

Rostrum

Maternal stress and T-cell differentiation of the developing immune system: Possible implications for the development of asthma and atopy

Leena C. von Hertzen, PhD *Helsinki, Finland*

The constant increase in asthma and atopy prevalences—despite improved treatment and knowledge of many aspects of the diseases—has raised growing concern. Accumulating evidence suggests that these increases in atopic diseases are largely attributable to environmental and lifestyle factors, and the lack of systemic childhood infections has in many studies emerged as a major factor. In addition to current high standards of hygiene and the lack or scarcity of such infections, another factor characteristic of our present-day lives could be involved. This review briefly outlines the possibility that prolonged maternal stress associated with sustained excessive cortisol secretion could affect the developing immune system—especially T_H1/T_H2 cell differentiation—and further increase the susceptibility to asthma and atopy in genetically predisposed individuals. This hypothesis is critically evaluated in the light of current knowledge. (*J Allergy Clin Immunol* 2002;109:923-8.)

Key words: *Asthma, atopy, stress, maternal, T-cell differentiation, fetus*

It has become increasingly clear that factors involved in the substantial increases in asthma and atopy prevalences during the last few decades are environmental in nature and associated with Western lifestyles and living conditions.¹ The decreased exposure to systemic childhood infections has been proposed as a major contributory factor. This hygiene hypothesis^{2,3}—the apparent inverse relationship between childhood infections and the subsequent occurrence of atopic diseases—has gained acceptance as one of the most plausible explanations for the current trends in atopic diseases. Indeed, several recent studies have lent further support to this hypothesis.⁴⁻⁶ In the absence or scarcity of certain childhood infections, the postnatal maturation of the immune system might not proceed optimally.⁷ Because atopic asthma is associated with predominant activation of T_H2 cells, infections that elicit a strong T_H1 response and a long-

Abbreviations used

ACTH: Adrenocorticotrophic hormone
CRH: Corticotrophin-releasing hormone
HPA: Hypothalamic-pituitary-adrenal (axis)
NK: Natural killer (cell)

lasting memory immunity, thus antagonizing T_H2 cell differentiation, might in early life be able to commit the biased T_H2 response to a T_H1 immunity in genetically predisposed children.⁸ Monocytes and alveolar macrophages from atopic individuals exhibit decreased IL-12 production, which is consequently associated with decreased IFN- γ and increased IL-5 production of T helper cells in vitro.^{9,10} In normal children, the initially low T_H2 immunity is converted to T_H1 immunity by the age of 5 years.¹¹ In atopic individuals, this conversion does not take place properly; instead, the T_H2 immunity associated with the production of IL-4, IL-5, IL-9, IL-10, and IL-13 is consolidated.¹² The key factor in the pathogenesis of atopic diseases has been found to be the efficacy of this immune deviation process. Recent research has provided convincing evidence that the risk for atopy and asthma is associated with a diminished capacity to produce IFN- γ during fetal life.^{12,13}

There is also compelling evidence that the gut is strongly involved in the proper maturation of the immune system. Atopy has recently been shown to be inversely related to orofecal and foodborne infections.⁵ Moreover, even the composition of the nonpathogenic intestinal microflora might play a role.¹⁴ The apparent involvement of both the respiratory tract and the gut (or more precisely, the gut- and bronchus-associated lymphoid tissues) is not unexpected, inasmuch as the 2 organs have a common embryologic origin.

In addition to the lack of systemic childhood infections, there might be another factor that could play a major role in the increases of atopic diseases: the influence of sustained maternal stress during pregnancy on the developing immune system. The significance of the prenatal intrauterine environment on the individual's subsequent health is well recognized. Severe stress might reduce gestational age and infant birth weight^{15,16} and further increase the individual's susceptibility to chronic

From the Finnish Lung Health Association.

Received for publication October 22, 2001; revised March 12, 2002; accepted for publication March 12, 2002.

Reprint requests: Leena C. von Hertzen, PhD, The Finnish Lung Health Association, Sibeliuskatu 11 A 1, 00250 Helsinki, Finland.

© 2002 Mosby, Inc. All rights reserved.

0091-6749/2002 \$35.00 + 0 1/88/124776

doi:10.1067/mai.2002.124776

diseases in later life.¹⁷ To date, hardly any attention has been devoted to the influence of persistently elevated maternal cortisol levels on the developing immune system or on the T_H1/T_H2 balance of the child.

CHRONIC VS ACUTE STRESS

Stress is generally defined as a state of altered homeostasis resulting from either external or internal stimuli.¹⁸ The stress response is initiated within the central nervous system and translated into action by the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system. These neuroendocrine pathways have been shown to modulate inflammatory and immune responses in which the nature of the stressor is a significant determining factor.¹⁸

Important distinguishing characteristics concerning stress include its duration (acute vs chronic) and the intensity and persistence of the stressor (intermittent vs sustained).^{19,20} *Acute stress* has been defined as stress that lasts for a period of minutes to hours; what is called *chronic stress* persists for days to months.¹⁹ The activation of the HPA axis in response to acute stress is relatively well understood, whereas the mechanisms underlying the response to chronic stress are less clear.²¹ Numerous studies have shown that stress can be immunosuppressive.²²⁻²⁵ However, recent research has provided evidence that stress can also enhance immunity and ameliorate autoimmune and inflammatory disorders. It has been suggested that stress conditions that are found to be immunoenhancing involve acute stress, whereas those found to be immunosuppressive involve chronic stress.¹⁹ Moreover, intermittent, repeated stress can induce even more robust and long-lasting effects than chronic, continuous stress.²⁶ Breakdown of the regularity of the circadian cortisol rhythm is in any case an important marker of chronic stress.^{19,27}

The deleterious effects of chronic stress are well recognized.²⁸⁻³⁰ Exposure to increased secretion of stress hormones for weeks, months, or years can result in pathophysiologic changes.²⁹ Chronic stress does not inevitably lead to psychologic, neuroendocrine, or immunologic habituation.²⁸ Indeed, habituation appears not to occur when stressors are long-term. Rather, the longer an individual is exposed to a specific stressor, the greater the likelihood of a change in baseline values²⁸ and a reset of their HPA axis activity.³¹

In Western societies, ever-increasing competition and occupational demands affect women to a growing extent. Chronic work overload is common, and there is evidence that salivary cortisol levels increase within a half hour of waking in people persistently stressed by chronic work overload.³² Noise, crowding, social isolation, and chronic sleep deprivation are other frequently occurring stressors associated with urban living in our time.

The relationship between stress and asthma from a biopsychologic point of view has been thoroughly reviewed previously.³³ The focus of the present article is on the possible effects of sustained maternal stress and

stress-induced elevation of cortisol levels on the developing fetal immune system, which might lead to an increased risk of atopic diseases in genetically susceptible children. On the basis of the reasoning presented below and knowledge of the interactions among behavioral, neural, endocrine, and immune processes as well as of the bidirectional interplay between the mother and fetus, the following hypothesis is proposed:

Hypothesis. Chronically elevated levels of maternal stress-induced hormones, especially cortisol, might influence T helper cell phenotype differentiation in the developing immune system and lead to increased risk of atopic diseases in genetically predisposed children.

DISCUSSION

Arguments supporting the hypothesis

1. Immunomodulatory effects of stress and glucocorticosteroids. An increasing body of evidence shows that corticosteroids drive the T_H1/T_H2 balance toward a T_H2 cytokine profile³⁴⁻³⁸ and might be among the most important determinants in the microenvironment that ultimately contributes to the development of a specific T_H1/T_H2 pattern.³⁴ The basal endogenous glucocorticoid level in each individual appears to be a crucial determinant in immune reactions; the impact of endogenous glucocorticoid levels on immunoregulation is often neglected and is greatly underestimated.³⁴ Corticosteroids have been found to inhibit the production of IL-12 in human monocytes and to enhance their capacity to induce IL-4 synthesis in CD4⁺ T cells.^{36,39} Inasmuch as IL-12 potently enhances IFN- γ production in T cells and natural killer (NK) cells,⁴⁰ inhibition of IL-12 from antigen-presenting cells is considered to be the major mechanism in the corticosteroid-induced T_H2 shift.⁴¹ Corticosteroids have also been found to inhibit monocyte/macrophage differentiation and many of their functions^{42,43} and to decrease NK cell activity.⁴⁴ (The immunomodulatory effects of glucocorticoids, which have been reviewed in detail elsewhere,⁴⁵ are not discussed here.) Furthermore, not only cortisol but also the other end products of the stress response, catecholamines, have been shown to drive the immune responses to a T_H2 -type immunity and to consolidate the effects of cortisol.⁴⁶ Indeed, Ikewana et al⁴⁷ (among the first) have recently published direct evidence that emotional stress in a murine model causes a shift in the T_H1/T_H2 balance toward a T_H2 -dominant immunity through the strong inhibition of IFN- γ production. Parallel to the reduction of IFN- γ levels and elevation of serum corticosterone levels, inhibition of the generation of cytotoxic T lymphocytes and a reduction of NK cell activity were found.

2. Maternal-fetal interactions: evidence obtained from animal models. Henry et al⁴⁸ examined in a rat model the influence of restraint stress during the third week of pregnancy on the development of the HPA axis and corticosteroid receptors of the offspring. Basal and stress corticosterone levels and hippocampal type I and type II corticosteroid receptors were measured in 3-, 21-, and 90-day-old male rats. In prenatally stressed rats the secretion

of corticosterone after exposure to novelty was found to be increased at 3 and 21 days and showed a longer duration at 90 days. The decrease of both types of corticosteroid receptors was found at 21 and 90 days of life. The authors concluded that maternal stress-induced corticosterone that crosses the placenta could play a decisive role in intrauterine immune modulation of the fetus and might lead to long-term changes in HPA axis activity in the offspring.

Kay et al⁴⁹ studied the effect of prenatal stress (noise and light stress 3 times weekly throughout the pregnancy) on immune function in rats. Measurements were performed in the offspring at the age of 2 months. Prenatal stress was found to suppress immune function, as shown by (1) decreased NK cell cytotoxicity in splenic and blood lymphocytes and (2) a decreased rate of proliferation of splenic lymphocytes to mitogens. Prenatal stress did not alter the distribution of subsets of lymphocytes, suggesting that the decreased proliferative and cytotoxic activity resulted from functional modifications of effector mechanisms in the cells rather than from changes in their migration between immune compartments. An action of maternal stress hormones on the developing fetal neuroendocrine system was considered a possible mechanism underlying the findings.⁴⁹

Coe et al⁵⁰ examined in a primate model the effect of adrenocorticotrophic hormone (ACTH) administered for 2 weeks, approximately 1 month before parturition, on cell-mediated immunity in the offspring. Lymphocytes obtained from infants after birth showed reduced responsiveness to allogenic cells in mixed lymphocyte cultures, reduced proliferation rate to a mitogen, decreased suppressor functions after stimulation with a mitogen, and reduced cytolytic activity against target cells. Differences were evident through 6 months of age, indicating that a disturbance such as increased HPA axis activity during the prenatal period can have long-lasting effects on postnatal immunity, irrespective of the normal birth weight and gestational age of the infant.⁵⁰

Most recently, Coe and Lubach⁵¹ showed in a primate model that corticosteroids in utero can influence the fetal immune system, the result being prolonged effects on immune responses after birth. Monkeys generated from dexamethasone-treated pregnancies (0.125 mg/kg; injections for 2 days, 1 month before parturition) tended to have depressed proliferative responses to a mitogen at the age of 1 to 1.5 years. Their cells were also less sensitive to in vitro incubation with cortisol, suggesting downregulation of hormone receptors on their cells. Higher levels of adrenal activity in the monkeys from corticosteroid-treated pregnancies were considered to be responsible for both the lower lymphocyte proliferative responses and the decreased sensitivity of the cells to in vitro exposure to cortisol.⁵¹ In line with these findings, maternal psychological stress has also been found to diminish the proliferative and cytokine responses of leukocytes and to induce glucocorticoid resistance in the offspring in a primate model.⁵²

3. Maternal-fetal interactions: evidence obtained from human beings. Wadhwa et al⁵³ carried out a study of 54 women in their second trimesters to examine the associ-

ation between maternal psychosocial factors and stress-related neuroendocrine parameters (ACTH, β -endorphin, cortisol) during human pregnancy. Measures of prenatal stress, social support, and personality were obtained through use of a self-report questionnaire. Maternal-placental-fetal neuroendocrine parameters were found to be significantly associated, both in magnitude and specificity, with features of maternal psychosocial functioning in pregnancy, irrespective of the systemic alterations associated with the endocrinology of pregnancy.

To date, direct evidence of the influence of stress on T-helper phenotype differentiation in the developing immune system from human beings has been scanty. There are several obvious problems, both ethical and practical (associated particularly with prospective studies), that might partly explain the scarcity of the available human data. Nonetheless, tentative evidence from human beings has been reported by Wright et al,⁵⁴ who examined adverse life events and perceived stress as predictors of wheezing in children with family histories of asthma and/or allergy. When each child was 2 to 3 months of age, the primary caregiver (n = 261) was administered a questionnaire on adverse life events during the previous year and the 10-item Perceived Stress Scale related to the previous month. This study revealed that the mean stress score was significantly higher in caregivers of children with histories of wheeze, reported by the age of 6 months, than in caregivers of children with no history of wheeze. Maternal perceived stress appeared to be associated with infant wheeze and to perhaps lead to wheeze in genetically predisposed children.

4. Cortisol crosses the placenta. Although it has been well established that corticosterone in rats crosses the placenta,⁵⁵ the available data on cortisol in human beings have been somewhat controversial.^{56,57} Recent research, however, has confirmed that maternal cortisol, to a significant extent, crosses the placenta. Gitau et al⁵⁸ measured plasma cortisol concentrations in paired maternal and fetal venous samples (n = 43) at 13 to 35 weeks' gestation; they found that fetal cortisol concentrations were significantly and linearly associated with maternal cortisol concentrations but that neither correlated with gestational age of the fetus. They further found that though most maternal cortisol is metabolized during the passage, the remaining 10% to 20% can still double the much lower fetal cortisol concentration. Consistent results were also obtained in an earlier study of maternal-fetal cortisol transfer that revealed that 15% of maternal cortisol crossed the placenta unmetabolized.⁵⁹ Maternal cortisol thus might have a major effect on the fetal cortisol concentration and further the differentiation of the T-helper cell phenotypes and the development of a T_H2-type immunity in the child.

5. Placental corticotropin-releasing hormone. Placental corticotropin-releasing hormone (CRH), which is identical to the corresponding hypothalamic peptide, is synthesized in trophoblast cells and released into both maternal and fetal circulations.⁶⁰ Cortisol stimulates the expression of the CRH gene in the placenta to cause,

paradoxically, a significant increase in CRHmRNA.^{53,61,62} Placental CRH stimulates both the maternal⁶³ and the fetal^{64,65} adrenal cortisol production, thus establishing a positive feedback loop.⁵³

Normally, the body has a tightly regulated control system to keep cortisol within an optimal time-integrated narrow range, which is quite stable in an individual subject.³¹ Unchecked excessive activity is undoubtedly detrimental to the organism,³¹ and during pregnancy the situation is even worse because the fetus too might be affected.

It must, however, be kept in mind that cortisol is essential to the normal maturation of T cells during ontogeny.⁶⁶ In normal pregnancy, as it advances, there is a progressive (and significant) increase in plasma concentrations of stress hormones, including CRH, ACTH, β -endorphin, and cortisol, with a peak at labor and delivery and then a rapid return to nonpregnancy levels.⁵³ Important questions therefore concern the magnitude (quantity and duration) of the elevation of maternal cortisol that might be deleterious and the period during pregnancy that is most critical to such cortisol elevation.

6. *Occurrence of asthma, atopy, and psychosocial stress increased.* The substantial increase in asthma and atopy prevalences, especially among children and young adults, in many affluent countries during the last decades has been shown in a number of epidemiologic studies.^{67,68} With respect to stress, much of the evidence is obtained from longitudinal studies of work-related stress. Corporate reorganizations and organizational downsizing might be major factors involved here. Indeed, an association between organizational downsizing and long-term sickness absence among the reduced staff has been shown.⁶⁹ Increased work load and time pressure might become significant stressors in such situations. A European survey on working conditions confirmed that the incidence of work-related time pressure and stress have increased considerably in the past 20 years.⁷⁰

In addition, time pressure, experienced formerly mostly by men, has now become a problem seen increasingly in women; in a recent study, nearly one half of a population of employees in the fields of health care and education reported time pressure as a major stress factor, which resulted in stress symptoms, headache, and neck and shoulder pain in many of them.⁷¹

Indirect evidence of increased occurrence of mental stress can also be obtained from statistics regarding drug consumption. In Finland, for example, the consumption of anxiolytics and hypnotics and sedatives has risen substantially in the past 15 years; in the case of hypnotics and sedatives, the increase has been 123%.^{72,73}

Weaknesses of the present data

1. Complexity of the neuroimmunomodulatory mechanisms involved in the maternal-fetal interactions leads to considerable difficulties in determining the relative role of a single variable. In human beings, the response to a stressor appears to be dependent not only on the nature, duration, and severity of the stressor but also on its interplay with a variety of host fac-

tors. In addition, physical states, personality traits, and coping ability have all been found to be of importance.⁷⁴ In human studies it is also difficult to quantify stress and to determine differences in the resistance of the individuals to the stress examined.⁷⁵ Moreover, data obtained from women are scanty, because psychoneuroimmunologic research has traditionally included more men than women. The existence of possible confounding variables in women, such as menstrual cycle, menopause, and use of oral contraceptives, has been suggested as partly explaining such choices.⁷⁶ As regards work-related stress, methodologic problems in research—eg, problems having to do with time pressure and work load—are also considerable. Time pressure, in particular, might be difficult to discover by standard quantitative survey methods.⁷¹

2. It has also been difficult to develop animal models of longer duration or intermittent life stressors and to reliably link the physiologic changes with clinical disease in human beings.²⁰ In the literature, the term *chronic stress* is often used to describe experimental systems in which an acute stress is repeated on a daily basis for a number of days.²¹
3. Direct evidence obtained from human beings is still very scanty. There are several major problems with performing prospective studies of pregnant women perceiving significant chronic stress. Such studies are difficult to design because, as noted above, the weeks of gestation that are most sensitive to the immunomodulatory effects of maternal cortisol are not known. Also unknown is the nature of the stressor that would have the strongest effect. Stress appears not to be a uniform, nonspecific reaction. Different stressors are proposed to have different effects—eg, on immune responses.⁴⁶
4. Pregnancy per se poses major problems for the study of stress-induced immunomodulation. The physiological response of pregnant women is complicated by the “background” changes in neuroendocrinal functions during pregnancy.⁵³

Testing the hypothesis

Despite the problems associated with performing a prospective study, the hypothesis must be tested. A longitudinal study with a large sample of pregnant women recruited from maternity clinics and a follow-up of at least 5 years might satisfactorily reveal whether the occurrence of asthma and atopy is increased in children whose mothers have reported significant psychosocial stress during pregnancy. Confounding factors are many and need to be carefully considered in the analysis.

CONCLUDING REMARKS

The idea that the maternal psychological state affects the intrauterine environment and even the fetus itself is not new.⁶⁹ There is convincing evidence that stress or anxiety during pregnancy can lead to preterm births,

reduced birth weights,^{15,77-79} and infant morbidity^{80,81} and that it can increase susceptibility to several chronic diseases and compromised immune function.^{17,81,82} Accumulating evidence obtained from both animal and human studies⁴⁸⁻⁵⁴ strongly suggests that maternal stress can alter the development of immune responses in the offspring.

Corticosteroids are known to be strong immunomodulators and to drive the T_H1/T_H2 balance toward a T_H2 type response.^{34-39,41} Inasmuch as maternal cortisol is able to cross the placenta,⁵⁸ it is hypothesized that prolonged excessive maternal cortisol secretion affects the developing immune system and T-helper cell differentiation favoring T_H2 immunity. In genetically susceptible children, this might lead to the development of asthma and atopy in later life. Chronic stress could be one additional factor in Western lifestyles that is involved in the current unfavorable trends of asthma and atopy prevalences.

REFERENCES

- Nowak D, Wichmann H-E, Magnusson H. Asthma and atopy in Western and Eastern communities—current status and open question. *Clin Exp Allergy* 1998;28:1043-6.
- Strachan DP. Is allergic disease programmed in early life? *Clin Exp Allergy* 1994;24:603-5.
- Romagnani S. Regulation of the development of type 2 helper cells in allergy. *Curr Opin Immunol* 1994;6:838-46.
- von Hertzen L, Klaukka T, Mattila H, Haahtela T. Mycobacterium tuberculosis infection and the subsequent development of asthma and allergic conditions. *J Allergy Clin Immunol* 1999;104:1211-4.
- Matricardi PM, Rosmini F, Riondino S, Fortini M, Ferrigno L, Rapicetta M, et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 2000;320:412-7.
- Gereda JE, Leung DYM, Thatayatikom A, Streib JE, Price MR, Klinnert MD, et al. Relation between house-dust endotoxin exposure, type 1 T-cell development, and allergen sensitisation in infants at high risk of asthma. *Lancet* 2000;355:1680-3.
- Holt PG. Environmental factors and primary T-cell sensitisation to inhalant allergens in infancy: reappraisal of the role of infections and air pollution. *Pediatr Allergy Immunol* 1995;6:1-10.
- Holt PG. Infections and the development of allergy. *Toxicol Lett* 1996;86:205-10.
- Kapsenberg ML, Hilken CM, Wierenga EA, Kalinski P. The role of antigen-presenting cells in the regulation of allergen-specific T cell responses. *Curr Opin Immunol* 1998;10:607-13.
- Tang C, Rolland JM, Ward C, Li X, Bish R, Thien, Walters EH. Modulatory effects of alveolar macrophages on CD4+ T-cell IL-5 responses correlate with IL-1 β , IL-6, and IL-12 production. *Eur Respir J* 1999;14:106-12.
- Yabuhara A, Macaubas C, Prescott SL, Venaille TJ, Holt BJ, Habre W, et al. Th2-polarised immunological memory to inhalant allergens in atopics is established during infancy and early childhood. *Clin Exp Allergy* 1997;27:1261-9.
- Holt PG. Development of T-cell memory against inhalant allergens: risks for the future. *Clin Exp Allergy* 1999;29(suppl 2):8-13.
- Prescott SL, Macaubas C, Smallacombe T, Holt BJ, Sly PD, Holt PG. Development of allergen-specific T-cell memory in atopic and normal children. *Lancet* 1999;353:196-200.
- Björkstén B, Naaber P, Sepp E, Mikelsaar M. The intestinal microflora in allergic Estonian and Swedish 2-year-old children. *Clin Exp Allergy* 1999;29:342-6.
- Wadhwa PD, Sandman CA, Porto M, Dunkel-Schetter C, Garite TJ. The association between prenatal stress and infant birth weight and gestational age at birth: a prospective investigation. *Am J Obstet Gynecol* 1993;169:858-65.
- Famelli M, Kitraki E, Stylianopoulou F. Maternal behavior of dams treated with ACTH during pregnancy. *Physiol Behav* 1995;57:397-400.
- Barker DJP. Fetal and infant origins of adult disease. London: BMJ Publishing; 1992.
- Sheridan JF, Stark JL, Avitsur R, Padgett DA. Social disruption, immunity, and susceptibility to viral infection. Role of glucocorticoid insensitivity and NGF. *Ann N Y Acad Sci* 2000;917:894-905.
- Dhabhar FS. Acute stress enhances while chronic stress suppresses skin immunity. The role of stress hormones and leukocyte trafficking. *Ann N Y Acad Sci* 2000;917:876-93.
- Busse WW, Kiecolt-Glaser JK, Coe C, Martin RJ, Weiss ST, Parker SR. Stress and asthma. NHLBI Workshop Summary. *Am J Respir Crit Care Med* 1995;151:249-52.
- Harbuz MS, Jessop DS, Chowdrey HS, Blackwell JM, Larsen PJ, Lightman SL. Evidence for altered control of hypothalamic CRF in immune-mediated diseases. *Ann N Y Acad Sci* 1995;771:449-58.
- Khansari DN, Murgu AJ, Faith RE. Effects of stress on the immune system. *Immunol Today* 1990;11:170-5.
- Kort WJ. The effect of chronic stress on the immune system. *Adv Neuroimmunol* 1994;4:1-11.
- Irwin M. Stress-induced immune suppression: role of brain corticotropin releasing hormone and autonomic nervous system mechanisms. *Adv Neuroimmunol* 1994;4:29-47.
- Black PH. Immune system-central nervous system mediators on the brain. *Antimicrob Agents Chemother* 1994;38:7-12.
- Post RM, Weiss SRB, Smith M, Rosen J, Frye M. Stress, conditioning, and the temporal aspects of affective disorders. *Ann N Y Acad Sci* 1995;771:677-96.
- Rosmond R, Dallman MF, Björntorp P. Stress-related cortisol secretion in men: relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities. *J Clin Endocrinol Metab* 1998;83:1853-9.
- Herbert TB, Cohen S. Stress and immunity in humans: a meta-analytic review. *Psychosom Med* 1993;55:364-79.
- McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998;338:171-8.
- Chrousos GP. The stress response and immune function: clinical implications. *Ann N Y Acad Sci* 2000;917:38-67.
- Chrousos GP. Editorial: A healthy body in a healthy mind—and vice versa—the damaging power of “uncontrollable” stress. *J Clin Endocrinol Metab* 1998;83:1842-5.
- Schulz P, Kirschbaum C, Pruessner J, Hellhammer DH. Increased free cortisol secretion after waking in chronically stressed individuals due to work overload. *Stress Med* 1998;14:91-7.
- Wright RJ, Rodriguez M, Cohen S. Review of psychosocial stress and asthma: an integrated biopsychosocial approach. *Thorax* 1998;53:1066-74.
- Wilckens T, De Rijk R. Glucocorticoids and immune function: unknown dimensions and new frontiers. *Immunol Today* 1997;18:418-24.
- Daynes RA, Araneo BA. Contrasting effects of glucocorticoids on the capacity of T cells to produce the growth factors interleukin 2 and interleukin 4. *Eur J Immunol* 1989;19:2319-25.
- Blotta MH, DeKruyff RH, Umetsu DT. Corticosteroids inhibit IL-12 production in human monocytes and enhance their capacity to induce IL-4 synthesis in CD4+ lymphocytes. *J Immunol* 1997;158:5589-95.
- Norbiato G, Bevilacqua M, Vago T, Clerici M. Glucocorticoids and Th1, Th2 type cytokines in rheumatoid arthritis, osteoarthritis, asthma, atopic dermatitis and AIDS. *Clin Exp Rheumatol* 1997;15:315-23.
- Ramirez F, Fowell DJ, Puklavec M, Simmonds S, Mason D. Glucocorticoids promote a Th2 cytokine response by CD4+ T cells in vitro. *J Immunol* 1996;156:2406-12.
- Larsson S, Linden M. Effects of a corticosteroid, budesonide, on production of bioactive IL-12 by human monocytes. *Cytokine* 1998;10:786-9.
- Trichieri G. Interleukin 12: a pro-inflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen-specific adaptive immunity. *Annu Rev Immunol* 1995;13:251-76.
- DeKruyff RH, Fang Y, Umetsu DT. Corticosteroids enhance the capacity of macrophages to induce Th2 cytokine synthesis in CD4+ lymphocytes by inhibiting IL-12 production. *J Immunol* 1998;160:2231-7.
- Baybutt HN, Holsboer F. Inhibition of macrophage differentiation and function by cortisol. *Endocrinology* 1990;127:476-80.
- Zitting BS. Neuroimmunomodulation of macrophage function. In: Glaser R, Kiecolt-Glaser J, editors. *Handbook of human stress and immunity*. London: Academic Press; 1994. p. 53-76.
- Bateman A, Singh A, Kral T, Solomon S. The immune-hypothalamic-pituitary-adrenal axis. *Endocrine Rev* 1989;10:92-112.

45. von Hertzen LC. Role of persistent infection in the control and severity of asthma—focus on *Chlamydia pneumoniae*. *Eur Respir J* 2002; 19:546-56.
46. Elenkov IJ, Chrousos GP. Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. *Trends Endocrinol Metab* 1999;10:359-68.
47. Ikewana K, Shimada M, Ohta A, Yahata T, Ohmi Y, Habu S, Nishimura T. The restraint stress drives a shift in Th1/Th2 balance toward Th2-dominant immunity in mice. *Immunol Lett* 1998;62:39-43.
48. Henry C, Kabbaj M, Simon H, LeMoal M, Maccari S. Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young and adult rats. *J Neuroendocrinol* 1994;6:341-5.
49. Kay G, Tarcic N, Poltyrev T, Weinstock M. Prenatal stress depresses immune function in rats. *Physiol Behav* 1998;63:397-402.
50. Coe CL, Lubach GR, Karaszewski JW, Ershler WB. Prenatal endocrine activation alters postnatal cellular immunity in infant monkeys. *Brain Behav Immun* 1996;10:221-34.
51. Coe CL, Lubach GR. Prenatal influences on neuroimmune set points in infancy. *Ann N Y Acad Sci* 2000;917:468-77.
52. Coe CL, Kramer M, Kirschbaum C, Netter P, Fuchs E. Prenatal stress diminishes the cytokine response of leukocytes to endotoxin stimulation in juvenile rhesus monkeys. *J Clin Endocrinol Metab* 2002;87:675-81.
53. Wadhwa PD, Dunkel-Schetter C, Chicz-DeMet A, Porto M, Sandman CA. Prenatal psychosocial factors and the neuroendocrine axis in human pregnancy. *Psychosom Med* 1996;58:432-46.
54. Wright RJ, Weiss ST, Cohen S, David M, Hawthorne J, Gold DR. Life events, perceived stress, home characteristics and wheeze in asthmatic/allergic families. *Am J Respir Crit Care Med* 1996;153:A420.
55. Zarrow MX, Philpott JE, Denenberg VH. Passage of 14C-4 corticosterone from the rat mother to the foetus and neonate. *Nature* 1970;226:1058-9.
56. Schwartz LB. Understanding human parturition. *Lancet* 1997;350:1792-3.
57. Benediktsson R, Seckl JR. Understanding human parturition. *Lancet* 1998;351:913-4.
58. Gitau R, Cameron A, Fisk NM, Glover V. Fetal exposure to maternal cortisol. *Lancet* 1998;352:707-8.
59. Pearson Murphy BE, Clark S, Donald I, Pinsky M, Vedady D. Conversion of maternal cortisol to cortisone during placental transfer to the human fetus. *Am J Obstet Gynecol* 1974;118:538-41.
60. Karalis K, Majzoub JA. Regulation of placental corticotropin-releasing hormone by steroids. Possible implications in labor initiation. *Ann N Y Acad Sci* 1995;771:551-5.
61. Frim DM, Emanuel RL, Robinson BG, Smas CM, Adler GK, Majzoub JA. Characterization and gestational regulation of corticotropin-releasing hormone messenger RNA in human placenta. *J Clin Invest* 1988;82:287-92.
62. Robinson BG, Emanuel RL, Frim DM, Majzoub JA. Glucocorticoid stimulates expression of corticotropin-releasing hormone gene in human placenta. *Proc Natl Acad Sci U S A* 1988;85:5244-8.
63. Goland RS, Jozak S, Conwell I. Placental corticotropin-releasing hormone and the hypercortisolism of pregnancy. *Am J Obstet Gynecol* 1994;171:1287-91.
64. Blumenfeld Z, Jaffe RB. Hypophysiotropic and neuromodulatory regulation of adrenocorticotropin in the human fetal pituitary gland. *J Clin Invest* 1986;78:288-94.
65. Jones CT, Edwards AV. Adrenal responses to corticotrophin-releasing factor in conscious hypophysectomized calves. *J Physiol* 1990;430:25-36.
66. Sacedon R, Vicente A, Varas A, Jimenez E, Munoz J, Zapata AG. Role of glucocorticoids in early T-cell differentiation. *Ann N.Y. Acad Sci* 2000;917:732-40.
67. Sears MR. Descriptive epidemiology of asthma. *Lancet* 1997;350(supp II):1-4.
68. Reijula K, Haahtela T, Klaukka T, Rantanen J. Incidence of occupational asthma and persistent asthma in young adults has increased in Finland. *Chest* 1996;110:58-61.
69. Kivimäki M, Vahtera J, Pentti J, Ferrie JE. Factors underlying the effect of organisational downsizing on health of employees: longitudinal cohort study. *BMJ* 2000;320:971-5.
70. Dhondt S. Time constraints and autonomy at work in the European Union. European Foundation for the Improvement of Living and Working Conditions. Luxembourg: Office for Official Publications of the European Communities; 1998.
71. Lehto AM. Time pressure as a stress factor. *Society and Leisure* 1998;21:491-511.
72. Finnish Statistics on Medicines. Helsinki: Kela Press; 1989.
73. Finnish Statistics on Medicines. Helsinki: Edita; 2001.
74. Conti A. Oncology in neuroimmunomodulation. What progress has been made? *Ann N Y Acad Sci* 2000;917:68-83.
75. Kopin IJ. Definitions of stress and sympathetic neuronal responses. *Ann N Y Acad Sci* 1995;771:19-30.
76. Benschop R, Geenen R, Mills PJ, Naliboff BD, Kiecolt-Glaser JK, Herbert TB, et al. Cardiovascular and immune responses to acute psychological stress in young and old women: a meta-analysis. *Psychosom Med* 1998;60:290-6.
77. Ferreira AJ. Emotional factors in prenatal environment. *J Nerv Ment Dis* 1965;141:108-18.
78. Perkin MR, Bland JM, Peacock JL, Anderson HR. The effect of anxiety and depression during pregnancy on obstetric complications. *Br J Obstet Gynaecol* 1993;100:629-34.
79. Heregaard M, Henriksen TB, Secher NJ, Hatch MC, Sabroe S. Do stressful life events affect the duration of gestation and risk of preterm delivery? *Epidemiology* 1996;7:339-45.
80. Cohen S, Evans GW, Krantz DS, Stokols D. Physiological, motivational and cognitive effects of aircraft noise on children. *Am Psychol* 1980;35:231-43.
81. Stott DN. Follow-up study from birth of the effects of prenatal stress. *Dev Med Child Neurol* 1973;15:770-87.
82. Barker DJP. Fetal origins of coronary heart disease. *BMJ* 1995;311:171-4.