

Foreword

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In 1936 a half page report appeared in *Nature* under the title “A syndrome produced by diverse noxious agents”, which was authored by Hans Selye of McGill University, Montreal, Canada [1]. The essence of this report was that rats exposed to a variety of noxious or toxic agents (e.g. cold, surgery, forced exercise, adrenaline, atropine, morphine, formaldehyde, etc.) responded to these diverse stimuli with pathophysiological changes that had some common features. The enlargement of the adrenals, the profound shrinkage of the thymus and of lymphoid organs and hemorrhage, especially in the gastrointestinal tract, has been noted as the most characteristic features of the stress reaction. If the treatment was continued with relatively slight injuries or small drug doses, the animals became resistant and their organs returned to the normal state. With further treatment the animals lost their resistance and succumbed with symptoms similar to those seen initially. The terms “general alarm reaction” and “general adaptation syndrome” were proposed for the description of these two phases of the response [2]. Subsequently the word “stress” was coined by Selye to denote the phenomenon, *stressors* were stimulators, which were capable of eliciting the *alarm reaction*. At some point it occurred to Selye that the reaction could, in fact, represent a nonspecific response to noxious agents and, indeed, when he performed the proper experiments, his suspicion turned out to be correct. He reported this in the *Nature* article [1]. In the same year a longer article was published by him [3], where he demonstrated that the involution of the thymus was, in fact, mediated by the adrenal gland as thymus involution was absent in adrenalectomized animals after stress. Selye also published a review article about his ideas on stress and disease [4].

The stress concept triggered a rise of interest in this subject, but the idea soon fell into disrespect, as it was impossible to address the problems involved at the level of scientific knowledge at the time and there were technological difficulties, which could not be resolved in those days. So the stress concept was forgotten and little if any activity were evident for some decades.

In 1975 Ader and Cohen reported that immune reactions are subject to Pavlovian conditioning [5]. In 1991 Besedovsky and colleagues championed that the brain and immune system interacts and described a substance mediating this interaction, which later on turned out to be interleukin 1 (IL 1) [6]. For more information on CRF and the HPA axis, please see the chapter in this book [7].

It was determined by us in 1978 that hypophysectomized (HYPOX) rats are immunodeficient [8] and that pituitary growth hormone (GH) and prolactin (PRL) regulate adaptive immunity. ACTH antagonized immune restoration in this system [9]. Soon it became obvious that adaptive immune function is stimulated by growth and lactogenic hormones (GLH), which involves GH, PRL, and placental lactogens (PL) [10]. The dopaminergic drug, bromocriptine turned out to be as immunosuppressive as was HYPOX [11]. Because dopamine inhibits prolactin secretion, this observation supplied additional evidence for the immunoregulatory effect of prolactin. The development of adjuvant induced arthritis was also dependent on pituitary hormones [12]. The new knowledge was summarized in a book entitled: *Pituitary function and immunity* [13].

The emerging knowledge appealed to an increasingly large number of investigators. By 2000 a substantial amount of knowledge was accumulated.

The term, Neuroimmune Biology was coined to denote this field of scientific enquiry [14].

Today it is clear, that the Nervous- Endocrine- and Immune systems form a regulatory circuitry, the Neuroimmune Supersystem [15], which regulates everything in health or disease and from conception till death. This book contains an update of the stress concept as it applies to current Biology and Medicine.

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