E. SCHARRER

Neuroendocrinology

ERNST SCHARRER & BERTA SCHARRER

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Preface

Il en est ainsi de la Neurologie et de l'Endocrinologie. Ces disciplines tendent aujourd'hui à se rapprocher l'une de l'autre à tel point que l'étude des régulations nerveuses et celle des régulations hormonales se confondent de plus en plus en une science de synthèse: la Neuro-endocrinologie.

G. ROUSSY AND M. MOSINGER, 1946, p. iii

When, in the course of phylogeny, multicellular organisms increased in size and complexity, two systems of communication developed serving tissues and organs. One, the endocrine system, utilizes the blood channels to dispatch chemical messengers, the hormones. These spread without direction through the whole organism. It is left to the target tissues to schedule their responses to these chemical stimuli according to timetables of their own. The other, the nervous system, transmits information from one part of the organism to another by means of chains of specialized cells, the neurons, with point-to-point precision and at high speeds.

The endocrine and the nervous systems by their particular contributions accomplish morphological and physiological integration. Morphological integration results from the control of growth and development in time and space. Its failure leads to disharmonious structural patterns and malformations. Physiological integration of the mechanisms that make up a living organism brings about those adjustments to the ever-changing environmental conditions which make survival possible.

So different are the modes of operation of the nervous and the endocrine systems that their study resulted in two separate scientific disciplines and clinical specialities, neurology and endocrinology. In the investigation of the nervous system on the one hand,

and of endocrine phenomena on the other, sight has sometimes been lost of the many instances of close interrelation of nervous and endocrine functions. It is only in recent years that the nervous control of organs of internal secretion has been studied. It has also become increasingly evident that the latter, through their hormones, act on the nervous system. Indeed, there are not many functions which are under neural or hormonal control exclusively; the great majority are under the overlapping authority of both the endocrine and the nervous systems. Thus, in tracing neural pathways, we encounter hormonal links and hormonal feedback which often lead to the central nervous system and through it rather than directly to an organ of internal secretion.

Furthermore, the nervous system possesses its own endocrine apparatus which produces and releases hormones. In dealing with these relationships we shall emphasize comparative biological rather than chemical or clinical aspects, and we shall illustrate principles by selected examples instead of attempting to cover the field of neuroendocrinology in its entirety.

The role of humoral agents in the transmission of nervous impulses will not be discussed in this book. Transmitter substances appear and disappear at synaptic junctions and are not hormones in the commonly accepted sense of the term. The reader interested in this important aspect of the physiology of the nervous system may wish to consult any one of a number of available reviews of this special field (Minz, 1955; Feldberg, 1956; Nachmansohn, 1959; von Euler, 1959; Welsh, 1959, 1961*a*,*b*; Florey, 1961; Koelle, 1962).

The plan for this book has been on our minds for some time, but its writing might have been postponed indefinitely had not the Department of Zoology of Columbia University through its chairman, Professor Lester Barth, extended an invitation to both of us to deliver the Jesup Lectures in October and November, 1960. The invitation carried with it the obligation and the privilege of publication of the lectures in the Columbia Biological Series. Although only a part of the material presented here was used then, we would like to claim for this book the indulgence that the reader is inclined to accord to "lectures," but will not bestow with equal charity on a "text."

In the course of years we have had with us staff members and guest investigators who have made significant contributions to the field of neuroendocrinology. To them, our office staff, the audio-visual department of our school, and the editors of Columbia University Press, in particular Mr. Robert Tilley, we wish to express our gratitude for their help and cooperation.

The manuscript was completed while we were both on sabbatical leave during the academic year 1961–62; we want to acknowledge here the contribution our administration has made by granting us the most precious commodity, namely, time. For the award of a fellowship, one of us (E.S.) is grateful to the Commonwealth Fund of New York City. We also wish to thank the United States Public Health Service for Grants No. B–840, B–2145, and A–3984, and a share in Interdisciplinary Grant 2M–6418. These grants enabled us and our associates to explore at first hand some of the problems that we are going to discuss in the following chapters.

Albert Einstein College of Medicine ERNST AND BERTA SCHARRER
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Introduction

HISTORICAL CONSIDERATIONS

A scientific concept, having acquired a status of acceptance and influence, usually becomes endowed, in retrospect, with a more or less legitimate history of its own, in the same way as a person who has reached an acknowledged social position may reconstruct an adequate line of respectable ancestors from weathered inscriptions on gravestones.

Some of the early reports claiming relationships between the brain and glands of internal secretion have this quality of ancient tales which, surprisingly, often turn out to be based on facts. For example, Gall (1818) and Vimont (1836) make precise statements to the effect that unilateral castration causes atrophy of the contralateral hemisphere of the cerebellum.[1] Since then, either investi-

[1] "Toutes les fois qu'on a enlevé un seul testicule à un animal, de quelque espèce qu'il soit, le lobe du cervelet, du côté opposé, s'atrophie visiblement, ou est altéré dans sa substance, d'une manière quelconque" (Gall, 1818, p. 112). "J'ai fait châtrer, unilatéralement, plusieurs lapins, les uns du côté droit, les autres du côté gauche. Les ayant fait tuer six à huit mois après, j'ai trouvé, sans exception, le lobe du cervelet, du côté opposé à celui où la castration avait été opérée, plus petit, et la bosse occipitale plus aplatie que l'autre" (Gall, 1818, p. 113). "Chez quatre autres lapins que j'ai fait nourrir pendant dix-huit mois j'ai trouvé après la mort une diminution apparente du lobe cérébelleux opposé" (Vimont, 1836. p. 321).

Both authors also describe a number of clinical cases which illustrate, in their view, a relationship between cerebellum and sexual behavior. Vimont finds correlations between the development of the cerebellum in different types of animals and their reproductive activities.

gators have neglected to check on the state of the cerebellum in castrated animals, or else the phenomenon, like the transformation of frogs into princes, no longer occurs.

Similarly, no meaningful connection was at first seen in cases of agenesis of the olfactory lobes and gonadal hypoplasia (Maestre de San Juan, 1856; Weidenreich, 1914), but as more such cases were published (Mirsalis, 1929; Kanai, 1940; Gauthier, 1960), a functional relationship had to be seriously considered and has indeed been confirmed by experimental studies. Still another ancient observation, namely, the absence of the adrenal cortex in anencephali (Morgagni, 1733; Sömmering, 1792; Meckel, 1802, etc.; for references see Zander, 1890, and Moeri, 1951), turned out to be correct and amenable to rational explanation. However, a critical mass of data is usually necessary before a relationship between two distant entities is recognized. Berthold (1849), in the first conclusive demonstration of the action of hormones, implicated the nervous system as a target organ, but this thought was not pursued until Steinach's experiments (1912) received widespread attention. Brown-Sequard, a contemporary of Berthold, never seems to have become interested in possible connections between the nervous system and the endocrine glands, although he was one of the pioneers in the investigation of both (Olmsted, 1946). Przibram (1914), like Brown-Sequard a highly imaginative and untiring experimenter with a wide range of interests, considered but quickly rejected the proposition that hormones may act via the nervous system.

A summary by Peritz (1913) of the information then available on the interrelationships of nervous system and internal secretion may be found in Oppenheimer's *Handbuch der Biochemie des Menschen und der Tiere*. Here the same questions, which even now can be answered only with a measure of uncertainty, are formulated and discussed on the basis of the limited data of the time, but no conclusions are drawn. Nor did Lewy (1929) arrive at a general concept that would have advanced the idea of an intimate relationship between neurology and endocrinology, although he did emphasize that "vegetative Kerne im Zentralnervensystem und Hypophysenhinterlappen ein einziges zusammengehöriges System bilden."

Such specific examples of close connections between nervous and endocrine mechanisms, usually the hypothalamic-hypophyseal system, are more frequently mentioned from about 1920 on (e.g., Monakow, 1919, 1921, 1922; Borberg, 1921; Hoskins, 1934; Roizin, 1936; Oliveira e Silva, 1938, 1939; Stockard, 1938) and are discussed in terms of their significance for analysis of integrated control of organ functions. Concurrently, under the influence of Pavlov, Russian physiologists explored many aspects of the control of endocrine functions by higher nervous centers and studied the effects of hormonal reactions on brain metabolism and function. However, it was not until 1946 that Roussy and Mosinger collected and correlated the relevant data then available in a volume of 1,106 pages, entitled *Neuroendocrinologie.* Their book, as well as *Lebensnerven und Lebenstriebe* by L. R. Müller (1931) and *Sistema Neurovegetativo* by Pi Suñer (1947), is primarily concerned with the relationships between the autonomic nervous system and the endocrines in mammals and is oriented towards clinical problems. A useful bibliography containing references to papers published in this area during the period from 1900 to 1950 has been edited by Fenz (1953) under the title *Bibliographia neurovegetativa.*

While these concepts were still in the realm of tentative speculation as far as man and the common laboratory mammals were concerned, the first decisive observations on the intimate relationship between internal secretion and nervous system were reported from unexpected quarters. In Poland, Kopeć (1917) found that the brains of caterpillars of the moth *Lymantria* produce a "pupation hormone," and soon afterwards in the United States Speidel (1919) described "gland-cells of internal secretion in the spinal cord of skates." It was many years until these discoveries were appreciated.

The study of neuroendocrine integration on a broad basis, extending equally to invertebrates and vertebrates, received much impetus from a series of symposia dealing with neurosecretion,[2] comparative endocrinology,[3] neuroendocrinology,[4] neurovegetative

[2] Naples, 1953 (Anonymous, ed., 1954); Lund, 1957 (Bargmann, Hanström, and Scharrer, eds., 1958); Bristol, 1961 (Heller and Clark, eds., 1962).

[3] Liverpool, 1954 (Chester Jones and Eckstein, eds., 1956); Cold Spring Harbor, 1958 (Gorbman, ed., 1959); Oiso, 1961 (Takewaki, ed., 1962*c*).

[4] Harriman, N. Y., 1956 (Hoagland, ed., 1957); Miami, Fla., 1961 (Nalbandov, ed., 1963).

research,[5] and various aspects of hypothalamic-hypophyseal physiology and pathology.[6] The very frequency of such conferences in recent years reflects the sudden expansion of research in this field. The published proceedings of these conferences, together with a number of reviews,[7] offer a wealth of up-to-date information. Much material of interest along these lines may also be found in the *Annual Reports on Stress*,[8] in publications of the Association for Research in Nervous and Mental Disease,[9] and in the Proceedings of the Laurentian Hormone Conference.[10] Many journals[11] currently publish papers in the field of neuroendocrinology.

Textbooks of neurology do not reflect this trend as much as do those of endocrinology (Friedgood, 1956; Turner, 1960; Gorbman and Bern, 1962). Much information on the interrelationships of nervous and endocrine mechanisms is woven into the excellent articles in *Sex and Internal Secretions* (W. C. Young, ed., 1961). Also in recent years laboratories have been established specifically for the study of neuroendocrinology, and the International Institute of Brain Research (IBRO), an agency of UNESCO, has ac-

[5] Schloss Burg a.d. Wupper, 1950 (*Acta Neuroveget.* 3: 1–266, 1952); Florence, 1953 (*Acta Neuroveget.* 9: 1–364, 1954); Freudenstadt, 1960 (*Acta Neuroveget.* 23: 1–248, 1962).

[6] Houston, 1955 (Fields, Guillemin, and Carton, eds., 1956); Bristol, 1956 (Heller, ed., 1957); Milan, 1956 (Curri, Martini, and Kovac, eds., 1958).

[7] Weill and Bernfeld, 1954; Barraclough and Sawyer, 1956; Escolar, Soler, Reinoso, Smith-Agreda, and Amat, 1957; Fortier, 1957; Greer, 1957; Rothballer, 1957; E. Scharrer, 1959; Harris, 1960; Jørgensen and Larsen, 1960; Lissák and Endröczi, 1960; Brooks, Gilbert, Levey, and Curtis, 1962; Szentágothai, Flerkó, Mess, and Halász, 1962.

[8] Selye, 1951; Selye and Horava, 1952, 1953; Selye and Heuser, 1954, 1956.

[9] Research Publications of the Association for Research in Nervous and Mental Disease, Vols. 9 (1928), 17 (1936), 20 (1939), and 29 (1949) (Baltimore, The Williams and Wilkins Co.).

[10] *Recent Progress in Hormone Research,* Proceedings of the Laurentian Hormone Conference (since 1947), G. Pincus, ed. (New York, Academic Press).

[11] For example: *Acta Endocrinologica,* C. Hamburger, ed., Periodica, Copenhagen; *Acta Neurovegetativa,* E. Anderson, C. Coronini, and A. Sturm, eds., Springer-Verlag, Vienna; *Annales d' Endocrinologie,* G. Laroche and A. Soulairac, eds., Doin and Masson, Paris; *Endocrinologia Japonica,* Y. Ito, ed., published by the Endocrinological Society of Japan; *Endocrinology,* F. G. Hofmann, ed., published by the Endocrine Society, United States; *Endokrinologie,* W. Berblinger, K. Seidel, W. Stepp, and E. Tonutti, eds., J. A. Barth, Leipzig; *General and Comparative Endocrinology,* A. Gorbman and E. J. W. Barrington, eds., Academic Press, New York and London; *The Journal of Clinical Endocrinology and Metabolism,* A. Albert, ed., published by the Endocrine Society, United States; *The Journal of Endocrinology,* P. Eckstein, ed., Cambridge University Press.

corded to neuroendocrinology status equal to that of such older and well-established divisions as neurophysiology and neuroanatomy.

While clinical neurologists were somewhat slow in extending their interests to the organs of internal secretion, psychiatrists embraced with alacrity the idea of a close interrelationship between nervous and endocrine functions. Freud himself believed that the disturbances which he tried to understand from the psychological point of view would eventually be amenable to treatment by hormones (Van Ophuijsen, 1951). And indeed, for a time, it became fashionable to treat the mentally ill with irradiation and surgical removal of endocrine organs or administration of hormones, although the causal relationships between psychiatric disorders and endocrine function were but little understood.

The fact that Bleuler could accumulate a bibliography of 2,700 references, published between Laignet-Lavastine's first papers on "Psychiatrie Endocrinienne" (1908) and his own "Endokrinologische Psychiatrie" (1954), does not mean that the area had been successfully explored. Quite the contrary; as Bleuler points out, the endocrine disturbances, if any, in cases of neuro- and psychopathic conditions and the psychological symptoms in patients suffering from endocrine malfunctions are of an unpredictable multitude, and no generally applicable conclusions have yet been reached beyond what Bleuler designates as the "endocrine psychosyndrome." The latter means that endocrine diseases are frequently accompanied by nonspecific psychological disturbances consisting of either hyperexcitability or lowered responsiveness, optimistic or pessimistic outlook, etc.

The hope that endocrine diseases might be heralded by discernible mental changes or vice versa, that developing neuro- or psychopathic states might provide early warnings of impending psychological crises in the form of measurable changes in hormone output, has not been fulfilled.[12] It is not merely doubtful that

[12] This does not preclude, on a practical level, the usefulness of psychotherapy in endocrine disturbances or the administration of hormones with beneficial effects in neuropsychiatric conditions. Subclinical symptoms such as premenstrual tension, irritability, melancholia, etc. often respond to very small doses of hormones. Presumably the normal hormone ratio had been disturbed and can be restored (Malleson, 1953).

further accumulation of casuistic material will be useful in the exploration of interrelationships between normal and abnormal behavior and the functions of the endocrine system, but it is quite obvious that clinical studies are singularly unsuitable for the elucidation of the basic underlying principles in this area (Reiss, 1950–51). A large part of human behavior is so densely interwoven with acquired and artificial components that it is next to impossible to isolate the effect of the administration of hormones without encountering any number of inconsistent side effects. Still, says Lhermitte (1951), "qui peut, en effet, douter aujourd'hui que le système endocrinien, source des hormones, exerce une importance de premier plan dans la régulation de la vie psychique, et quel psychiâtre pourrait ignorer les profonds dérèglements qu'entraîne le dysfonctionnement de l'appareil hormonal dans le comportement mental et social de l'homme?"

This sentiment has popular appeal. For good reasons man is increasingly concerned with his own behavior and its dependence on biochemical factors. Contemporary writers reflect this particular facet of the *Zeitgeist* by freely referring to the role of glands of internal secretion in human behavior with evident confidence that the general reader is familiar with both the vocabulary and the underlying concepts.

Thus, after a slow start, the investigation of neuroendocrine relationships is now quickly gathering momentum. The borderlines of the vast territory are yet to be defined; the reports of explorers who have crossed it in various directions are detailed and accurate in spots while contradictory in others. However, the major landmarks can be discerned and future excursions may be charted with increasing confidence.

Part I

THE PRINCIPLE OF NEUROENDOCRINE INTEGRATION

The blood pours out something—through the spermatic arteries to the genitals, so also it receives as a recompense a certain ferment from the parts—to wit certain particles imbued with a seminal tincture are carried back to the blood . . . which make it vigorous and inspire into it a new and lively virtue.

THOMAS WILLIS, QUOTED BY R. G. HOSKINS, 1941, p. 16

The meaning of the term "neuroendocrine integration" may best be explained by the description of a hypothetical situation (Fig. 1) which has, however, very real and practical implications. Endocrine organ A, stimulated by factors that need not be discussed in this connection, releases hormone α. Its increasing titer in the blood stimulates endocrine organ B to produce and release hormone β. As hormone α continues to stimulate organ B, the increasing blood concentration of hormone β begins to exert an inhibiting effect on organ A. As a result, the latter reduces its output and eventually ceases to release hormone α. Thus hormone β not only serves its particular function whatever that may be, but also regulates its own production by its inhibitory effect on organ A.

As long as the question is only one of equilibrium between two organs of internal secretion, the intervention of the nervous system is not required. However, endocrine organs cannot by themselves make decisions on the basis of information other than the type just described. For example, environmental conditions may change in

such a way that either organ A should continue to stimulate organ B irrespective of the blood titer of hormone β, or should stop releasing its hormone although organ B may have hardly begun to respond to the stimulus of α. In order to accomplish such adjustments, the feedback cycle must be open to allow the entry of mes-

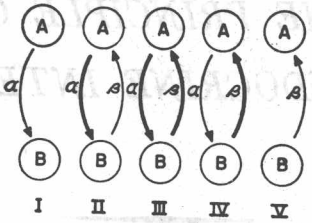

Fig. 1. Different phases of hormonal feedback as described in the text (I–V)

Hormone concentration in the circulating blood is indicated by thickness of arrows.

sages that may change the existing pattern. The control of ovarian function may serve to illustrate this point.

The mechanism for release of gonadotropins[1] in mammals was originally conceived as a simple feedback of gonadal steroids to the pituitary (Moore and Price, 1932). However, if this were the only determining factor, external and internal conditions such as photoperiods, availability of food, social contacts, etc. could not affect the reproductive timetable. Channels must exist, therefore, through which these modifying influences enter the control system and become integrated with or supersede the ovarian feedback mechanism. This integration can only take place in the central nervous system. In later chapters we shall adduce evidence that this principle applies not only to mammals, but to other animals as well, including insects (B. Scharrer, 1958*a*, 1959).

In the same way, earlier evidence to the effect that the secretion of hypophyseal adrenocorticotropic hormone (ACTH) is regulated by the blood level of adrenocorticoids is no longer considered adequate

[1] In accordance with the arguments presented by Stewart and Li (1962), we use throughout this text the suffixes "tropin" and "tropic" (see also "Terminology for the anterior pituitary hormones," *Science* 138:723–30, 1962).

to explain adrenal cortical function; here too, control is exerted by the central nervous system (Sayers, Redgate, and Royce, 1958).

The resulting relationship resembles the concept of feedback as it is used in physics, and a comparison may be helpful at this point.

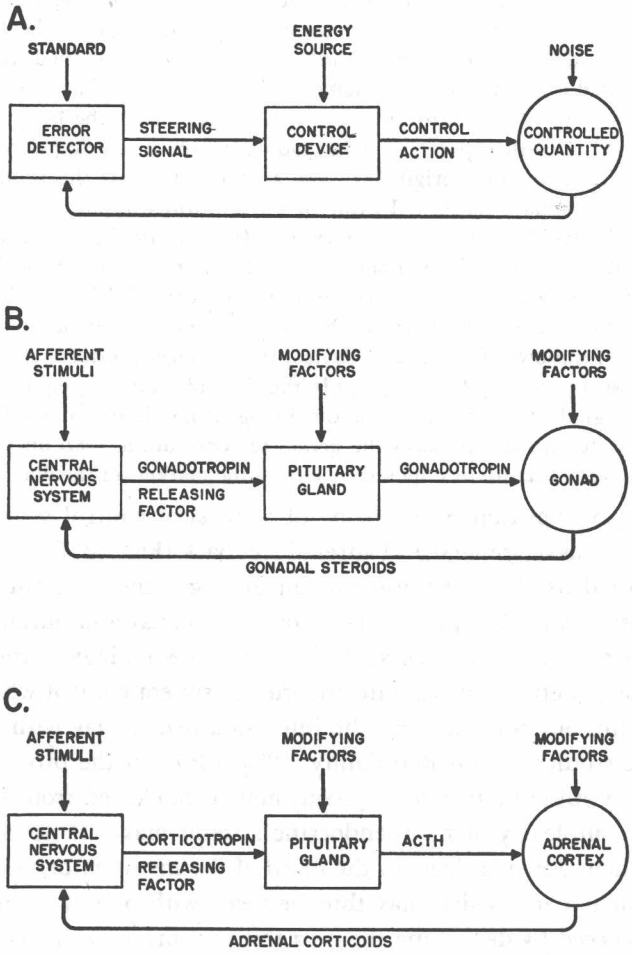

Fig. 2. Comparison of concepts of feedback systems in physics and neuroendocrinology

(A) Feedback system as of a thermostat controlling a furnace; (B) analogous hormonal feedback system controlling gonadal functions; (C) corresponding control system of the adrenal cortex.

The diagram shown in Fig. 2A is borrowed, in part, from the preface of a publication on homeostatic mechanisms (Brookhaven, 1958), as is the accompanying text:

The following is a very simple scheme of a feedback system: It consists of two "black boxes" (meaning objects of unspecified nature which perform certain stated functions) and a circle indicating an object or property; these are connected by arrows. We have some controlled quantity the level of which depends on some control action and on some unspecified perturbations lumped together under the name "noise." The control action, in turn, originates from some control device which operates with the help of some source of energy, the operation being modulated by a steering signal. The steering signal, in turn, originates from an error detector the function of which is to compare the actual value of the controlled quantity with some standard imposed from without the system. In terms of the thermostat, the controlled quantity is the temperature in the living room which depends on the heat produced by the furnace and heat loss, modified by irregular perturbations such as changes in the outside temperature or opening of doors and windows. The control device, the furnace, produces its controlling action by means of a fuel supply the flow of which is regulated by a steering signal which comes from the living room; it originates from an error detector which compares the actual temperature as seen on the thermometer with a standard imposed by setting the marker on the dial.

The juxtaposition of a scheme of a physical control system and two diagrams of gonadal and adrenal feedback (Fig. 2B, C) should be understood as the illustration of an analogy; the diagram of the thermostat is oversimplified and those of gonadal and adrenal control are even more so. We shall not carry the analogy beyond this point or penetrate deeper into theories of system control which are not within our competence. The interested reader may wish to consult the studies of von Bertalanffy (1955, 1957) on the problems inherent in applying to living systems models borrowed from physics.

The complexity of neuroendocrine systems makes it necessary to break them down, at least in the mind of the investigator, into their component parts which may thus be dealt with one at a time. We shall proceed by describing them in this way prior to the discussion of the role of neuroendocrine systems in particular functions, e.g., reproduction, metabolism, etc. Following the custom in neurology of describing nervous reflex connections beginning with the afferent limb, we shall first deal with afferent pathways leading to the central