INVITED COMMENTARY

Stressful life events and Graves’ disease

Luca Chiovato and Aldo Pinchera
Istituto di Endocrinologia, University of Pisa, Tirrenia-Pisa, Italy

The search of an explanation for the onset of any disease state is reflected in all cultures, and the idea that psychic distress may predispose to illness is centuries old. Recently, scientific evidence was provided for an interaction between the central nervous and the immune systems (1). Psychological stimuli may set off patterns of neurotransmitters, hormones and cytokines, which act on receptors within the immune system and alter immune function either directly or through induction of other substances (1, 2). As a consequence, during stressful life events, alterations in the neuroendocrine system may functionally affect the immune system. The cause of Graves’ disease is unknown, but there is compelling evidence that its pathogenesis is auto-immune. It is therefore possible that stress-related changes in immune function could precipitate the disease in individuals genetically predisposed to thyroid autoimmunity. Despite this theoretical chain of events and an array of early clinical evidence, the role of stress in the onset of Graves’ disease has remained controversial.

The occurrence of life stresses before the onset of hyperthyroidism is an old observation, and it remains the impression of many clinicians that emotional stress can precede Graves’ disease. A possible role of stress as a precipitant of Graves’ disease was noted in Parry’s initial report, and thereafter by Graves, Basedow and others (3). By the end of the 19th century the condition was considered to result from prolonged worry or sudden shock, and in a 1950 review concluded that severe emotional stress precedes the onset of hyperthyroidism in over 90% of cases (3). Apart from anecdotal reports, early clinical studies suggested a relationship of stressful life events with hyperthyroidism, but had considerable drawbacks, lacking structured methods of data collection, precise definition of what constituted a stressful life event, and appropriate control groups. Contradictory findings were obtained in early epidemiological surveys. An increase in Graves’ disease was reported during major wars (Kriegsbaseelow) (3), but not during the German occupation of Brussels in World War II or during the civil unrest in Ireland (4). The latter study did not show any increase in per capita rates of antithyroid drug utilization before and after the civil disorders developed. In the same setting, relapse of thyrotoxicosis after cessation of carbimazole was unrelated to involvement in bomb-blasts.

More recent investigations involved either standardized interviews (5–7) or population-based case-control studies using self-rated questionnaires (8, 9). The semistructured Paykel’s Interview for Recent Life Events was used in patients with newly diagnosed hyperthyroidism, but results were not unanimous. Gray and Hofstenberg (5), by interviewing patients attending a general hospital, were unable to show any difference in the number and nature of life events affecting “thyrotoxic” patients up to 6 months before the onset of symptoms as compared to controls with non-toxic goitre. Using the same interview, Sonino et al. (6) in Italy reported a significantly higher frequency of positive and negative life events during the year before the first sign of hyperthyroidism in patients with Graves’ disease as compared to normal controls. Several methodological precautions used in the latter study (exclusion of patients with Graves’ hyperthyroidism only, balance for sociodemographic variables between patients and controls, rigorous event definition, delay of interview until hyperthyroidism was controlled by therapy, use of a blind rater for judging the impact of events) could account for the different findings of an association of stressful life events with Graves’ disease as compared to the previous investigation. On the other hand, the heterogeneous pattern of life events recorded by Sonino et al. (6) is in contrast to previous research in psychiatric patients in whom the precipitation of disease was linked only to negative (undesirable and uncontrolled) life events. Assessment of the contextual threat of events by leaving the judgement to an independent rater may be misleading in some cases. As discussed by Rosch (3), the same event may be desirable to some people but undesirable to others. A typical example is the death of a partner, which is generally considered to be the most stressful life event. However, the death of an abusive, wife-beating husband might actually result in a welcome relief for his widow. In the latter case, simply giving a fixed score might be incorrect as an indicator of stress.

Population-based case-control studies were performed in Sweden and England. In Sweden, Winsa et al. (8) mailed a questionnaire about life changes to 219 patients with Graves’ disease and 372 matched normal controls. Patients reported more negative life events in the 12 months preceding the diagnosis of hyperthyroidism, and the negative life event scores were significantly higher in patients than in controls. It was concluded that negative life events were risk factors for Graves’ disease. Similar results were obtained in a population-based case-control investigation performed in England (9). In both studies heredity was also found to be a risk factor for Graves’ disease. Selection bias could be reasonably excluded in these epidemiological studies.
because patients consisted of the majority of recognized cases in the geographical area.

In this issue of European Journal of Endocrinology, Radosavljevic et al. (10) provide further evidence for a role for stressful life events in the precipitation of Graves' disease. Using Paykel's interview, these authors found that patients with Graves' disease attending a medical centre in Belgrade reported significantly more life events in the year preceding the diagnosis than controls recruited from patients suffering from non-thyroid and non-autoimmune diseases. When the prevalence of each life event was analysed separately, eight were found to occur with a significantly greater frequency in patients with Graves' disease. Among them, arguments with a spouse, a fiancé or a superior at work could be influenced by the insidious onset of hyperthyroidism (disease-dependent events). However, the remaining five events appeared to be independent of the disease. Life changes in the latter group were related to work (change in time spent on work, change in the work condition, unemployment for at least 1 month) and to financial difficulties, or involved separation from a family member due to hospitalization for serious illness. In patients with Graves' disease, disease-independent life events were more frequent, although only slightly, than disease-dependent events. The latter observation confirms previous findings reported by Sonino et al. (6), and supports the concept that stressful life events precede the onset of Graves' disease and not vice versa. Participation in the ongoing Balkan war did not precede the onset of Graves' disease with a greater frequency. This observation is in keeping with the study in Northern Ireland, indicating that the civil unrest did not result in an increased consumption of antithyroid drugs (4).

Retrospective studies concerned with life events have inherent risks because the excess of unfavourable life events in patients with Graves' disease as compared to controls may be the consequence rather than the cause of illness (3). Neurobehavioural changes associated with thyrotoxicosis include anxiety and dysphoria, emotional lability, insomnia and, at times, intellectual dysfunction. Increased anxiety and/or hyperreactivity to stressors can be an early and insidious manifestation of Graves' hyperthyroidism, preceding more specific clinical symptoms by months. In this condition, events such as marital separation could be the consequence of the anxious and irritable mood associated with thyrotoxicosis rather than its cause. Recall bias is also a serious concern. Patients with Graves' disease may be more likely than healthy controls to report life events or selectively remember more upsetting events, especially if such life changes are thought to be a consequence or a cause of their disease. This confounding factor may be particularly relevant if patients are questioned during the acute phase of disease, because they may be more prone to distort the magnitude or the meaning of life changes. Personality differences may also affect recall. Subjects with type A personality tend to be more dissatisfied with their life and are predisposed to recall more negative than positive events (3). Quantifying individual stress in objective terms is also a major limitation of retrospective studies in which the number and magnitude of life events preceding the onset of hyperthyroidism were taken as a measure of stress. The most obvious problem is the difficulty in controlling appropriate modulating influences, such as social support and coping skills. Coping refers to cognitive and behavioural efforts to manage a troubled person–environment relationship, and coping skills give a measure of how people react to stressful life events. To address these aspects of stress, a study in Hong Kong (7) evaluated life events, daily hassle and coping in patients with Graves' disease during the year preceding diagnosis. Graves' patients reported more negative events than controls, while positive and neutral events were similar in both groups. Each group had similar coping resources and utilized coping strategies to the same extent. Thus, given more negative events in patients with Graves' disease, they perceived them as having greater severity. Graves' patients also reported more daily hassle (daily irritations and frustrations) and had higher hassle scores than controls (7).

Taking into account all the limitations and possible biases of the above studies, it appears that the majority of recent reports provide circumstantial evidence that patients with Graves' disease have more stress, and that an excess occurred before the onset of hyperthyroidism. The problem still remains to demonstrate a cause and effect relationship, and to clarify the mechanisms by which stress might precipitate Graves' disease. Early suggestions that the effect might be mediated via the hypothalamic–pituitary–thyroid axis were not supported (11). Stress is the reaction of the body to stimuli that disturb its normal physiological equilibrium. Regardless of the nature of stress, the final common pathways are: stimulation of the hypothalamic–pituitary–adrenocortical (HPA) axis, with consequent increases in serum glucocorticoids and activation of the autonomic nervous system, followed by release of catecholamines (2). This altered neuroendocrine equilibrium has a significant impact on the immune response through direct interaction of hormones and neuropeptides with specific receptors on immune cells and indirectly by affecting the production of cytokines (1). These interactions provide means by which stressful life events might influence the development of infectious, neoplastic and autoimmune diseases. Organ-specific autoimmune diseases are believed to be associated with an immune dysregulation that predisposes to autoimmunity, while other factors focus the immune response against a given organ. The type of disorder in immunoregulation is still hypothetical and could involve loss of antigen-specific T-suppressor cell function, intrinsic T-cell hyperactivity, defective clonal inactivation of immature self-reactive B lymphocytes, autoreactive T cells escaping central or peripheral tolerance, T helper 1 (Th1)–Th2 imbalance or chronic specific antigenic stimulation by external insult to

Downloaded from Bioscientifica.com at 10/15/2018 10:36:22PM via free access
the thyocyte or via an antigenic stimulus of microbial origin having cross-reactivity with self-antigens. Regulatory autoreactive T cells have been described in experimental autoimmune thyroiditis, and a partial defect in thyroid-specific T suppressor cells in Hashimoto’s thyroiditis and Graves’ disease has been reported by Volpé (11). Although the existence of thyroid-specific T suppressor cells is still debated, the hypothesis has been put forward that stress, by further lowering the T suppressor cell numbers or function, could be additive to the antigen-specific genetic defect, and thus contribute to precipitate thyroid autoimmunity (11).

An alternative hypothesis to explain the role of stressful life events in the precipitation of organ-specific autoimmunity involves a defective activation of the HPA axis during stress (1, 2). Stressful experiences and bereavement are generally associated with an impairment in several parameters of immune function. Activation of the HPA axis and the subsequent increase in circulating glucocorticoids play a major role in this transient immunosuppression that may actually protect the organism against an overreaction that could lead to autoimmune disease (1, 2). In contrast to this chain of events, experiments in BB rats indicate that the onset of autoimmune diabetes may be promoted by stress (12). How could the latter phenomenon possibly occur? Pharmacological doses of glucocorticoids are required for their immunosuppressive effect, while physiological concentrations of these hormones are essential to promote an immune response (1, 2). Clinical observations indicate that, while glucocorticoids in large doses will suppress the manifestations of Graves’ disease, in lower amounts they may even precipitate the disease (11). This observation is in keeping with experimental and clinical evidence indicating that a defective activation of the HPA axis may render animals more susceptible to the development of autoimmunity. A diminished adrenocortical activity in Lewis compared to Fisher strain rats makes the former more susceptible to the induction of rheumatoid arthritis (1, 2). The development of spontaneous autoimmune thyroiditis in OS chickens is influenced by a reduced glucocorticoid tonus (1, 2). A subgroup of patients with severe rheumatoid arthritis have hyporeactive HPA axis (1, 2). From these data it may be inferred that a defective activation of the HPA axis during stress may increase the susceptibility of genetically predisposed individuals to the development of autoimmunity.

In conclusion, several studies published in the last few years incriminate stressful life events in the precipitation of Graves’ disease. In view of the difficulty, limitations and possible biases of these studies, the controversy over the role of stress in the induction of Graves’ disease remains to be settled. While negative life events are recorded more frequently in Graves’ patients than in controls, the difference is far from impressive, suggesting that other factors such as different environmental agents and especially genetic influences are more relevant for the development of the disease. As correctly pointed out by Volpé (11), any evaluation of the role of stress should take into account that patients with Graves’ disease have a genetic predisposition to their disease. It may well be that normal persons can easily resist the influences of the same stress that would precipitate Graves’ disease in genetically predisposed subjects. In view of this consideration, the appropriate study should be carried out prospectively in a genetically predisposed population, e.g., the families of patients with Graves’ disease. The association between stress and changes in immune function is still incompletely understood to establish a causal link between stressful life events and Graves’ disease. The mechanisms leading to thyroid autoimmunity in general and to Graves’ disease in particular also remain to be defined completely. Lack of an animal model for Graves’ disease represents a further limitation to our understanding of the possible role of stress in precipitating Graves’ disease. However, the framework of notions on the relationship between nervous and immune systems has been set up. We therefore anticipate that in the near future improved knowledge at biological level of interactions between higher centres and the immune and endocrine systems will allow a better elucidation of the pathophysiology of stress and of its reflections on autoimmunity.

References

Luca Chiovato. Istituto di Endocrinologia, University of Pisa, Viale del Tirocino 64, 56118 Terrenas-Pisa, Italy

Received March 13th, 1996
Accepted March 14th, 1996