Diagnosis and Management of Endocrine-related Tumors

edited by
RICHARD J. SANTEN, M.D. and ANDREA MANNI, M.D.

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Foreword to the series

Where do you begin to look for a recent, authoritative article on the diagnosis or management of a particular malignancy? The few general oncology textbooks are generally out of date. Single papers in specialized journals are informative but seldom comprehensive; these are more often preliminary reports on a very limited number of patients. Certain general journals frequently publish good indepth reviews of cancer topics, and published symposium lectures are often the best overviews available. Unfortunately, these reviews and supplements appear sporadically, and the reader can never be sure when a topic of special interest will be covered.

Cancer Treatment and Research is a series of authoritative volumes which aim to meet this need. It is an attempt to establish a critical mass of oncology literature covering virtually all oncology topics, revised frequently to keep the coverage up to date, easily available on a single library shelf or by a single personal subscription.

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Where can you go to find quickly a recent authoritative article on any major oncology problem? We hope that Cancer Treatment and Research provides an answer.

WILLIAM L. MCGUIRE
Series Editor

Preface

Patients with a variety of tumors present to the physician because of clinical manifestations of hormones secreted in excess. This phenomenon attracted the investigative interest of such pioneers as Harvey Cushing who recognized that pituitary tumors may cause acromegaly and Charles Mayo who associated hypertension with adrenal medullary neoplasms. Current interest in endocrine-related tumors has intensified because of the explosive development of newer methodology for their study. Specific measurements of secretory products, hybridization assays to identify products of genomic translation and quantitative assessment of tissue hormone receptors have provided means of characterizing and precisely following patients with endocrine-related tumors. Treatments based upon these advances are rapidly proliferating. The current volume attempts to synthesize much of this recent information with the goal of providing a sound basis for making clinical judgements regarding diagnosis and management.

Tumors of endocrine glandular tissues commonly confront practicing physicians with difficult management problems. Several unique features of these tumors necessitate collaboration among various specialty disciplines in order to resolve these problems and to provide a high level of clinical care. For example, endocrine neoplasms secrete active hormones or hormone precursors which produce clinical manifestations most familiar to endocrinologists. Certain therapies such as radioactive iodine for thyroid cancer take advantage of the hormone-responsiveness of these tumors to facilitate treatment. These aspects require individuals trained in endocrinology to implement complex diagnostic and therapeutic maneuvers. The use of C-peptide, proinsulin and insulin assays in the diagnosis of insulinoma involves specialists in the area of diabetes/metabolism in the management of these patients. The characteristic physiologic effects of certain tumors necessitate the participation of specialists in other areas. The multilevel influences of gastrointestinal transport on gastrin release and of gastrin on acid output requires the participation of trained gastroenterologists in the management of the Zollinger-Ellison syndrome. The physiologic effects of the catecholamines on blood pressure involve hypertension subspecialists in the diagnosis and management of pheochromocytoma. A high level of specific expertise is required for surgical management of patients with islet cell adenomas, hyper-

parathyroidism, thyroid carcinoma, especially when near total thyroidectomy is required, and for micro and macroadenomas of the pituitary. The special skills required necessitate the involvement of endocrine surgeons and neurosurgeons with expertise in the management of these entities. Radiologists are required to place catheters supraselectively to allow hormone measurements in veins draining certain hormone-secreting tumors. Finally, medical and surgical oncologists and radiation therapists participate in the planning and implementation of strategies to reduce tumor bulk and eradicate anatomically or physiologically important metastases. Taken together, these considerations serve to emphasize the importance of a multidisciplinary approach to diagnosis and management of endocrine-related tumors. However, a firm understanding of basic endocrinologic principles must provide a conceptual framework for management of each of these clinical disorders and serves as the theme of this book. To accomplish this aim and also to provide a broad perspective, the authors in this volume were chosen to represent a variety of disciplines including gastroenterology, endocrinology, surgery, metabolism, neurosurgery and physiology.

The organization of this volume reflects an anatomic orientation. The first 4 chapters consider pituitary tumors from a global standpoint and then according to specific secretory and non-secretory lesions. The emphasis of each is upon precise documentation of anatomy, physiology and clinical manifestations prior to and after treatment approaches. A large body of original data accumulated by the investigative group at Case Western Reserve University in Cleveland allows a number of sound conclusions based upon their extensive expertise. Three subsequent chapters address the diagnostic, medical and surgical management of patients with thyroid cancer. Two of these review primary data and utilize this material to make recommendations regarding overall management. These chapters, taken together, illustrate the lack of uniformity of treatment approaches adapted at various centers in the United States with respect to thyroid cancer.

The medical and surgical management of hyperparathyroidism provided a major field for vigorous debate in the 1970's. More recently, these controversies have been largely resolved. The development of more precise assays for PTH, the identification and follow up without surgery of a large number of patients with asymptomatic disease, and the anatomic/microscopic classification of adenomatous vs. hyperplastic forms of hyperparathyroidism provided a sound basis for resolution of several previously controversial issues. These concepts are explored in the two chapters which address parathyroid tumors. Finally, neoplasms of the adrenal cortex are reviewed with primary attention to their clinical characteristics in an additional chapter.

The spectrum of islet cell tumors of the pancreas either as isolated entities or as part of the multiple endocrine neoplasia Type I syndrome has attracted considerable attention recently. A new discipline of gastroenterologic endocrinology evolved because of the myriad of hormones made by these tumors. Recent observations regarding the molecular heterogeneity of circulating GI hormones,

the neural crest derivation of several of them, and the pluripotential of their secretory capacity have stirred intensive investigative interest in this field. Chapters by the investigators at the University of Michigan provide a provocative conceptual background and detailed clinical information upon which to base therapeutic recommendations. The chapter by Dr. Denis McCarthy provides a unique perspective to the discussion of the treatment of the Zollinger-Ellison syndrome. At the NIH and later at the University of New Mexico, this author has carefully studied a large cohort of patients undergoing intensive medical therapy with histamine H_2 receptor blockers. The necessity for surgical intervention in many of these patients at some time in their treatment course has provided a rational basis of information upon which to recommend individual therapy tailored to each patient's needs. The in-depth discussion of the physiologic mechanisms which control the release of gastrin provides a framework for evaluating gastrin elevations in patients with disordered gastrointestinal function in association with gastric hyper- and hyposecretory states. The companion chapter on multiple endocrine neoplasia-type I provides a compendium of basic and clinical, detailed information regarding these commonly encountered syndromes. Finally, a comprehensive approach to the diagnosis and management of pheochromocytoma, based upon a broad personal experience, is presented.

In many areas of clinical management, insufficient prospective data exist to provide sound scientific support for particular treatment approaches. This applies to two particular areas covered by this volume, namely, prolactinomas and thyroid cancer. With respect to functioning pituitary tumors, the development of radioimmunoassays and of potent dopamine agonists for treatment has been too recent to allow prospective comparison of various medical and surgical approaches. Thyroid cancer, on the other hand, is sufficiently uncommon and indolent that no one center can accumulate adequate prospectively collected information. As a consequence, the treatment of thyroid cancer and of functioning pituitary tumors is controversial. The last chapter attempts to identify differing recommendations among various authors covering these topics. The Editors have attempted to reconcile this diversity and to provide a middle ground regarding the management of both of these clinical problems. This chapter is intended only as a working construct to provide guidelines for management until more definitive information becomes available.

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Contents

1. Approach to the pituitary tumor: anatomic, diagnostic and surgical considerations

ROBERT B. PAGE and RICHARD J. SANTEN

1. Introduction

Patients harboring putative pituitary tumors reach neurosurgeons through three lines of referral. Neurologists refer patients with symptoms and signs of intracranial mass such as dulled affect, lethargy, hemiparesis, seizures or failing vision [1]. Their goal of therapy is total removal of the intracranial mass which has arisen from the sellar region and restoration of brain function. Ophthalmologists refer patients with specific visual disturbances. Their goal is decompression of the visual or oculo-motor pathways with restoration of normal vision [2]. Endocrinologists refer patients with symptoms and signs of endocrine dysfunction. These may be manifestations of pituitary hypofunction with gonadal, adrenal, and/or thyroid underactivity or even, in the case of children, failure to grow at a normal rate [1, 2]. Endocrine abnormalities may also be caused by hyperfunction of adenomatous pituitary tissue with oversecretion of prolactin (PRL) [3, 4, 5], of luteinizing hormone (LH) [6, 7], or of follicle stimulating hormone (FSH) [8, 9] causing inferility, of growth hormone (GH) causing acromegaly [10, 11, 12], of adrenocorticotrophic hormone (ACTH) causing Cushing's disease [13, 14] or of thyroid stimulating hormone (TSH) causing hyperthyroidism [15, 16]. The endocrinologists' goal is complete tumor removal and restoration of pituitary function.

The goal of the neurosurgeon is to localize the tumor as precisely as possible, to approach it by the most direct route, to remove all or as much of the tumor as possible, and to withdraw causing little or no disturbance and leaving little evidence of entry. Four approaches to pituitary tumors are commonly employed by neurological surgeons: from below by the transphenoidal route, from the front by the subfrontal route, from the side by the temporal route and from above by the transventricular route. The approach chosen by a surgeon to manage a particular patient will be dictated by the anatomy of the pituitary gland, the tumor, and the brain in that patient; the objective of treatment and the experience of the surgeon. A clear understanding of the anatomic interrelationships of the pituitary with neural, vascular and osseous structures is required to develop safe and effective treatment.

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2. Correlative anatomy

2.1 *Pituitary*

2.1.1 *Neurohypophysis.* The pituitary gland lies beneath the brain and is comprised of neural and glandular tissue. Its neural portion, the neurohypophysis, is a diverticulum of brain [17] made up of axon terminals, fenestrated capillaries, and glial cells [18, 19, 20] (Fig. 1). The neurohypophysis is subdivided into three regions [21]. The *median eminence* (infundibulum) is its most rostral region and forms the floor of the third ventricle. The *neural lobe* (infundibular process) is its most caudal region and lies within the sella turcica at the base of the skull. The *infundibular stem* passes from the median eminence through the subarachnoid space and diaphragma sellae to the neural lobe and forms the neural component of the pituitary stalk [22].

The primate *median eminence* is divided into an external and an internal zone [23, 24, 25]. The external zone is the terminus of aminergic and peptidergic neuronal systems which originate in the hypothalamus [26]. The dopaminergic tubero-infundibular tract originates in the hypothalamic arcuate (tuberal) nuclei and terminates in the perivascular space of fenestrated median eminence capillaries [27]. Peptidergic neuronal systems containing gonadotropin releasing hormones (GNRH), corticolibrin (CRF), somatostatin (SOM), thyrotropin releasing hormone (TRH), oxytocin (OXY), and vasopressin (AVP) also terminate in the perivascular space of external plexus capillaries [28, 29, 30]. On the basis of anatomic studies in rats, GnRH fibers have been found to originate in the medial preoptic region and pass anteriorly to the median eminence. CRF, TRH, and SOM systems have been found to originate in the hypothalamic periventricular nucleus and in the parvocellular division of the paraventricular nucleus. These fiber systems, with systems containing oxytocin and vasopressin which also

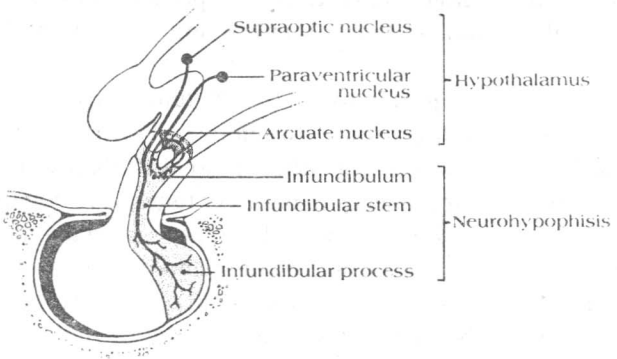

Figure 1. Schematic representation of the human pituitary gland. The neurohypophysis and its neural connections with the hypothalamus are emphasized. The terminology (infundibulum, infundibular stem and infundibular process) emphasizes the unity of the neurohypophysis. Note that infundibulum is a synonym for median eminence and infundibular process for neural lobe.

originate in the paraventricular nucleus, pass ventrolaterally to the lateral preoptic region and then course ventromedially to terminate in the median eminence external zone [31]. Peptidergic neuronal systems terminate in the perivascular space of median eminence capillaries. Their neurosecretions regulate adenohypophyseal function [for review see 28, 32]. The internal zone is made up of fibers of the supraoptico-hypophyseal tract. These fibers contain oxytocin and vasopressin and they pass through the median eminence and infundibular stem to terminate in the neural lobe [29].

The *infundibular stem* is comprised of at least two neuronal fiber tracts: the supraoptico-hypophyseal tract [29] and the dopaminergic tubero-hypophyseal tract [33]. Both these fiber tracts pass through the infundibular stem to terminate in the neural lobe. Terminals of the peptidergic neurosecretory system containing TRH and SOM are also present in this region.

The *neural lobe* is the terminus of the supraoptico-hypophyseal and of the tubero-hypophyseal tracts. In this region of the neurohypophysis magnocellular neurons of the supraoptico-hypophyseal tract terminate in the perivascular space of fenestrated capillaries [34, 35]. Their neurosecretions regulate the function of distant target organs such as the kidney, uterus, and breast.

2.1.2 *Adenohypophysis*. The glandular portion of the pituitary is called the adenohypophysis (Fig. 2). It is generally believed to arise from the primitive foregut – the stomodeum. A diverticulum of ectodermal tissue (Rathke's pouch) migrates cranially from the roof of the primitive mouth to become applied to the evaginating neurohypophysis [36]. The posterior wall of this ectodermal pouch becomes adherent to the neural lobe to form the pars intermedia. In humans, this region of the adenohypophysis is identifiable only in fetal stages and in adult pregnant females. The anterior wall of the Rathke's pouch enlarges greatly to become the pars distalis which lies within the sella turcica with the neurointer-

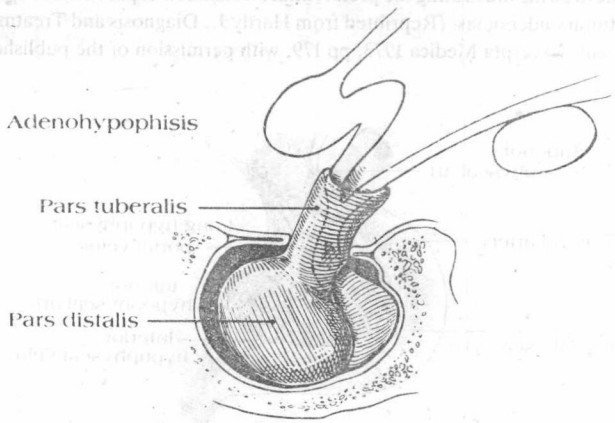

Figure 2. Schematic representation of the human pituitary gland from the same perspective as in Fig. 1. The pars tuberalis lies above the sella turcica. The pars distalis lies within it.

mediate lobe but is separated from it by Rathke's (hypophyseal) cleft. Tissue from Rathke's pouch also migrates cranially to become applied to the infundibular stem and median eminence as the pars tuberalis [37]. The median eminence with the pars tuberalis makes up the tuber cinereum [38]. Thus, the adenohypophysis, like the neurohypophysis, is subdivided into three regions: the pars tuberalis, the pars intermedia, and the pars distalis.

Within the adenohypophysis there is a regional segregation of glandular cells along functional lines [39, 40] (Fig. 3). In the pars tuberalis, only gonadotrophs and thyrotrophs can be identified by immunohistochemical techniques [41]. Immunohistochemical studies have demonstrated cells containing alpha-melanocyte stimulating hormone (aMSH) in the portion of the pars distalis apposed to the neural lobe of the human pituitary – that region corresponding to the pars intermedia of lower species [42]. Within the pars distalis, gonadotrophs, thyrotrophs, and corticotrophs lie mostly in the central mucoid wedge whereas lactotrophs and somatotrophs predominate in the lateral wings [43].

2.1.3 *Pituitary vasculature.* The adenohypophysis does not possess a direct arterial supply (Fig. 4). Its pars distalis is not innervated from the central nervous system [19]. Both nutrient blood flow and regulatory signals come from the neurohypophysis. The neurohypophysis receives arterial blood at its rostral pole (the

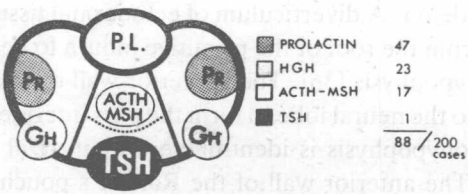

Figure 3. Schematic drawing illustrating the preferential localization of pars distalis epithelial cells and sites of various pituitary adenomas. (Reprinted from Hardy J., Diagnosis and Treatment of Pituitary Tumors. Amsterdam: Excerpta Medica 1973, pp 179, with permission of the publisher).

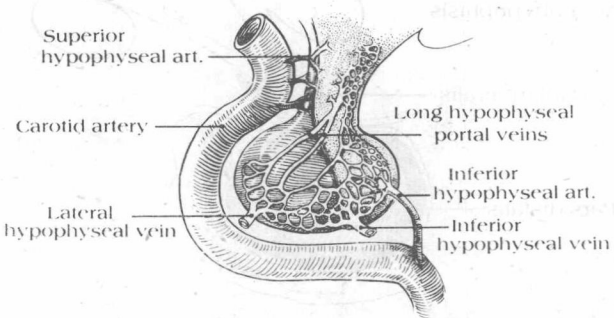

Figure 4. Schematic representation of the blood supply to the human pituitary gland with same perspective as Fig. 1.