Stress and allergy

J Montoro,[1] J Mullol,[2,3] I Jáuregui,[4] I Dávila,[5] M Ferrer,[6] J Bartra,[7,3] A del Cuvillo,[8] J Sastre,[9,3] A Valero[7,3]

[1] Unidad de Alergia, Hospital La Plana, Vila-Real (Castellón), Spain
[2] Unitat de Rinologia & Clínica de l'Olfacte, Servei d'Oto-rino-laringologia, Hospital Clínic Immunoal·lèrgia Respiratòria Clínica i Experimental, IDIBAPS. Barcelona, Spain
[3] Centro de Investigación Biomédicac en Red de Enfermedades Respiratorias (CIBERES)
[4] Servicio de Alergología, Hospital de Basurto, Bilbao, Spain
[5] Servicio de Inmunoalergia, Hospital Universitario, Salamanca, Spain
[6] Departamento de Alergia e Inmunología Clínica, Clínica Universitaria de Navarra, Pamplona, Spain
[7] Unitat d'Al·lèrgia, Servei de Pneumologia i Al·lèrgia Respiratòria, Hospital Clinic (ICT), Barcelona, Spain
[8] Clínica Dr. Lobatón, Cádiz, Spain
[9] Servicio de Alergia, Fundación Jiménez Díaz, Madrid, Spain

n **Abstract**

In recent years it has been seen that the nervous and immune systems regulate each other reciprocally, thus giving rise to a new field of study known as psychoneuroimmunology. Stress is defined as a general body response to initially threatening external or internal demands, involving the mobilization of physiological and psychological resources to deal with them. In other words, stress is characterized by an imbalance between body demands and the capacity of the body to cope with them. The persistence of such a situation gives rise to chronic stress, which is the subject of the present study, considering its repercussions upon different organs and systems, with special emphasis on the immune system and - within the latter - upon the implications in relation to allergic disease. Activation of the neuroendocrine and sympathetic systems through catecholamine and cortisol secretion exerts an influence upon the immune system, modifying the balance between Th1/Th2 response in favor of Th2 action. It is not possible to affirm that chronic stress is intrinsically able to cause allergy, though the evidence of different studies suggests than in genetically susceptible individuals, such stress may favor the appearance of allergic disease on one hand, and complicate the control of existing allergy on the other.

Key words: Stress; chronic stress; allergy; psychoneuroimmunology.

n **Resumen**

En las últimas décadas se ha observado que los sistemas nervioso e inmunitario se regulan recíprocamente, lo que ha generado una nueva corriente de estudio denominada psiconeuroinmunología. El estrés se define como una respuesta general del organismo ante demandas externas o internas, inicialmente amenazantes, que consiste en movilizar recursos fisiológicos y psicológicos para poderlas afrontar. Es decir, será el desequilibrio entre las demandas al organismo y la capacidad del organismo para sobrellevarlas lo que caracterizará una situación estresante. El mantenimiento de esta situación caracteriza al estrés crónico que va a ser el motivo de estudio de este artículo por sus repercusiones en distintos órganos y sistemas con especial atención al inmunitario, y dentro de éste, las implicaciones en la alergia. La activación de los sistemas neuroendocrino y simpático, mediante la secreción de catecolaminas y cortisol, van a tener influencia sobre el sistema inmunitario modificando el equilibrio existente entre la respuesta Th1/Th2 favoreciendo la respuesta Th2.No podemos afirmar que el estrés crónico *per se* provoque alergia, pero la evidencia de los distintos estudios apoya que en individuos genéticamente predispuestos pueda, por un lado, favorecer la aparición de patología alérgica y, por otro, dificultar su control cuando ya existe.

Palabras clave: Estrés. Estrés crónico. Alergia. Psiconeuroinmunología.

Introduction

In recent decades, many studies have demonstrated a relationship between the nervous and immune systems. The mechanisms used by both systems in their activation processes share common elements that prevent them from acting as independent entities; rather, the two systems can be said to regulate each other reciprocally. This finding has given rise to a new field of study known as psychoneuroimmunology.

The present study reviews the concept of stress and its

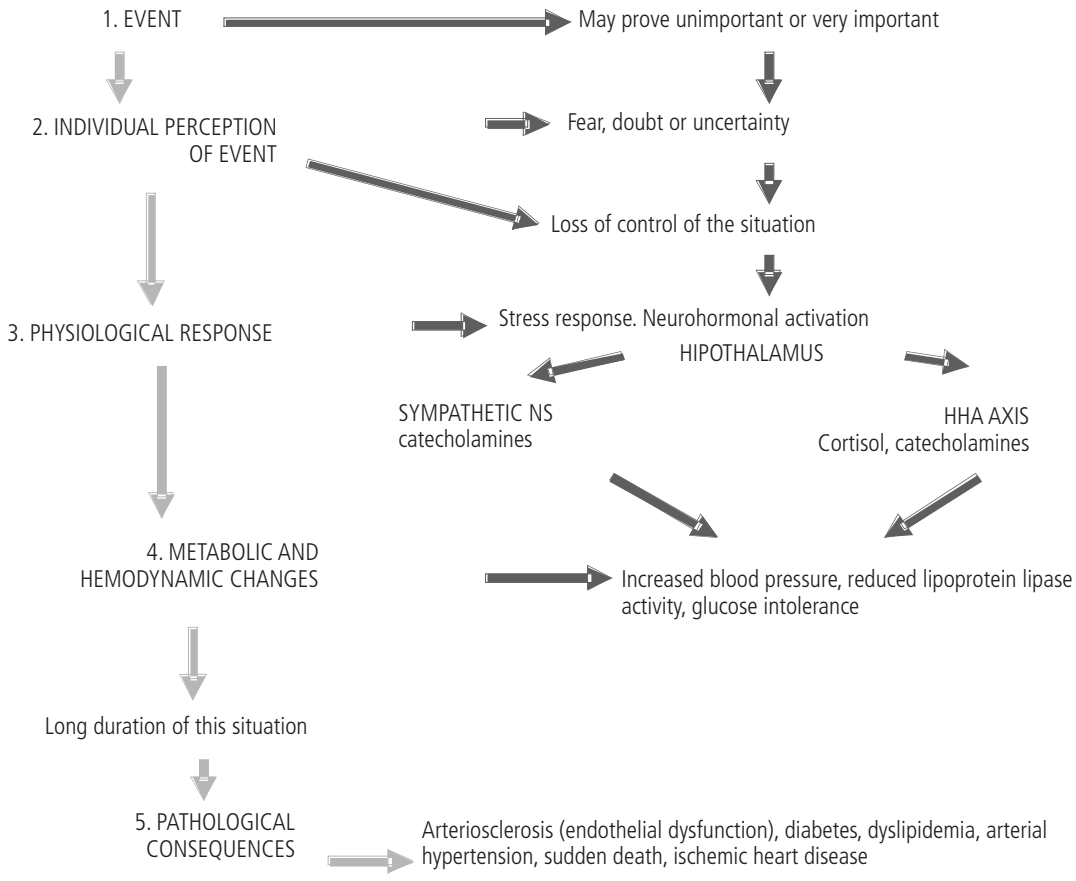

Figure 1. General adaptation syndrome. Modified from (1).

repercussions upon different organs and systems, with special emphasis on the immune system and - within the latter - upon the implications in relation to allergic disease.

What is stress?

"Stress" is curiously difficult to define, despite the fact that it is a widely used and apparently simple term. In our daily lives we use the word "stressing" in reference to any situation that generates brief anxiety or nervousness, in the absence of any organic or mental repercussions. In other words, in most cases we banalize and wrongly use the concept of stress – generalizing its application to situations which in fact are not truly "stressing" in any way.

The psychiatric setting likewise lacks a single definition of stress. Moreover, there are different types of stress, e.g., physical stress produced by disease; mental stress produced by an emotional problem such as loss of employment or the death of a relative; or combinations of both types of stress. Based on its duration, stress in turn can be classified as acute (lasting days) or chronic (lasting months or years).

Nevertheless, there is agreement that stress, or the stressing situation that causes it, triggers a response on the part of the body aimed at coping with the situation, and which implicates both the nervous and the endocrine system (Figure 1). This response was described by Hans Selye in 1936 as a general adaptation syndrome.

Thus, stress may be defined as "a general body response to initially threatening external or internal demands, involving the mobilization of physiological and psychological resources to deal with them" [1]. In other words, stress is characterized by an imbalance between body demands and the capacity of the body to cope with them [2] (Figure 2). Stressing situations may be those that entail a sensation of uncontrolled danger; lack of capacity to carry out an activity; changes in life that require personal adaptation; or uncertainty as to which important decision to take in a given moment in life.

Activation of the neuroendocrine system as an initial response to stress is not the same in intensity or duration in all individuals. In general terms, it can be stated that if the stressing situation is short-lasting (hours or days), it is unlikely to have deleterious effects for the body – though there always may be exceptions in people with previous illnesses

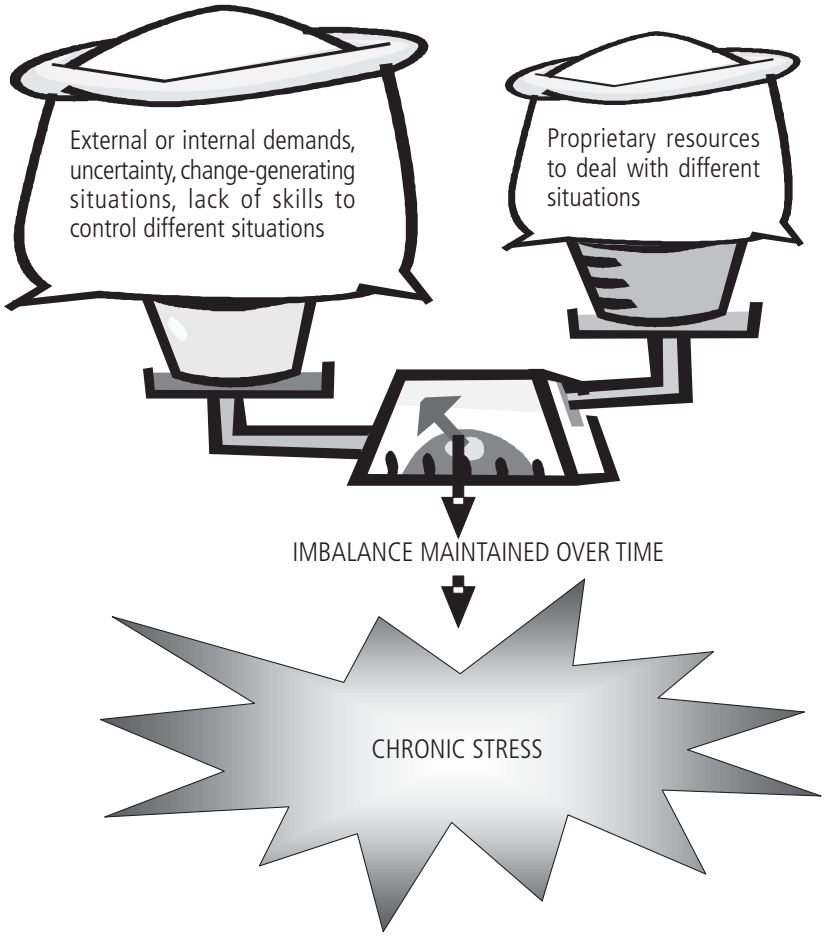

Figure 2. Persistence of the imbalance between the body demands and the body resources needed to deal with them leads to the appearance of chronic stress.

(fundamentally cardiovascular disorders) that may worsen as a result, or even in apparently healthy individuals [3,4]. The same cannot be said of stressing situations that last for months or years (Figure 1). Under such circumstances, referred to as chronic stress, the initial adaptation or adjustment mechanisms aimed at compensating the imbalance produced by the stressing agent are exhausted, and the individual can only hope to "bear" the stress – i.e., confronting the situation is no longer possible, and the individual adopts a submission-like attitude towards the problem. This is the type of stress that we relate to disease.

In effect, chronic stress has been associated to different pathologies:

- Cardiovascular: arteriosclerosis [5], ischemic heart disease [6,7], hypertension [8,9].
- Psychiatric: depression [10,11], tendencies towards unhealthy behavior [12].
- Endocrine: diabetes [13], dyslipidemia [13,14].
- Gastrointestinal: irritable bowel syndrome [15].
- Neurological: Cerebrovascular accidents [16].

The association between stress and neoplastic disease deserves special mention. On one hand, chronic stress is considered to reduce NK cell activity, increasing vulnerability to infection [17], while on the other hand it complicates the mechanisms of DNA repair – thus favoring the appearance of neoplastic phenomena [18]. However, other studies not only have failed to observe any such association [19,20], but actually report a decrease in neoplastic risk among chronically stressed individuals [21,22].

Stress and the immune system

The link between the central nervous system (CNS) and the immune system is represented by the hypothalamic-hypophyseal-adrenal (HHA) axis, which secretes corticotropin-releasing hormone (CRH), and the autonomous nervous system (ANS). The latter in turn is composed of the sympathetic (noradrenergic) and the parasympathetic (cholinergic) systems – both of which originated in the CNS, with noradrenalin and acetylcholine as neurotransmitters, respectively – and the

non-adrenergic, non-cholinergic (peptidergic) system, which is fundamentally located in the gastrointestinal tract. The main peptides of this system are vasoactive intestinal peptide (VIP), substance P (SP) and calcitonin gene-related peptide (CGRP). The ANS innervates important organs and systems related to the immune system, such as the liver, spleen, thymus gland, bone marrow, lymph nodes, skin, digestive tract and respiratory apparatus [23].

The CNS and immune system inter-communicate via neurotransmitters, cytokines and endocrine hormones [24]. The CNS modulates the immune system through the action of neurotransmitters (acetylcholine, noradrenalin, serotonin, histamine, glutamic acid, gamma-aminobutyric acid (GABA)), neuropeptides (adrenocorticotropic hormone (ACTH), prolactin, vasopressin, bradykinin, somatostatin, VIP, SP, neuropeptide Y, encephalin, endorphin), neurological growth factors (neuron growth factor (NGF)), and hormones (adrenalin and corticoids). In turn, the immune system modulates nerve cell function via cytokines (tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-ß)), chemokines, interferon and nitric oxide (NO) [25]. Most immune cells have surface membrane receptors for neurotransmitters, neuropeptides and hormones [24], and their behavior therefore can be influenced directly through such receptors or indirectly as a result of cytokine action [26], in the event of CNS activation.

From the allergological perspective, the sequence of events linking the CNS, the ANS, the immune system and the consequences derived from such mutual activation can be summarized as described below.

Perception of the stressing situation leads to activation of the hypothalamic paraventricular nucleus, which secretes

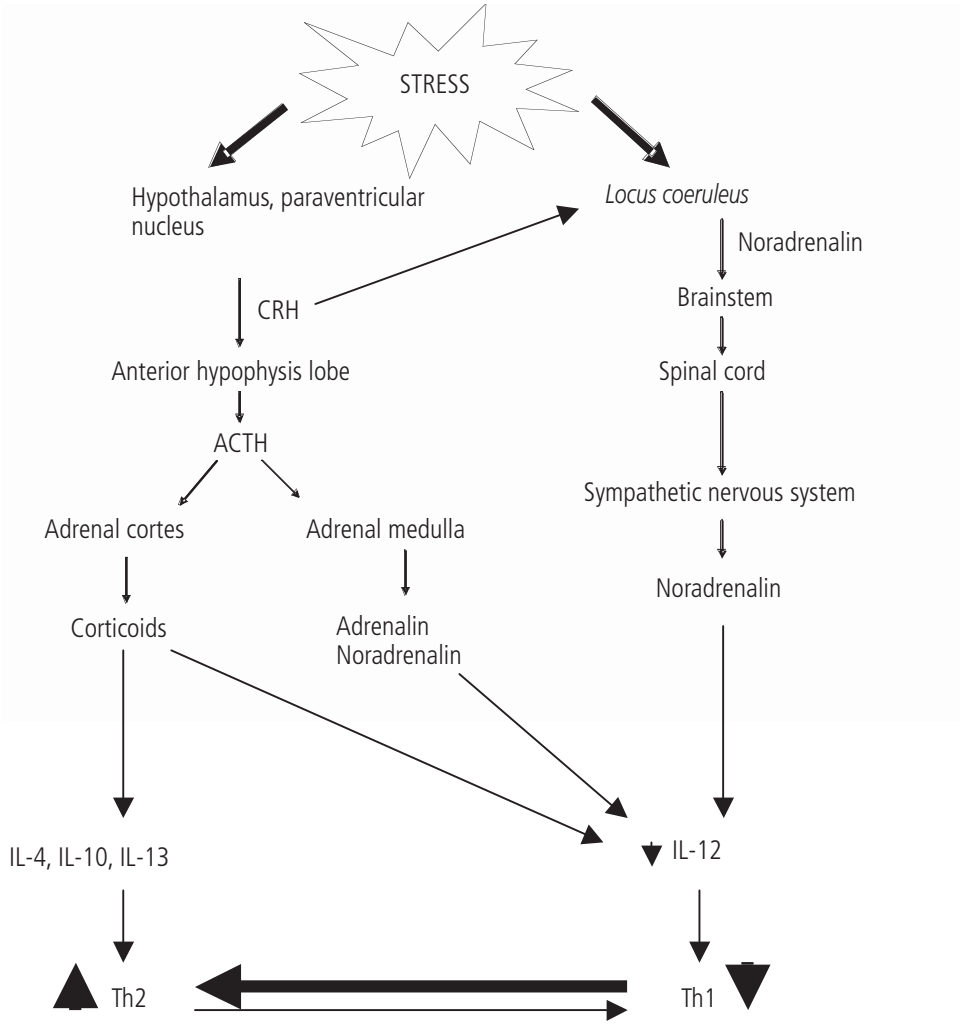

Figure 3. The secretion of catecholamines and corticoids secondary to sustained chronic stress-induced activation of the neuroendocrine and sympathetic systems produces Th1/Th2 imbalance in favor of a Th2 mediated response.

CRH, and of the noradrenalin-producing center or locus coeruleus, which in turn is also activated by CRH. CRH activates the HHA axis, inducing the secretion of ACTH by the anterior hypophyseal lobe. This latter hormone in turn activates the secretion of corticoids by the adrenal cortex and of catecholamines (adrenalin and noradrenalin) by the adrenal medulla. On the other hand, the locus coeruleus secretes noradrenalin, activating the sympathetic nervous system, and releasing noradrenalin at the sympathetic nerve endings.

The catecholamines and corticoids suppress the production of IL-12 by the antigen-presenting cells (APCs), which is the main Th1 cell response-inducing stimulus [27], while the corticoids exert a direct effect upon the Th2 cells, increasing the production of interleukins IL-4, IL-10 and IL-13 (28). All this gives rise to a Th1/Th2 imbalance in favor of Th2 cell mediated response, with dysregulation of the neuroimmunologic homeostatic mechanisms secondary to chronic stress, which ultimately affects cytokine expression and favors an "allergic" inflammatory response (Figure 3).

It should be remembered that the lymphoid organs and blood vessels receive predominantly sympathetic and peptidergic innervation, with direct action on the part of the neuropeptides SP, CGRP and VIP. These are potent vasodilators, resulting in increased vascular permeability on one hand, while SP action upon the monocytes and macrophages on the other hand increases the production of TNF-α and IL-12, in contrast to the situation observed with CGRP and VIP (29). SP and CRH, synthesized at peripheral level within inflammatory foci, are able to degranulate mast cells – thereby reinforcing the inflammatory manifestations [29]. SP and CGRP have been identified in the bronchial mucosa of asthmatic patients as neurogenic inflammation inducing agents following their release from sensory nerve fibers [30]. Stress leads to the release of SP [31,32], and the main receptor of the latter (neurokinin-1 (NK-1)) is located in bronchial vessels, bronchial smooth muscle, epithelial cells, submucosal glands and immune cells. In other words, stress produces a neurogenic inflammatory phenomenon in the bronchial mucosa of asthmatic patients, either directly through action upon the cells that conform the bronchial anatomy, or indirectly via the activation of immune cells [33].

Neurotrophins constitute a family of proteins that act as nerve growth factors, and as linking elements between neurons, immune cells and tissue structure cells. There are four types of neurotrophins: NGF, brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and neurotrophin 4 (NT-4). All of them have been described in different respiratory as well as dermatological allergic disorders, and their spectrum of action is not limited to the nervous system but also extends to the immune cells (monocytes, macrophages, mast cells, T lymphocytes, eosinophils), structural cells (keratinocytes, epithelial cells), and angiogenic phenomena [34]. It has been reported that eosinophils and submucosal glands are the principal source of NGF in the nasal mucosa [35]. A regulatory effect upon eosinophil survival within the lungs also has been described on the part of the epithelial cells of the airway, through the increased expression of neurotrophins (NGF/BDNF) during allergic chronic inflammation of the airway [36]. The neurotrophin BDNF has been shown to increase the production of specific IgE and reduce the Th1 cytokine profile – shifting the balance in favor of a Th2-mediated response [37]. It is therefore evident that the interconnection between the two systems is complete and complex, and that the interactions between them are bidirectional.

Relationship between the nervous and immune systems. clinical implications in allergy

Do all the above described neuroimmune connections have a clinical correlation? In practical terms, do such inter-relations have practical repercussions in the form of symptoms? Do they complicate disease control? Do they favor the appearance of disease? Do they reduce the efficacy of medical treatment?

Wright et al.[38] studied 499 children and their families, with a history of atopy, recruited in the first 48 hours after delivery, with the purpose of examining the influence of maternal stress from the first 2-3 months of life upon the immune response of the infants. The results showed infant perception of maternal stress in the first 2-3 months of life to be associated to an increase in total IgE expression, in allergen-specific proliferative lymphocyte response and TNF-α, with a decrease in interferon-γ (IFN- γ), at 2-3 years of age. The study concluded that early exposure to stress could produce changes in immune reactivity among susceptible children – enhancing the type Th2 mediated inflammatory response.

Von Herzen [39] considered that chronic maternal stress with excessive and sustained cortisol secretion can affect Th1/Th2 differentiation both in the fetus and in the newborn infant, and is able to increase susceptibility to allergic diseases in genetically susceptible individuals.

In murine models it has been shown that prenatal stress increases bronchial hyper-responsiveness and Th2 response to allergens in the adult mouse. A probable contributing factor in this sense is inadequate lung organogenesis secondary to application of the prenatal stressing agent in the mentioned developmental period [40]. Chida et al., likewise based on a murine model, observed an increase in bronchial hyper-responsiveness and in the number of eosinophils in bronchoalveolar lavage after bronchial provocation with antigen, and a reduction in HHA axis response during such bronchial provocation. These findings in adult mice subjected to physical or mental stress in a specific early period of life (4 weeks of age) could not be reproduced when the stressing agent was applied at a later stage [41]. This reduction in HHA response in the face of stressing situations in allergic patients has been described by a number of authors, and has been regarded as commonplace – thereby increasing the probability of triggering an inflammatory cascade in response to stressing agents [42,43].

It is important to point out that not only differences in neuroimmune response among allergic patients have been described. Marshall et al. reported that the presence of chronic stress secondary to final examinations in a group of health students induced cytokine profile dysregulation in favor of a type Th2 response [44]. In another study involving atopic

patients with bronchial asthma, the Th2 cytokine profile and eosinophil presence in sputum were seen to increase after specific bronchial provocation during the examination period (stress), compared with the results obtained in periods without examinations [45]. Kilpeläinen et al., in a study of 10,667 Finnish students between 18-25 years of age, concluded that backgrounds of stress in life can favor manifestations of allergic rhinoconjunctivitis and asthma [46].

In different studies, Kimata H et al. [47-51] have shown that relaxing experiences such as listening to classical music, or pleasurable experiences such as kissing or laughing, for periods of approximately 30 minutes, modify the behavior of the immune cells of allergic patients upon incubating the cells in culture medium with the allergen to which they are sensitized – converting the type Th2 response into a type Th1 response, and reducing the prick test response to the allergen, and the neurotrophin levels. These same authors described the opposite situation in which patients with atopic dermatitis subjected to stressing situations (combat videogames for two hours, or repeated mobile phone calls with different incidents in the course of 30 minutes) increased prick test response, as well as Th2 cytokine, neuropeptide and neurotrophin activity [52]. Ippoliti et al., in a study in asthmatic children and adolescents subjected to stressing family factors (parent separation/divorce, economical problems, unemployment) showed an inferior clinical response after 6 months of specific sublingual immunotherapy against domestic dust mites, compared with other children not exposed to such stress. Although both groups showed improvements in symptoms, peak expiratory flow and serum eosinophilic cationic protein (ECP) levels, they were significantly greater in the group not subjected to stress [53]. Wainwright et al. showed that in individuals with a prior diagnosis of asthma, negative life events in childhood and adolescence, as well as a lack of social support to cope with them, were associated to a current increase in the number of hospital admissions due to asthma. In this context, the authors suggested that psychosocial factors should be taken into account in the long-term management of asthmatic patients [54].

Discussion

The described studies show not only that a true connection exists between the nervous and immune systems, but also that both systems operate on common biochemical and cellular bases [55] – the interactions between them being multiple, complex, and sometimes contradictory. In situations of chronic stress, the released hormones and neuropeptides lead to immune changes, specifically to an imbalance between Th1 mediated action and Th2 response, in favor of the latter. Activation of the HHA axis, with the persistent secretion of glucocorticoids, reduces IL-12 secretion on the part of antigen-presenting cells; this in turn reduces Th1 mediated response – disrupting the constant Th1/Th2 balance in favor of Th2 action. In the same way as occurs with ß2-adrenergic agonists, this situation over the long term could induce increased susceptibility to allergic diseases [56]. The psychological dimension in turn adds to the immune component of stress, i.e., behavioral disorders induced by the persistence of a situation that is difficult to cope with, and which leads to diet deficiencies, increased consumption of toxic substances (tobacco, alcohol) [57], and poor patient compliance with the prescribed allergy treatment.

In a recent metaanalysis, Chida et al. demonstrated that the relationship between psychosocial factors and atopic diseases is bidirectional, i.e., on one hand the negative psychosocial factors influence the development and prognosis of atopic disorders, while on the other hand the latter exert a negative effect upon the mental health of the patient [59].

Of particular interest are the studies published by Kimata [47-52], in which brief pleasurable stimuli (lasting minutes) induced changes in the behavior of the immune cells of allergic patients after culture in a patient serum-free medium, and incubation with the allergen to which the patients were allergic. These surprising findings raise the question as to which factor or factors act upon the cells, changing an initial Th2 response to a Th1 mediated response after such a brief stimulus.

Do psychological interventions have an impact upon the immune system? Could psychological measures alone, or as a complement to medical management, be used to treat diseases in which the immune system is strongly implicated? In a metaanalysis designed to answer this question, Miller and Cohen [60] found that the immune system shows a variable and scant response to psychological interventions – only hypnosis and classical conditioning being seen to induce changes in immune cell behavior.

It therefore must be taken into account that the studies made are subject to important variability, intrinsic to the personality of the individual being studied, and that not all subjects respond in the same way to the same stimulus. Indeed, a given individual may respond differently to one same stimulus at different times in life. Furthermore, no reproducible measurement "instruments" have been developed for application in this field. It is not easy to quantify the action of chronic stress by means of objective laboratory tests.

In sum, can we affirm that chronic stress produces allergy? At present it is not possible to answer this question affirmatively, though the evidence obtained from different studies supports the idea that chronic stress in genetically susceptible individuals can favor the expression of allergic disease on one hand, and complicate the control of existing allergic disease on the other.

Adducing a "problem of nerves" as the explanation for a disease or its lack of control, without a more in-depth evaluation of the situation, thus seems to simply reflect our ignorance of the disease. Nevertheless, on assessing all the prior information, attention also must focus on the psychological dimension of the patient when the pieces of the diagnostic or therapeutic "puzzle" fail to fit correctly.

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J. Montoro

Unidad de Alergia
Hospital La Plana
Crtra. Vila-Real a Burriana km. 0'5
12540 Vila-Real (Castellón)
España