Árvay, Prof. Dr. A., University Clinic of Gynecology, Debrecen (Hungary)
Bajusz, E., M.D., Ph.D., Bio-Research Institute, 9 Commercial Avenue, Cambridge, Massachusetts (USA)
Bauer, H.G., M.D., 500 East 77th Street, New York, N.Y. (USA)
Brinck-Johnsen, Dr. T., Department of Pathology, Dartmouth Medical School, Hanover, New Hampshire (USA)
Estep, H., M.D., Endocrine Research Laboratory, Medical College of Virginia, Hospital Division, MCV Station, Richmond, Virginia (USA)
Fujita, T., M.D., Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Hongo, Tokyo (Japan)
Gilroy, J., M.D., Department of Neurology, Harper Hospital, 3825 Brush Street, Detroit, Michigan (USA)
Ibayashi, H., M.D., Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Hongo, Tokyo (Japan)
Kahana, L., M.D., Division of Internal Medicine, Tampa General Hospital, Tampa, Florida (USA)
Kahana, Shirley, M.D., Division of Internal Medicine, Tampa General Hospital, Tampa, Florida (USA)
Kind, H. Th., M.D., Psychiatrische Universitätsklinik Burghölzli, Zürich (Switzerland)
Lansing, R.W., Ph.D., Department of Psychology, University of Arizona, Tucson, Arizona (USA)
Lebovitz, H.E., M.D., Department of Medicine, Division of Endocrinology, Duke University Medical Center, Durham, North Carolina (USA)
Leonard, Dr. A. S., Department of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota (USA)
Levi, J., M.D., Laboratory for Clinical Stress Research, Department of Medicine, Karolinska Sjukhuset, Stockholm (Sweden)
Liss, L., M.D., Division of Neuropathology, College of Medicine, Ohio State University, 410 West 10th Avenue, Columbus, Ohio (USA)
Marks, Dr. V., Department of Chemical Pathology, Area Laboratory, West Park Hospital, Epsom, Surrey (England)
Meyer, J.S., M.D., Department of Neurology, Harper Hospital, 3825 Brush Street, Detroit, Michigan (USA)
Murphy, B.E.P., M.D., Ph.D., Clinical Investigation Unit, Queen Mary Veterans Hospital, 4565 Queen Mary Road, Montreal, P. Q. (Canada)
McKenzie, J. M., M.D., Department of Medicine, Royal Victoria Hospital, McGill University Medical School, Montreal, P.Q. (Canada)
McPherson, H. T., M. D., Department of Medicine, Duke University Medical Center, Durham, North Carolina (USA)

VI Contributing Authors
Nakao, K., M. D., Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Hongo, Tokyo (Japan)
Nichols, J., M.D., Ph. D., Department of Pathology and Oncology, University of Kansas Medical Center, Rainbow Boulevard at 39th Street, Kansas City, Kansas (USA)
Ohsawa, N., M.D., Third Department of Medicine, University of Tokyo, Faculty of Medicine, Hongo, Tokyo (Japan)
Plager, J.E., M.D., Ph. D., The Medical Foundation of Buffalo Inc., 73 High Street, Buffalo, N.Y. (USA)
Rodeck, Prof. Dr. H., Vestische Kinderklinik, Lloydstrasse 5, Datteln (Germany)
Seip, M., M. D., Rikshospitalet, Barneklinikken, Universitetsklinik, Pilestrredet 32, Oslo (Norway)
Solomon, S. H., M.D., Department of Medicine, Royal Victoria Hospital, McGill University Medical School, Montreal, P. Q. (Canada)
Trunnell, J.B., M. D., Center for Cell Research, Brigham Young University, Provo, Utah (USA)
Vermeulen, Prof. Dr. A., Medical Clinic, University of Ghent, Akademisch Ziekenhuis, Ghent (Belgium)
Volpé, R., M. D., University of Toronto, The Toronto Professional Building, Suite 1204, 123 Edward Street, Toronto, Ontario (Canada)
Yoshida, S., M.D., Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Hongo, Tokyo (Japan)

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The expediency of verbal communication concerning complex issues necessitates the use of brief, stereotyped expressions intended to broadly characterize the cardinal features of the subject in question, without any direct reference to points considered to be of secondary significance. Such linguistic simplifications, if perpetuated, are liable to distract attention from momentous and basically important correlations existing between subject areas and thus hamper expansion of our understanding of the function of the living organism as a whole.

The terms «neurology» and «endocrinology» are cases in point, with far-reaching implications concerning the historical development of medical sciences. For centuries, almost all physiologic and pathologic processes have been interpreted in the light of the concept presently still in vogue, i.e., that there are two separate main integrative systems, the neural and endocrine systems, by which the function of various organs are co-ordinated. However, the achievements of investigative medicine have made it increasingly clear during the last two decades that by establishing these two separate scientific disciplines and clinical specialities namely, neurology and endocrinology, we have largely succeeded in obscuring the fact that the two major co-ordinative circuits of the body accomplish morphologic and physiologic integration. The onset of nervous control over the functional activities of the pituitary and other endocrine organs is now well established; but on the other hand, it is also clear that the endocrine apparatus, through its hormones, basically influences the function of the nervous system. Moreover, experimental medicine has succeeded in revealing that the central nervous system is, in a sense, a complex endocrine system producing hormonal substances, i.e., true neurohormones, for the control of internal secretory activities of glandular organs and, most probably also, for regulating a number of other bodily functions. Some neurons in the brain of man and other vertebrates possess characteristics of both nervous and endocrine cells and thus appear to be capable of transmitting neural messages via the secretion of neurohormones. Consequently, neuroendocrinology, the science or analysis of neuro-endocrine relationships, has gradually
become established; and as is shown on the pages of the present book, it is no mere composite of neural and endocrine mechanisms, but reveals altogether novel aspects in the physiology of integrative systems as well as fascinating new concepts in the physiopathology and therapy of many diseases ranging from cardiovascular maladies to central nervous disorders.

It is no exaggeration to state that the practice of clinical medicine in the coming decades will be largely dependent on neuroendocrinologic and biochemical developments, since studies on neuroendocrine interrelationships have already acquired such a broad significance as to encompass almost all specialities of medicine and biology as well. It appears that subcellular biochemical events are under both neural and hormonal control, and that the regulating effects of the fast-acting nervous apparatus and the much slower responding endocrine system not only overlap but are actually interrelated. In fact, one of the main questions of modern biochemistry today is: how do interacting neural, neuroendocrine and hormonal mechanisms govern the fine metabolic activities of cells, tissues and organs under various physiologic and pathologic conditions?

It is worth mentioning—especially because the value of symptomatology has been pushed aside by current interest in and routine application of automatic, scientific and diagnostic methods—that, in reality, it was the art of observing that opened our minds to the existence of an intimate interplay between the neural and hormonal mechanisms. The association between certain periods of life, such as puberty, pregnancy, and the menopause, and the ensuing basic changes in the mental state initiated the first speculations on the possible effects of varying endocrine conditions upon the function of the central nervous system.

On merely theoretic grounds, Kraepelin1, as early as in 1896, regarded dementia praecox as a likely endocrine disorder; and in 1905, Freud2 suggested that certain neuropsychologic diseases, which he was seeking to understand by purely psychoanalytic means, might have endocrine in nature. Still another ancient observation, that the absence of the adrenal cortex in anencephaly (originally described

by Morgagni in 1733) indicated a possible relationship between the adrenal gland and the brain structures, turned out to be correct and amenable to rational explanation. Interestingly, the first paper based on clear-cut experimental observations that established the existence of neuro-endocrine relationships, and written by Berthold in 1849, passed unnoticed in the literature until 1912, when Steinach’s somewhat less original but still significant investigations received widespread attention. Berthold’s findings—described in an outstanding paper reporting the effects of grafted gonadal tissues on sexual behavior of gonadectomized cockerels and concluding that blood-borne secretions of the testis influence the activity of the central nervous system—have been amply confirmed by modern experimental techniques in both man and other species; this phenomenon indeed represents one of the most classical examples of hormonal effects upon neural circuits: the animal’s personality, which expresses itself in its sexual activity, fades out completely in the absence of some hormones and reappears unaltered, following administration of appropriate gonadal steroids to the castrated animal, to the same degree and in the same quality expressed prior to the surgical intervention. After these pioneer observations, several decades were allowed to pass before both experimental and clinical medicine succeeded, quite recently, in proving beyond any doubt that other endocrine secretions besides gonadal hormones also exert a decisive influence upon the development and function of the brain and that endocrine imbalances may play an important role in the etiology of nervous diseases. It appears, in general, that while both clinical neurologists and endocrinologists were slow to extend their interest to each-other’s field, psychiatrists were relatively early embracing the idea of a close relationship between endocrine and nervous functions. Nevertheless, the fact that Bleuler was able to accumulate a bibliography of 2,700 references that were published between 1908, when Laignel-La-


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vastine’s first papers on ‘Psychiatrie Endocrinienne’ appeared, and
1954, when his own ‘Endokrinologische Psychiatrie’ was published does not mean that the area had been successfully explored. The hope that endocrine diseases might be recognized by mental symptoms or, vice versa, that neuro- or psychopathic states might provide early warnings of impending disorders in the form of measurable changes in hormone output has not been fulfilled. In spite of this initial disappointment, the relationship of the psyche to the endocrine system continues to excite the interest of the students of human and animal behavior. The illusion is now treasured that the solution of several physio-pathologic problems of neuropsychiatric diseases only awaits advances in clarifying neuro-endocrine relationships. The realization that, in the past, investigators limited their work to the analysis of effects on the psyche of individual endocrine glands, ignoring for the most part the complexities of endocrine homeostasis and that of neuroendocrine integrative mechanisms, provides new avenues and hopes along these lines.

Although the feed-back action of hormones upon the brain represents one of the most important aspects of clinical neuroendocrinology involving practically the entire field of psychiatry, the majority of chapters in the present volume are devoted to problems of the central-neural regulation or endocrine secretions and to the description of methods and means by whose application disorders of neuro-endocrine relationships can be recognized in man.

Among the first attempts to correlate the information available on the interrelationships between the nervous system and internal secretions was that of Peritz who, in 1913, contributed a pertinent chapter to Oppenheimer’s «Handbuch der Biochemie des Menschen und der Tiere». But it was not until 1946 that two outstanding clinicians, Roussy and Mosinger, dedicated an entire volume entitled ‘Neuroendocrinologie’ to a synthesis and critical evaluation of the relevant data then available in the literature. Under the influence of Pavlov’s studies, physiologists and clinical investigators have concurrently ventured into the exploration of several aspects of possible neuroendocrine interactions, as is well reflected in the book entitled ‘A

neuroendokrin betegségek kórtana és diagnosztikája’, written in 1957 by Julesz, a Hungarian endocrinologist. Of course, the authors of these early attempts were forced to base their concepts on shaky data and the resulting tentative speculations gained little attention on the part of practicing physicians. Although in more recent textbooks and symposium volumes a number of specific examples of the close connections between neural and endocrine mechanisms are mentioned, in Williams’ widely known ‘Textbook of Endocrinology’, a volume comprising 1204 pages at its last edition in 1962, only seven pages in all are devoted to clinical neuroendocrinology.

On the other hand, we have recently published two extensive volumes8,9 in order to collect and correlate the great many experimental data that have established beyond any doubt the regulatory influence of the central nervous system over the functions of the pituitary and other endocrine organs as well. During these endeavors to synthesize facts, observations and ideas, it became evident that investigations of neuro-endocrine relationships in laboratory animals had already yielded a number of new general concepts, in the light of which many of our earlier beliefs on the mechanism of physiologic and pathologic processes had to be re-examined and reformulated. It appeared likely, furthermore, that the basic principles involved in experimental and clinical neuroendocrinology are identical and that many of the conclusions arrived at by animal experimentation may well be applied to the theory and practice of medicine. Hence, the question arose: what then hinders the development of clinical neuroendocrinology?

First of all, our information as to the precise pathways of neuroendocrine mechanisms in humans, the extent of neural regulatory influences over the secretory activities of endocrine glands, the onset and physiologic significance of neurohormones, and also the quality of response of the brain to hormonal feed-back actions in man are still very fragmentary, often merely indirect and sometimes primarily interstitial. In addition, it is true to say that, in general, there are species variations, especially with respect to the extent of neural involvements in endocrine secretory functions; hence, it is often difficult if not impossible to extrapolate from conditions in animals to

9 Bajusz, E. (Ed.): Physiology and Pathology of Adaptation Mechanisms: Neural Neuroendocrine-Hormonal
conditions in man. Furthermore, the more restricted nature of the investigative procedures applicable to human subjects has also greatly hindered the adaption of neuroendocrine thinking among clinicians. Another factor, clearly indicating the difficulties encountered when attempting to apply knowledge obtained in animal physiology to human life processes, involves the neuroendocrine response of the organism to environmental influences. We are now beginning to realize that civilized man differs from animals and even from primitive man in his response to environmental changes: in economically well-established industrial countries, socio-economic relationships rather than immediate physical danger provide the most commonly occurring stressful stimuli. Moreover, when the general adaptive reactions of the organism are activated in civilized man, the somatomotor components are more or less effectively suppressed: the originally well co-ordinated neuroendocrine pathways (which involve somatomotor, visceromotor, and hormonal discharges) become dissociated. Hence, it is not surprising that the consequences of such adaptive reactions are different in man from those seen in animals and may even differ from man to man, depending upon the time of onset and intensity of the secretion of various hormones (i.e., corticoids, catecholamines, growth hormone, thyroxine, gonadal hormones) and also upon the resulting interaction between the various activated endocrine influences that are known to induce changes in the chemical milieu of vital organs.

As we see it today, it is mainly for the reasons outlined above that, although the science of experimental neuroendocrinology is now well established, we are only beginning to appreciate the possible practical importance of neuroendocrine thinking in clinical medicine. In other words, we have been forced to realize that neuroendocrinology has gained recognition as a field of research, but not yet—in spite of many earlier attempts along these lines—as a well-defined, clearly delineated speciality in clinical medicine. However, the future of clinical neuroendocrinology looks promising and there can be little doubt that it is bound to be of the utmost importance.

The need for studies on neuroendocrine relationships in man is great. Methods for collecting reliable, meaningful data and means of ascertaining the role played by inappropriate neuroendocrine adaptive responses of human beings should be devised and those already
existing must be further elaborated. The possibility that neuroendocrine pathways play a decisive role in the etiology of various diseases

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can no longer be excluded. Hence, it appeared to us important to familiarize the readers of the present book with some of the investigative approaches successfully applied to problems of clinical neuroendocrinology, since the future development of this discipline depends largely upon the use of appropriate diagnostic tests and upon the proper interpretation of the results obtained. Furthermore, we sincerely believe that, in this early stage of clinical neuroendocrinology, it is more appropriate to illustrate by means of selected papers how neuroendocrine correlations have been, and can be, established in man than merely to present more or less logically arranged chapters dealing with reviews of the available data.

It is with great pleasure that I acknowledge the introductory article of Dr. Hans Bauer of New York, one of the eminent pioneers in the field of clinical neuroendocrinology. My sincere appreciation is due, furthermore, to all the contributors, not only for their valuable co-operation, but also for their forbearance of some, albeit minor, editorial alterations. Last but not least, I would like to express my thanks to the National Institutes of Health, U.S. Public Health Service (Division of Research Facilities and Resources), Bethesda, Maryland for providing the ‘General Research Support Grant No. S-01-05525-01 ’ to my Institute, which helped to defray the costs of work involved in the organizing and editing of this volume.

I would finally like to mention that the title of this book was chosen in accordance with the purposes outlined above: it is intended to introduce the clinician and interested investigators to a new and rapidly growing field of the medical sciences. I am sure this book will ‘survive’ several editions and, as the growth of our knowledge permits, we are planning to change the character and subject of certain chapters in order to progress from ‘An Introduction to Clinical Neuroendocrinology’ to a standard ‘Textbook of Clinical Neuroendocrinology’-

Cambridge, Massachusetts, November 1966 Eörs Bajusz