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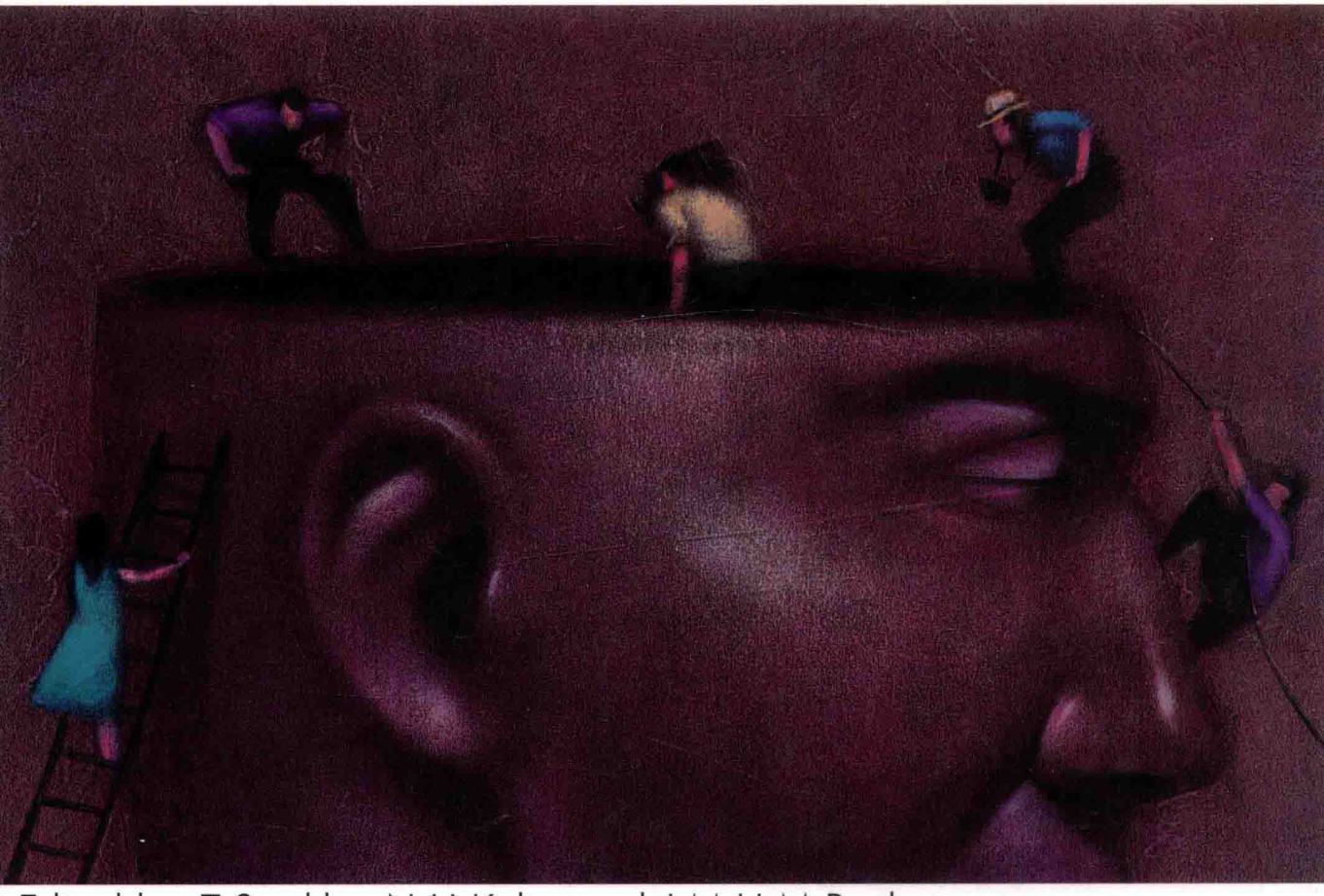
Handbook of Stress and the Brain

Part 1 The Neurobiology of Stress



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HANDBOOK OF STRESS AND THE BRAIN

Part 1: The Neurobiology of Stress

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Preface

Stress is a phenomenon being all around us, but seemingly being too well known and too little understood at the same time, despite the fact that the field has advanced enormously over recent years. We have learned that stress can shape various types of behaviour in the individual long after exposure to the stressor itself has terminated. Exposure to a stressful stimulus during the perinatal period, for example, can have long-term consequences over weeks and months, well into adulthood. This is accompanied by a variety of characteristic neurochemical, endocrine and anatomical changes in the brain, leading, for example, to changes in neural plasticity and cognitive function, motivation and emotionality.

We have started to discover the differentiated effects of various stressors in the brain and how expression of a wide variety of gene products will be altered in the CNS as a function of the type and duration of the stressor. Activity in higher brain areas in turn will shape the response to acute and chronic stress and there are intricate interactions with, for example, immune functions. Cytokines will access the brain and affect its function at various levels.

It has become increasingly clear that stress serves as one of the main triggers for psychiatric and non-psychiatric disorders, including depression, anxiety, psychosis, drug abuse and dementia. Recognizing these intricate relationships has initiated a wealth of research into the development of novel animal models and novel treatment strategies aiming at influencing stress responsivity in patients suffering from these diseases.

Moreover, novel technologies, such as molecular techniques, including gene targeting methods and DNA microarray methods start to unravel the cellular events taking place as a consequence of stress and facilitate the understanding of how stress affects the brain.

Thus, the topic of stress, the brain and behaviour gains increasing relevance, both from a basic scientific and clinical perspective, and spans a wide field of expertise, ranging from the molecular approach to in-depth behavioural testing and clinical investigation. This book aims at bringing these disciplines together to provide an update of the field and an outlook to the future. We think these are exciting times in a rapidly developing area of science and hope that the reader will find it both useful as an introductory text as well as a detailed reference book. The Handbook of Stress and the Brain is presented in two parts, i.e. Part 1: The Neurobiology of Stress, and Part 2: Stress: Integrative and Clinical Aspects.

This part, Part 1, addresses basic aspects of the neurobiology of the stress response including the involvement of neuropeptide, neuroendocrine and neurotransmitter systems, and its corollaries regarding gene expression and behavioural processes such as cognition, motivation and emotionality.

Thomas Steckler
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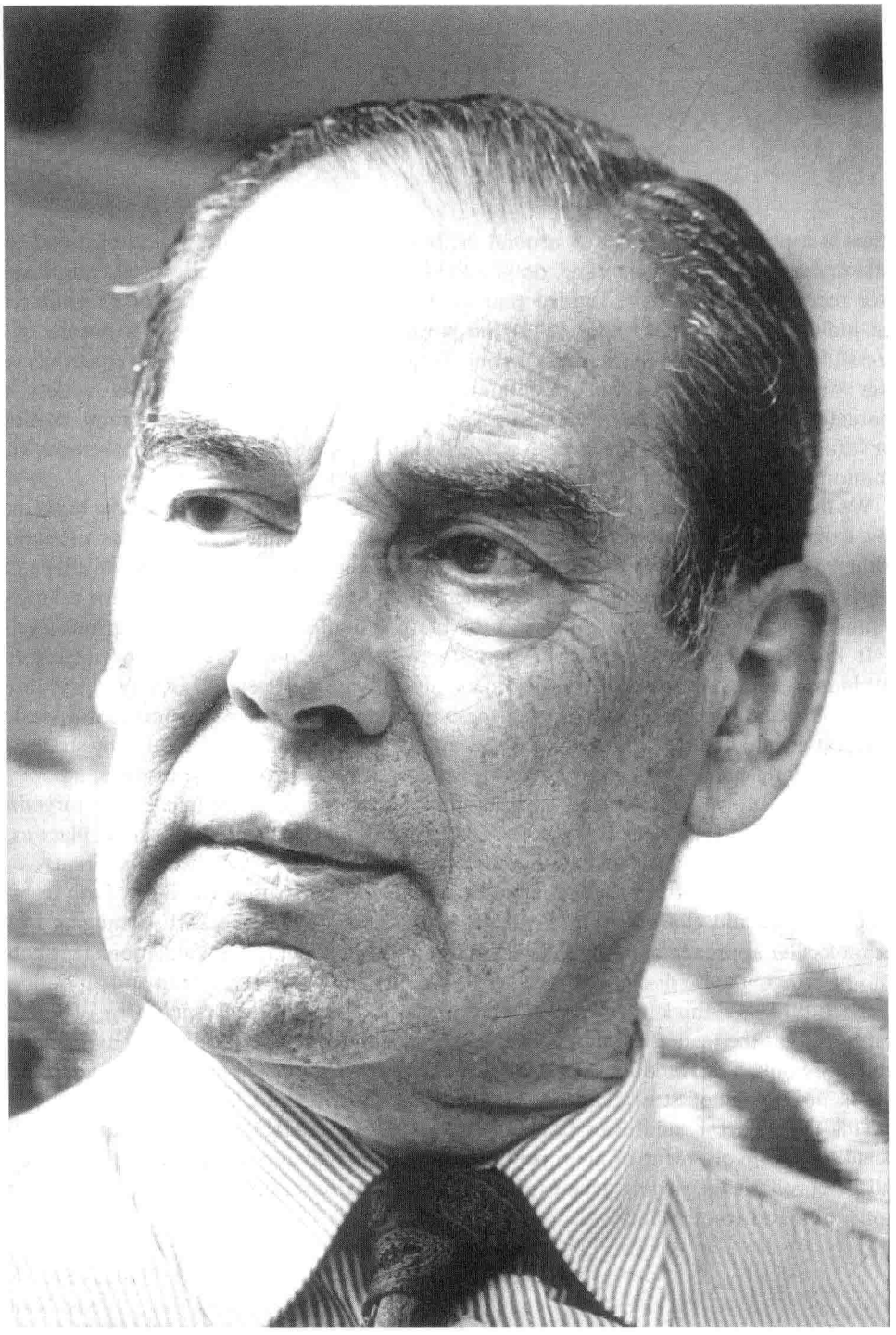

A Memorial for David de Wied (1925–2004)

It is almost an eerie coincidence that this volume, dedicated to the subjects of Stress and Behavior, should be published at a time when the field has lost one of its giants and the man whose work has inspired much of what is written here. On February 21, 2004 Professor David de Wied died. David had just celebrated his 79th birthday. For me not only did the field lose one of its founding fathers but I lost a dear friend. Professor de Wied was born on January 12, 1925. His life prior to embarking on his professional career was marked by a period of several years when he went underground and was in hiding during the German occupation of Holland. Following the war he decided to attend the University of Groningen to study medicine. This involved a tremendous effort since he had lost many precious academic years. He did receive his medical degree in 1955. I shall not document the details of his remarkable academic achievements. These are presented in detail in a volume dedicated to David on his 75th birthday (Smelik and Witter, 2000) and more recently by de Kloet (2004). In my chapter on the history of stress research I devoted several pages to David de Wied and his importance to the field, but his impact on the field was of such significance that it is worth repeating.

David was in every sense a pioneer and a visionary. I have often wondered how one defines a visionary. Perhaps the critical dimension is the ability to see relationships between events that are not immediately apparent to normal mortals. He is best known for his formulation of the "neuropeptide concept" although throughout his career he made many other major contributions. In its simplicity the neuropeptide concept postulated that there were peptides produced in the brain and pituitary that directly influenced brain function, and of particular importance, behavior. The field of hormones and behavior at the time when David began to work on the effects of peptides on behavior was almost exclusively dedicated to studying the effects of gonadal steroids on sexual behavior. There were a few scattered reports of effects of thyroid and adrenal steroid compounds but they had little impact. The demonstration that neuropeptides could influence complex behavioral processes such as learning and memory was indeed revolutionary and met with a great deal of skepticism when first introduced. However, the skeptics were silenced when he continued to demonstrate the powerful influence of these molecules on behavior. It was primarily based on this work that fundamental behavioral processes were integrated into the general rubric of neuroendocrinology and new dimensions of the effects of the hormones of the hypothalamic–pituitary–adrenal axis on behavior were introduced. The neuropeptide concept pre-dated the characterization of the "releasing hormones" synthesized in the hypothalamus. That these hormones have been shown to have a profound influence on behavior is one of the legacies of David's work.

In 1963 he became Professor of Medical Pharmacology at the University of Utrecht which in 1968 became the Rudolf Magnus Institute of Pharmacology in honor of the Dutch pharmacologist Rudolf Magnus. This institute rapidly became the Mecca for the study of hormones and behavior. It was *the* place to visit and study if your field of interest

encompassed neuroendocrinology and behavior. Investigators came from every part of the world to study at the institute. On the numerous occasions that I lectured in the institute I was always prepared to be challenged by David and his students. The discussions were vigorous, animated and sometimes heated, but always stimulating and provocative.

David's legacy extends well beyond his scientific contributions. There are multitudes of Ph.D. and post-doctoral students as well as collaborators who are indebted to him. They were privileged to share his scientific rigor, and perhaps of more importance, his unique intellect. On the occasion of his 75th birthday celebrations the room was filled with many of these students and colleagues. What was impressive is that many of them are now the current leaders in the field.

Although he is best known for his life as a scientist there was much more to the man. He had other passions that made up his life. He was an avid art collector and loved music. Until his death he continued to play the violin and take music lessons. We shared a common love for both music and art. One of our secret ambitions was to perform the famous tenor and baritone duet from Bizet's "The Pearl Fisher." There were two problems, first neither of us could qualify as a tenor and second we really did not sing very well. This did not prevent us from singing opera at any occasion whether it be a dinner at a congress or a party in Hungary.

David was a complex man. He received numerous prestigious honors throughout his career and yet in his later years he did not feel he had achieved the recognition he deserved. Perhaps the problem with being the originator of a concept that gains universal acceptance is that its origin is often forgotten. David had the most unusual sense of humor I have encountered. On one occasion my youngest daughter spent a weekend with us and David and his wife Lie on the Italian Riviera. She spent the first day terrified of him until she realized that he was indeed one of the funniest people she had ever met. She spent the next few days in almost constant laughter.

It was my dream and hope that David and I would have a grand celebration for our joint 80th birthdays in 2005. We were both overjoyed when we experienced the millennium. That dream has now been shattered. I will continue to revere and respect him for all the contributions he has made to biology and to the quality of all our lives. We shared many adventures, many avid scientific discussions and the pleasure of watching the growth of our science. These memories are always present and it was indeed a privilege to have shared these with him over many years.

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References

De Kloet, E.R. (2004) In honour of David de Wied. Psychoneuroendocrinology (in press).

Smelik, P.G. and Witter, A. (2000) David de Wied a biographical sketch. In: David de Wied (Honorary Editor), Neuropeptides, Basics and Perpectives. Elsevier, Amsterdam.

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