gy states in simple chemical equilibria, and states of binding in complex multiple equilibria. These distributions are described with the use of the appropriate partition functions, from which averages for the system are evaluated. For multiple equilibria, the appropriate partition function is the molecular grand partition function ξ, frequently called the binding polynomial. The mathematical methods that are used to formulate and evaluate the partition function (the matrix method, sequence generating functions, the maximum term method) are developed and applied. The relatively self-contained and practical development of these methods from statistical mechanics is a major strength of the book.

Unfortunately, the lack of a general overview of methods of analysis of complex multiple equilibria, coupled with the lack of a general discussion of the origins and implications of cooperativity in the interactions of biological molecules, may reduce the potential impact of the book. Various methods of analysis of these systems are available. The statistical mechanical approach described by Poland has been principally applied to highly cooperative conformational transitions of polypeptides and nucleic acids. A related but distinct statistical thermodynamic treatment using the concepts of binding potentials, binding polynomials, and linked function analysis (developed to analyze cooperative ligand binding to hemoglobin) has been extensively applied to the analysis of macromolecular binding. Thermodynamic analysis (using free energy level diagrams) and conditional probability theory have also been applied to cooperative ligand-binding equilibria. Reference to these and other numerical methods would be appropriate. Another omission of note occurs in the discussion of intermolecular interactions. The book is primarily devoted to a quantitative description of the energetics of various direct interactions between charged species, neutral species, or both. However, a large number of noncovalent association reactions involving biological molecules are entropy-driven processes occurring in aqueous solution as a result either of the release of structured water in the association of hydrophobic surfaces or of the release of counterions in the association of oppositely charged polyelectrolytes.

These omissions result in part from the difficulty of covering in one book a broad and active field (work more recent than 1974 is not covered in the book); they do not detract from the strength of the book as a clearly written introduction for the experimentalist to a complex but increasingly essential body of knowledge. The uninitiated reader should be forewarned, however, that there are a number of minor errors (typographical errors, problems with significant figures, notation, and legends to figures or tables) in the book.

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Neuroendocrinology

The Hypothalamus. SEYMOUR REICHLIN, ROSS J. BALDESSARINI, and JOSEPH B. MARTIN, Eds. Raven, New York, 1978. xiv, 490 pp., illus. $35. Research Publications: Association for Research in Nervous and Mental Disease, vol. 56.

This book focuses primarily on aspects of the hypothalamus that are related to the regulation of secretion of anterior and posterior pituitary hormones. The extent of the progress being made in the field can be gauged by comparing the current volume with a 1940 book, *Hypothalamus and Central Levels of Autonomic Function*, also published under the sponsorship of the Association for Research in Nervous and Mental Disease. In the 1940 volume, Ernst and Berta Scharrer summarized their then controversial hypothesis that neurons in the supraoptic and paraventricular nuclei had a neurosecretory function, that is, secreted hormones into the general circulation. This hypothesis was based entirely on histological studies indicating the similarities between these cells and known endocrine cells. No evidence was available at that time concerning the nature of the proposed secretory material except that it seemed to be proteinaceous. Furthermore, it was not known from what site the material was secreted.

On the basis of a large body of data, which is summarized in chapters by Hökfelt *et al.*, Defendini and Zimmerman, McKelvy and Epelbaum, and Renaud, we now know that these neurons synthesize vasopressin or oxytocin, two nonapeptides. The hormones are then transported to the terminals of these neurons in the posterior pituitary by rapid axonal transport and secreted when the neurons fire in response to certain physiological stimuli (for example, high plasma osmolarity for the vasopressin neurons and suckling for the oxytocin neurons). Renaud refers to an elegant series of studies by Lincoln and Wakerley in which bursts of firing in neurons of the paraventricular and supraoptic nuclei were correlated temporarily with brief rises in intramammary pressure (presumably caused by release of oxytocin) in lactating rats with suckling pups.

A second, originally controversial, hypothesis vital to the book was not yet formulated when the 1940 book was published. This hypothesis, proposed by G. W. Harris, is that secretion of tropic hormones by cells in the anterior pituitary gland is itself regulated by hormones secreted by neurons in the hypothalamus. Harris proposed that these hypothalamic hormones were secreted into a portal circulation that connected the median eminence, an area at the base of the hypothalamus, with the anterior pituitary gland. The history of the isolation, structural analysis, and synthesis of three such hypothalamic hormones, thyrotropin-releasing hormone (TRH), luteinizing-hormone–releasing hormone (LHRH), and growth-hormone–release–inhibiting hormone (somatostatin) by Guillemin, Schally, and their co-workers is well known to readers of *Science*. One of the more unpredictable outcomes of studies of these hormones, which is discussed in various chapters in this book, is that they may have a much broader function than was previously imagined. Take TRH for instance. When antibodies against this tripeptide were prepared and immunohistochemical studies performed, heavily stained processes were found in the external layer of the median eminence as one might predict. However, processes were also found in other areas of the hypothalamus and in a number of extrahypothalamic sites such as the ventral horn of the spinal cord. Furthermore, TRH, at least as measured by radioimmunoassay, has a wide phylogenetic distribution including species in which it does not affect thyrotropin secretion by the pituitary and species that have no pituitary. Finally, iontophoretic studies have indicated that TRH depresses the firing rates of neurons in many areas of the brain. As discussed below, it has been proposed that TRH may function as a neurotransmitter at certain central synapses. Perhaps the situation is as though dopamine—considered by some to be a prolactin-release–inhibiting factor—had first been characterized by this activity rather than by its concentration in neurons in certain extrapyramidal regions of the brain.

Even the exact neuroendocrine function of TRH (and of other hypothalamic hormones) is unclear. For instance, TRH releases prolactin as well as thyrotropin. Furthermore, Knigge and others in this volume discuss the hypothesis that hypothalamic hormones are secreted not

only by nerve endings in the median eminence into the hypophyseal portal vessels but also by nerve endings elsewhere in the brain into the cerebrospinal fluid from which they are thought to be taken up by specialized cells ("tanycytes") at the base of the third ventricle and released into the portal circulation. However, convincing evidence for this hypothesis is still lacking.

The current interest in the function of specific peptides in the nervous system goes far beyond the hypothalamic releasing and release-inhibiting hormones. Hökfelt *et al.* present immunohistochemical studies of the distribution in the central nervous system of neurons containing substance P, vasoactive intestinal polypeptide, gastrin, prolactin, angiotensin II, and the enkephalins, and Snyder presents evidence for the existence of specific receptors in the brain for the latter two peptides and for neurotensin. At least in the hypothalamus a number of these peptides have been found to be concentrated in subcellular fractions containing pinched-off nerve endings, and several of the peptides have been found to affect the firing rates of neurons in various parts of the brain. Thus these substances have joined the excitatory and inhibitory amino acids (glutamate and glycine, for example) as neurotransmitter candidates.

One other major development in neurobiology that is well illustrated in this volume is the recent availability of histochemical procedures for mapping the distribution of a wide variety of substances in the nervous system. Perhaps the first such breakthrough was the development of the Falck-Hillarp fluorescence technique, which allowed the mapping of noradrenergic, dopaminergic, and (with somewhat less sensitivity) serotonergic neurons. More recently autoradiographic and immunohistochemical methods have been developed to measure the distribution of certain membrane receptors (for example opiate and muscarinic receptors), different peptides (for example, TRH, LHRH, the enkephalins), specific enzymes involved in the synthesis of neurotransmitters (for example, tyrosine hydroxylase, the enzyme that catalyzes the rate-limiting step in the synthesis of norepinephrine), and intracellular receptors for specific steroids (for example, estradiol). The power of these techniques is illustrated in chapters by Hökfelt *et al.*, Defendini and Zimmerman, Pfaff, and McEwen *et al.* For instance, figure 14 (p. 92) shows consecutive sections cut through the mediobasal hypothalamus and stained for LHRH, TRH, somatostatin, or tyrosine hydroxylase, each of which shows a distinct distribution.

These methods show good anatomical resolution, but they are not highly quantitative. With the development of increasingly sensitive biochemical techniques for assaying these substances, many attempts have been made to complement these histochemical studies with biochemical measurements of individual cell groups (for example, the supraoptic nucleus). The main problem in interpreting such studies is that there is often a lack of verification of the anatomical identity of the region dissected. That this is a problem even in studies on larger blocks of tissue, such as the whole hypothalamus, is evident from the large variation in weights (sometimes as much as threefold) reported by different laboratories for what is supposedly the same structure. One wonders whether it wouldn't be useful for a group of neuroanatomists to attempt to standardize a set of landmarks for such dissection procedures.

The Hypothalamus is an extremely readable and interesting collection of papers. In general, the authors have summarized the state of research in their fields rather than simply describing research in their own laboratories. The book is well edited, and the micrographs are particularly well reproduced. Like the 1940 volume, this book will serve as a useful reference for students and researchers.

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