesis of RA is profoundly complex. The hypothesized neuroendocrine dysfunctions are believed to contribute to chronic preclinical upregulation of inflammatory pathways and endothelial microvascular activation, and perhaps even to somatic remodeling of the immune system (reviewed in Masi 2000). The author indicated such interactions in the mini-review and illustrated them in Fig 1 (Imrich 2002). However, in the Table 1, the effects of glucocorticoids were indicated as "increased overall cytokine synthesis". Most investigators would summarize physiological and pharmacological effects of glucocorticoids as "decreased overall cytokine synthesis". Could the author please provide evidence available for the Table 1 entry on glucocorticoids and submit a corrected Table, if appropriate.

Alfonse T. Masi, MD., DR.P.H.
Professor of Medicine
University of Illinois
College of Medicine at Peoria

References

Imrich R: The role of neuroendocrine system in the pathogenesis of rheumatic diseases (minireview). Endocrine regulations, 36, 95-106, 2002

Masi AT, Chatterton RT, Aldag JC, Malamet RL: Perspectives on the relationship of adrenal steroids to rheumatoid arthritis. Ann N Y Acad Sci, **966**, 1-12, 2002

Heikkilä R, Aho K, Heliövaara M, Knekt P, Reunanen A, Aromaa A, Leino A, Palosuo T: Serum androgen-anabolic hormones and the risk of rheumatoid arthritis. Ann Rheum Dis **57**, 281-285, 1998

Masi AT: Hormonal and immunologic risk factors for the development of rheumatoid arthritis: an integrative physiopathogenetic perspective. Rheum Dis Clin North Am **26**, 775-803, 2000

Masi AT, Aldag JC, Chatterton RT, Adams RF, Kitabchi AE: Adrenal androgen and glucocorticoid dissociation in premenopausal rheumatoid arthritis: a significant correlate or precursor to onset? Z Rheumatol **59** Suppl 2:II/54-61, 2000

Masi AT, Da Silva JAP, Cutolo M: Perturbations of hypothalamic-pituitary-gonadal (HPG) axis and adrenal androgen (AA) functions in rheumatoid arthritis. Bailličre's Clin Rheumatol **10**, 295-332, 1996

Author's Response

To the editor:

I thank Professor MASI for his supportive comments regarding my minireview entitled "The role of neuroendocrine system in the pathogenesis of rheumatic diseases" (IMRICH 2002).

The concepts, which MASI and colleagues (2000), raise many new questions to endocrinologists and rheumatologists as well as to investigators in the field of human physiology itself.

As mentioned, relative adrenal cortical glucocorticoid hypofunction indicated by low serum levels of dehydroepiandrosterone sulfate (DHEAS), may be a predisposing factor to rheumatoid arthritis in a subset of younger onset women. The hypotheses proposed by MASI and collaborators assume the presence of subclinical adrenal/gonadal mass hypocompetence as a constitutional polymorphic variant opposite to polycystic ovarian syndrome (PCOS). One of the possible alternative mechanisms, which may contribute to androgen insufficiency, may result from the interindividual variability of feedback sensitivity of the HPA or HPG axes. Different set points of HPA or HPG axes would thus result in different baseline levels of peripheral hormones (e.g. glucocorticoids or androgens). Such dysfunctions of feedback mechanism could further contribute to chronic preclinical upregulation of inflammatory pathways and endothelial microvascular activation, as reviewed by MASI (2000). These alternative mechanisms have been previously mentioned by MASI et al. (1996) and the Fig. 10 of this review attempts to differentiate trophic from tropic dysfunctions. The dilemma of trophic vs. tropic dysfunctions needs further critical investigation. However, to reveal such subtle changes of HPA or HPG axes activity, it seems necessary to develop new methodological approaches.

Recently debated questions of female androgen insufficiency supports the perspectives outlined in Masi's letter. It was concluded that the role of androgens in women's health has been generally neglected and is not well recognized or understood (BACHMANN et al 2002). The presented definition and guidelines together with identified research needs and priorities are giving hope that androgen insufficiency will be better evaluated and treated in the future as well as in the subgroup of patients affected with chronic inflammatory diseases such as RA.

Regarding the question of "the glucocorticoids cause increased overall cytokine synthesis" indicated in Table 1 of my minireview (IMRICH 2002), I would like to apologize for incorrect direction of arrows caused by technical problems during the processing of the manuscript. Table 1 as was originally intended is shown below.

RICHARD IMRICH, MD.
Institute of Experimental Endocrinology
Slovak Academy of Sciences
Bratislava, Slovakia

References

BACHMANN G, BANCROFT J, BRAUNSTEIN G, BURGER H, DAVIS S, DENNERSTEIN L, GOLDSTEIN I, GUAY A, LEIBLUM S, LOBO R, NOTELOVITZ M, ROSEN R, SARREL P, SHERWIN B, SIMON J, SIMPSON E, SHIFREN J, SPARK R, TRAISH A: Female androgen insufficiency: the princeton consensus statement on definition, classification, and assessment. Fertil Steril, **77,** 660-665, 2002

IMRICH R: The role of neuroendocrine system in the pathogenesis of rheumatic diseases (minireview). Endocrine regulations, **36**, 95-106, 2002

MASI AT: Hormonal and immunologic risk factors for the development of rheumatoid arthritis: an integrative physiopathogenetic perspective. Rheum Dis Clin North Am, **26**, 775-803, 2000

MASI AT, DA SILVA JAP, CUTOLO M: Perturbations of hypothalamic-pituitary-gonadal (HPG) axis and adrenal androgen (AA) functions in rheumatoid arthritis. Bailličre's Clin Rheumatol, **10**, 295-332, 1996

Table 1. Effects of selected hormones and neuropeptides on immune parameters.

Hormone/Neuropeptide	Effects
ACTH	↓ Ig and IFNγ synthesis ↑ B cell proliferation ↑ NK cells activity
Glucocorticoids	↓ overall cytokine synthesis
CRH	↑ T cell proliferation ↑ IL-2 receptors expression ↑ IL-1 , IL-6 in macrophages
Epinephrine	↑ NK cells activation ↓ CD4+ lymphocytes ↑ CD8+ lymphocytes ↓ lymphocytes proliferation
α-endorphine	↓ antibody production
β-endorphine	↑ lymphocytes proliferation
γ-endorphine	↓ antibody production ↑ NK cells activation
Prolactin	↑ IL-2 receptor expression ↑ T cell proliferation
Growth hormone	↑ antibody production ↑ NK cells activation ↑ IL-1, IL-2, TNFα production
TSH	↑ antibody production ↑ T and B cells proliferation
αMSH	↓ antibody production ↓ IL-1 activity ↓ monocytes secretion of IL-2
VIP	↓ NK cells activity ↓ T cells activity
Somatostatin	↓ T cells proliferation
Estrogens	↑ lymphocytes function
Substance P	↑ mast cells mediators release ↑ macrophage phagocytosis
Met-enkephalin	↑NK cells activity ↑IFNγ synthesis ↓ antibody production