An intricate balance between soluble mediators (i.e., cytokines), released by activated cells of the inflammatory/immune systems, and products of the neuroendocrine system such as neuropeptides and steroid hormones, maintains homeostasis in the presence of an arthritic stress [1–3].

Generally, inflammatory cytokines [i.e. interleukin (IL)-6, IL-1, tumour necrosis factor alpha (TNF-α)], as soluble products of synovial arthritis, stimulate the production of corticotrophin-releasing hormone (CRH) in the hypothalamus: CRH release leads to pituitary production of adrenocorticotropic hormone (ACTH), followed by glucocorticoid secretion by the adrenal cortex and indirect perturbations of gonadal function [4, 5].

Conversely, peripheral products of the hypothalamus–pituitary–adrenal (HPA) and –gonadal (HPG) axes modulate cytokine production. For example, adrenal and gonadal androgens, in particular dehydroepiandrosterone sulphate (DHEAS) and both testosterone and dihydrotestosterone (DHT), have been found to repress the expression and activity of the human IL-6 gene promoter, thus supporting the concept of anti-inflammatory/immunosuppressive effects exerted by androgens [6–8].

Notably, glucocorticoids are the most potent endogenous inhibitors of immune and inflammatory processes, including pro-inflammatory cytokine production [9].

Peripheral levels of IL-6 and, to a lesser extent, those of TNF-α and IL-1β, are tonically inhibited by basal levels of glucocorticoids.

Interestingly, during the arthritic inflammatory conditions that require glucocorticoid therapeutic administration, the acute deficiency syndrome at the time of their withdrawal might be explained by the unopposed IL-6 increased production [10].

On the other hand, in systemic arthritic conditions, such as rheumatoid arthritis (RA), the increased IL-6 levels stimulate secretion of CRH, ACTH and cortisol; however, the overall HPA activity seems normal and insufficient to inhibit ongoing inflammation. In particular, a relative deficiency of adrenal glucocorticoid production, with compensatory ACTH hypersecretion, is frequently observed in RA, and chronically elevated cytokines might directly cause the observed decrease in adrenal production [11].

However, immune-mediated synovial inflammation may also arise from glucocorticoid resistance in the target tissue. In RA, the concentration of glucocorticoid receptors in circulating leucocytes has been found to be reduced by ~50% [12, 13]. Therefore, in systemic arthritic conditions (i.e. RA), the anti-inflammatory use of glucocorticoids as low-dose oral administration or high-dose pulse therapy, or intra-articular injection, should be regarded as a sort of replacement therapy, with modulating effects on activated T lymphocytes and macrophages [14].

A further anti-inflammatory activity exerted by glucocorticoids in arthritis is related to their influence on arachidonic acid metabolism. Generally, cyclooxygenase-1 (COX-1, constitutive) is the principal enzyme involved in producing prostaglandins that regulate cellular house-keeping functions such as gastric cytoprotection, vascular homeostasis and kidney function.

In contrast, and interestingly, a second cyclooxygenase (COX-2, inducible) appears to be expressed mainly by macrophages in inflamed tissues (i.e., synovial tissue), and following cytokines or other mediators of inflammation (i.e., nitric oxide) [15]. COX-2 is inhibited by glucocorticoids, and this specific modulation might explain the reduced range of some side-effects (i.e., gastric, renal) during therapeutic anti-inflammatory treatment with such steroids [16].

In addition to the anti-inflammatory/immunosuppressive effects exerted by androgens on peripheral cytokine production, a direct influence of androgens on cartilage metabolism and their role in RA progression and joint destruction should also be considered. Androgens appear to protect the cartilage from the inflammation-induced breakdown in male animals, presumably through the control of local cytokine production and their release in granulomatous tissues [17].

Furthermore, androgens increase proteoglycan synthesis in cultured human articular chondrocytes, but do not inhibit chondrocyte proliferation in culture. These observations suggest that long-term androgen replacement may help prevent joint damage and disability, at least in male RA patients [18].

A further aspect of joint damage is the reduced bone mineral density (BMD) in men with RA. Corticosteroid therapy contributes to low BMD in RA, as well as to decreased levels of the adrenal androgen DHEAS. In men with RA, BMD correlates with such lower levels of DHEAS, presumably contributing to low BMD [19].

Although oestrogen therapy can prevent bone loss from the spine, it may not prevent bone loss at sites near inflamed rheumatoid joints. The immune-enhancing activity exerted by oestrogens on synovial macrophages, through the increase in IL-1 synthesis, may be involved in the juxta-articular osteoporosis [20]. Low serum DHEAS was found to be predictive of femoral BMD in RA patients [21].

RA patients (~75%) improve or even remit during pregnancy, starting during the first trimester [22]. Hormonal and related immune response changes observed during pregnancy and postpartum might contribute to the variations in disease activity in RA.
as well as in systemic lupus erythematosus (SLE) patients. During normal pregnancy, both free and total cortisol levels are increased, the circadian secretion persists, but evening levels do not decline as in non-pregnant women [23]. Oestrogens and progesterone are synthesized in large amounts and they decrease metabolic clearance of cortisol, by a direct action on liver enzymes involved in its inactivation [24]. Since high concentrations of oestrogens seem to exert immunosuppressive activities, this effect, at least partially, should account for the improvement of arthritic symptoms in pregnant patients.

On the other hand, during pregnancy, prolactin (PRL) reaches highest levels in the third trimester. Optimum concentrations are required for maximal lymphocyte stimulation; however, lower or higher levels cause decreased or negative responses [25]. Therefore, elevated PRL concentrations in pregnancy and early lactation might induce immunosuppression.

The maternal production rate of the adrenal androgen DHEAS is increased at least two times during pregnancy, but serum levels seem unchanged. On the contrary, serum levels of gonadal androgens increase. Serum total testosterone reaches levels 4–5 times higher than in menstruating women, whereas serum free testosterone increases only in the third trimester [23].

The hormonal changes characterizing the pregnancy are primarily directed towards a reduction of the immune/inflammatory response, at least in RA, and recently pregnancy and the postpartum period have been suggested to represent a model of how abrupt changes in steroid hormone levels may regulate the immune response [26].

A selective neuroendocrine control of Th1–Th2-type cytokine balance has recently been proposed [26]. Cellular immunity in active RA is considered to be primarily promoted and regulated by a Th1-type or pro-inflammatory cytokine production: IL-12, interferon gamma (IFN-γ), TNF-α and IL-2. Conversely, humoral immunity is regulated by Th-2-type or anti-inflammatory cytokines: IL-4, IL-5, IL-10 and IL-13.

The cytokine expression during pregnancy seems to shift towards a Th2-type profile; in particular, high levels of anti-inflammatory IL-10 are expressed in placental tissues. Similarly, the administration of corticosteroids seems to increase serum levels of IL-10 and generally seems to polarize towards a Th2-type cytokine pattern [14]. Conversely, RA can flare up in the postpartum period, because the levels of IL-10 decrease to normal or even subnormal concentrations, following the decrease in serum levels of gonadal and adrenal steroids.

In conclusion, it has been suggested that the plasma increase in oestrogens, androgens and cortisol in the third trimester of pregnancy may induce an improvement in RA as a consequence of a suppression of the pro-inflammatory Th1-type cytokine pattern and a potentiation of the anti-inflammatory Th2-type cytokine pattern. A protective effect for oral contraceptives (OCs) against the development of RA has been suggested and attributed to the immunosuppressive activity exerted by increased levels of circulating oestrogens and progesterone [27]. However, a recent study showed that only current OC use protects against the development of inflammatory polyarthritis, such as RA, and no effect was apparent for past use [28]. Otherwise, past use of OCs was associated with a slight increased risk of developing SLE, whereas experimental studies showed therapeutic effects of the oestrogen antagonist, tamoxifen, on murine SLE [29, 30].

Sex hormones might influence synoviocyte apoptosis (programmed cell death) and proto-oncogene expression, since oestrogens seem to inhibit apoptosis, whereas androgens seem to induce apoptosis [31].

Low levels of androgens, as observed in sera and synovial fluids of RA patients, may reduce synoviocyte apoptosis and enhance synovial tissue proliferation [32]. On the other hand, activation-induced macrophage apoptosis may serve to restrict the destructive potential of inflammatory macrophages.

Recent studies showed that testosterone therapy dramatically suppresses the lymphocyte infiltration in, and significantly improves the functional activity of, lacrimal glands in the MRL/lpr female mouse model of Sjögren’s syndrome [33]. A subsequent study has shown that androgen treatment influences the expression of proto-oncogenes, with decreased bcl-2 and c-myc mRNA levels, as well as apoptotic factors in salivary and lacrimal tissues of the same model of Sjögren’s syndrome [34]. Conversely, the recent observation of oestrogen-induced decrease of apoptosis of peripheral blood mononuclear cells (PBMCs) of SLE patients suggests that the presence of oestrogens may allow the survival of autoimmune cells [35].

If sex hormones, as well as cytotoxic agents, do modulate synovial macrophage apoptosis, such an approach would promise an important pathway of control in arthritis.

The complex interactions and the molecular basis of common pathways between inflammatory/immunological and neuroendocrine circuits are a matter of continuous and intensive research, and might offer a highly promising strategy for therapeutic manipulations of arthritis [36, 37].

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During the 1970s, I remember reading a letter to the editor of a scientific journal, written by a Scandinavian epidemiologist. The writer pointed out that in the year (I think) of 1973, the birth rate in Sweden was higher than at any period since the Second World War. It was also noted that more storks were seen flying over Swedish airspace during that year, than ever before, and the suggestion was made that we now had good data supporting the role of storks in childbirth. I do not remember the correlation coefficient, the relative risk, or any $P$ values, but the results seemed quite compelling at the time.

We are now given data by a different Nordic country, revealing that patients with ankylosing spondylitis have an increased risk of early deaths from alcohol-related accidents and violence. Needless to say, this emotive title will have a damaging affect on the morale of our many peace-loving, teetotal, spondylitic patients, not to mention the further discrimination that these individuals may suffer at the hands of insurance companies. To what extent can the data from the University of Oulu, Finland, be extrapolated to the rest of the world?

Myllykangas-Luosujarvi et al. [1] began their investigation accepting that patients with ankylosing spondylitis ‘have an increased incidence of deaths from accidents and violence’, which, in part, was blamed on the vulnerability of the affected spines. Additional background data relate to the recognized deaths from malignancies in individuals who have received irradiation for their spinal pain [2, 3] and, indeed, the excess mortality, even among those individuals who have not been given radiotherapy [4, 5]. The increased prevalences of infection, cardiovascular disease, gastrointestinal disorders and amyloidosis have all been blamed for this increase in death rate [6]. The authors point out that the above-named references were cohort studies where the observed deaths were compared with the expected number of deaths in a control reference population. By contrast, the Finnish researchers studied all cases with ankylosing spondylitis who had died during a 1 yr period in 1989. These subjects were identified by computer linkage and the 71 with ankylosing spondylitis were assessed in terms of death certificate data. In addition, a second cohort study, dealing with all ankylosing spondylitis deaths (389 patients), during an earlier period of 1961–1969, was also reviewed.

In the first study, the authors showed that the mean age of death for the men was 66 yr, and for the women 71 yr, compared to values in the Finnish population of 72 and 80 yr, respectively. Thus, there is a shortening of life expectancy of between 6 and 9 yr. Sixteen of these deaths related to accidents or violence, giving a relative risk of 1.87 in comparison to the normal Finnish population. In total, the proportion of alcohol-related deaths was higher among the spondylitics than in the Finnish population, giving a weighted relative risk of 2.84. In the earlier cohort study, there were 16 deaths from accidents and violence, compared to the expected 11.4. Eight of the 16 were alcohol related, compared to less than 4.3 expected. The authors point out that, given that accident- and violence-related deaths are even greater in teenagers and those in their early 20s, the age-adjusted surplus of alcohol deaths amongst spondylitics would be even greater than now observed, given that for most, the diagnosis was made after the age of greater risk.

Many readers may inappropriately consider that the consumption of alcohol in Finland is greater than in other countries. However, apparently, the consumption is comparable to that seen in Great Britain and the USA. Moreover, the share of deaths from alcohol-related diseases and accidents is similar in Finland and the USA [7].

As an explanation for their finding, the authors offer the possibility that alcohol or lifestyle patterns associated with drinking (e.g. smoking) may aggravate the symptoms and signs of ankylosing spondylitis, or that the pain of ankylosing spondylitis may be associated with emotional problems which, in turn, lead to relief drinking, perhaps parallel to the situation with psoriasis. Thirdly, the patients may be prone to ‘uncontrolled drinking’ on a genetic basis.

Of note, the authors quote unpublished data suggesting that age-adjusted mortality from alcohol-related conditions in rheumatoid arthritis was only half that found in the general population. Nevertheless, it should be pointed out that patients with rheumatoid disease tend to be older women, and the age at onset is greater, perhaps explaining some of the differences.

How should the average patient with ankylosing spondylitis, or the typical rheumatologist dealing with such patients, deal with these new data? First, even if there is no systematic bias resulting in spurious findings, there is still uncertainty about the survival characteristics of our patient population. Most of the published data emanate from major academic units, where, over the decades, only those with more severe disease (and perhaps co-disorders) have been studied. Thus, the suggestion that survival is several years less for a spondylitic patient than for a control subject may not relate to the general population of patients. Indeed, our own research has shown that, at least in terms of occupation and employment status, the vast majority of our patients are in full-time employment until close to the normal retirement age [8]. Similarly, one can perhaps assume that there are patients with mild ankylosing spondylitis in Finland who do not get into the computer-linkage system, and will be unavailable for study. As always, the iceberg phenomenon is difficult to define.

The degree to which there is an inter-relationship between alcohol, alcohol abuse, alternative therapies and non-steroidal anti-inflammatory drugs used by our
patients is unknown, but is worth considering. For example, indomethacin can have psychological side-effects and it remains possible that this drug, together with alcohol, has a particularly negative effect. Nevertheless, in informal conversation with our patients, several admit to the fact that non-steroidals do not work very well, and more pain relief and ‘muscle relaxation’ can be acquired with a little bit of alcohol rather than a lot of tablets.

Apart from deaths, we do not know whether liver dysfunction or other alcohol-related disease is more prevalent in ankylosing spondylitis patients than in age-matched controls. Moreover, the degree to which patients, as a whole, drink more remains unknown, and the Finnish data may relate to a small minority of alcohol abusers.

In terms of practical advice to our patients, the avoidance of tobacco is a must, and a sensible approach to drinking is clearly imperative. Nevertheless, at least until more definitive studies are carried out in different countries, we must stress to the insurance companies that these data emanate from a single study in a Finnish population, and may not relate to our entire population of patients.

Finally, the degree to which one can extrapolate from 17 Finnish spondylitics who died an alcohol-related death to the remaining millions of patients with ankylosing spondylitis can only be guessed at. Indeed, recent data from Berlin [9] suggested that no less than 1.9% of the population have a spondylarthropathy, and almost half of these have ankylosing spondylitis. These figures, derived from HLA B27 blood donors, confirm our earlier data, published in the New England Journal of Medicine [10]. By extrapolation, in terms of the UK, we would anticipate that there are some 400,000 patients with ankylosing spondylitis. Do they drink heavily? And what about other rheumatic diseases? Psoriatic arthropathy, for instance, may also be associated with an increase in death rate, at least some of which can be explained in terms of injuries and poisonings, in men, but not in women [11].

Clear, we need further studies relating to this important and perturbing finding, but meanwhile it is worth remembering that no confirmatory data have appeared supporting the relationship between storks and babies.

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