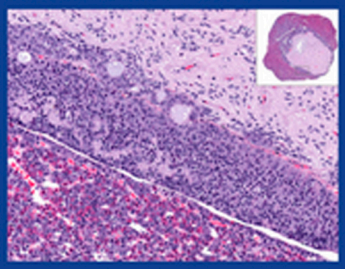
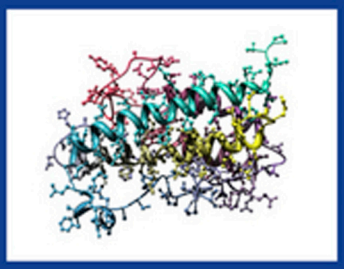
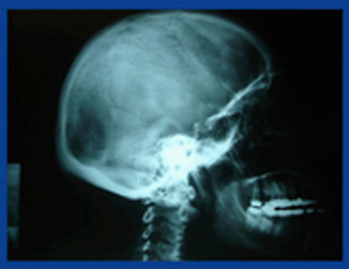


Pituitary Disorders

Diagnosis and Management

Edited by Edward R. Laws, Shereen Ezzat, Sylvia L. Asa,
Linda M. Rio, Lorin Michel & Robert Knutzen

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Diagnosis and Management

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Introduction

For many patients, their ailment is all in their head.

In 1886, Pierre Marie recognized and chronicled a disease of the pituitary, one of the first so ascribed, called acromegaly. The official recognition of the disease as an enlargement of the pituitary gland was discovered in postmortem studies in 1887 and reported by Dr. Oskar Minkowski, although giants had been reported throughout the course of history. The story of David and Goliath, a biblical tale, talks of the diminutive David able to slay the great giant named Goliath. There is no mention of Goliath having suffered from acromegaly, but it is entirely possible that, if the fable is true, the post-diagnosis would be as well.

In 1924, the Soviet physician Nikolai Mikhailovich Itsenko reported on two patients suffering from an adenoma in the pituitary gland. These patients were producing large amounts of adrenocorticotropic hormone (ACTH), causing the adrenal glands to produce excessive amounts of cortisol. It was not until 1932, however, that the American neurosurgeon Harvey Cushing described the clinical features associated with a pituitary tumor secreting ACTH. This came to be known as Cushing's disease, and the clinical manifestations of excess circulating cortisol as Cushing's syndrome. Cushing is considered by many to be the father of modern neurosurgery and it is his influence that has helped to drive the field of endocrinology, the study of hormonal influences on both medical disease and mental health disorders, and the gathering of knowledge of the pituitary gland itself.

As early as 1936, Dr. Russell T. Costello, a pathologist at the Mayo Clinic, published his findings from a 1000-cadaver autopsy series. He established firmly that pituitary tumors (adenomas) were found in 22.5% of the adult population. Extensive studies, done more recently, echo Dr. Costello's findings. They confirm (with minor variations) the enormous proliferation of pituitary tumors, cysts and lesions. Today we know that these tumors are not rare and that, in fact, nearly one in five persons has pituitary disease. Many remain undiagnosed.

In the past 15 years, the clinical appreciation of the impact of pituitary disorders has accelerated rapidly – perhaps dangerously so. The continual churn of developments has left little time for the advancing knowledge and proper medical practice guidelines to percolate through the medical, patient and public sectors and allow for uniform improvement in understanding and patient care. Medical treatments, hormone replacements, surgical and radiological treatment options flourish, to the great satisfaction of the inventing scientists and academic medical practitioners, while leaving the great majority of patients untreated or undertreated – and, in too many instances, un- or underdiagnosed.

Physicians, neurosurgeons, endocrinologists, nurses, nurse practitioners and mental health professionals – those on the front lines of pituitary disease, diagnosis and treatment – are dedicated to helping their patients to find solace, and helping those treating the disease to obtain the tools required. As popular newspapers and magazines publish more and more articles on difficult medical and mental health problems, not to mention the information available on the internet, people are slowly realizing that many common problems are linked to pituitary disease. This master gland can send confusing signals that do not necessarily lead to the formation of cysts, lesions, and tumors. Hypo- or hyper-secretion of hormones can (in itself) lead to dire problems requiring intensive

medical intervention. In addition, nonsecreting (nonfunctioning) tumors can cause severe distress when they grow and invade nearby areas of the brain. The distress to the patient is both physical and emotional. This is why neurosurgeon Dan Kelly calls the pituitary gland "the crossroads of mind and body."

In 1913 Cushing said, "It is quite probable that the neuro-pathology of everyday life hinges largely on the effects of the discharge of the ductless gland upon the nervous system."

Dr. Shereen Ezzat, Professor of Medicine at the University of Toronto, puts it this way: "One in five individuals may have an abnormal growth on their pituitary gland, causing significant health complications that, if left undiagnosed and untreated, can impair normal hormone function and result in a reduced lifespan."

Hormonally challenged patients come in many shapes and sizes but they have an almost universal story to tell, one we should all be listening to. Luckily, today's experts, like those featured in this extremely necessary book, are writing new chapters almost daily, dealing with diagnosis, treatment and living with pituitary disease, providing perhaps the definitive proof that for pituitary patients, their ailment is truly all in their head.

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Acromegalic Patient

Abbreviations

ACTH	adrenocorticotropin
ADH	antidiuretic hormone
AhR	aryl-hydrocarbon receptor
AIP	aryl-hydrocarbon receptor interacting protein
AIRE	autoimmune regulator
APUD	amine precursor uptake and decarboxylation
AVP	arginine vasopressin
BMI	body mass index
CAH	congenital adrenal hyperplasia
CBG	Cortisol-binding globulin
CD	Cushing's disease
CDGP	constitutional delay of growth and puberty
CDKI	cyclin-dependent kinase inhibitors
CNC	Carney complex
CNS	central nervous system
CPHD	combined pituitary hormone deficiency
CPID	combined pituitary deficiency
CPP	central precocious puberty
CRH	corticotropin releasing hormone
CRHT	CRH testing
CS	Cushing's syndrome
CSF	Cerebrospinal fluid
CT	computed tomography
CVA	cerebrovascular accident
DA	dopamine agonist
DDAVP	desmopressin
DHEA	dehydroepiandrosterone
DHEAS	dehydroepiandrosterone sulfate
DI	diabetes insipidus
DRE	dioxin-responsive element
ESS	empty sella syndrome
FAP	familial adenomatous polyposis
FDA	Food and Drug Administration
FIPA	familial isolated pituitary adenoma
FSH	follicle stimulating hormone
FT	free testosterone
GAB	granulosa cell aromatase bioassay
GFAP	glial fibrillary acidic protein
GH	growth hormone
GHD	growth hormone deficiency
GHR	growth hormone receptor
GHRH	growth hormone releasing hormone
GHRP	growth hormone releasing peptide
GIP	gastric inhibitory polypeptide
GnRH	gonadotropin releasing hormone
HPA	hypothalamic–pituitary–adrenal
HPG	hypothalamic–pituitary–gonadal
HPO	hypothalamus–pituitary–ovarian
HPRT	hypoxanthine phosphoribosyl transferase
HPT	hypothalamic–pituitary–thyroid
ICP	intracranial pressure
ICTP	C-terminal cross-linked telopeptide of type I collagen
IFS	isolated familial somatotropinoma
IM	intramuscular
IPSS	inferior petrosal sinus sampling
ITT	insulin tolerance test
KALS	Kallmann's syndrome
LAH	lymphocytic adenohypophysitis
LAMB	lentigines, atrial myxomas, and blue nevi
LCCSCT	large-cell calcifying Sertoli cell tumors
LDT	low-dose test
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
LINH	lymphocytic infundibuloneurophyophysitis
LOH	loss of heterozygosity
LPH	lymphocytic panhyophysitis
LPS	lumboperitoneal shunt
LV	left ventricular
LyH	lymphocytic hypophysitis

MEF mouse embryonic fibroblasts
MEN multiple endocrine neoplasia
MLL mixed lineage leukemia
MLPA multiplex ligation-dependent probe amplification
MT metyrapone testing
NAME nevi, atrial myxomas, and ephelides
NES nuclear export signal
NFPA nonfunctioning pituitary adenoma
NOS oxide synthase
NS Nelson's syndrome
OGTT oral glucose tolerance test
OSA obstructive sleep apnea
PAP pituitary adenoma predisposition
PCOS polycystic ovary syndrome
PD Parkinson's disease
PKA protein kinase A
PMS psammomatous melanotic schwannoma
POMC pro-opiomelanocortin
PPNAD primary pigmented nodular adrenocortical disease
PRL prolactin
PTN pleiotropin
PTTG pituitary tumor transforming gene
QoL Quality of life
RCC Rathke cleft cyst
REM rapid eye movement (sleep)
RER rough endoplasmic reticulum
RTH resistance to thyroid hormone
RXR retinoid X nuclear hormone receptor
SA somatostatin analog
SC subcutaneous
SDH succinate dehydrogenase
SDHB succinate dehydrogenase B subunit
SDHD succinate dehydrogenase D subunit
SDS standard deviation score
SDT standard dose test
SHBG sex hormone binding globulin
SIADH syndrome of inappropriate antidiuretic hormone hypersecretion
SR slow release
SS Sheehan's syndrome
SSA somatostatin analog
TCDD 2,3,7,8-tetrachloro-*p*-dioxin
TIBC total iron-binding capacity
TPR tetratricopeptide repeat
TR thyroid hormone receptor
TRH thyrotropin releasing hormone
TRT testosterone replacement therapy
TSG tumor suppressor gene
TT Total testosterone
UFC urine free cortisol
VAS ventriculoatrial shunt
VPS ventriculoperitoneal shunt
VDR vitamin D receptor
WDT water deprivation test
WHO World Health Organization
XRE xenobiotic or Ah-responsive element

SECTION 1
Overview

CHAPTER 1
The Endocrine System

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Normal Development and Structure

The endocrine system is composed of cells and organs that have, as their primary function, the production and secretion of hormones. They are generally classified into three broad categories: peptide hormone-producing, steroid hormone-producing, and thyroid hormone-producing.

Peptide Hormone-Producing Cells

The majority of endocrine cell types produce peptide hormones. This group of endocrine cells have a characteristic morphology that is called "neuroendocrine" because of its similarity to neural cells [1]. They have sufficient neural differentiation structurally and functionally that they have been called "paraneurons." Historically they were classified as the APUD (amine precursor uptake and decarboxylation) system. It was previously suggested that they derive embryologically from the neural crest, but this has not been proven for all members of this group of cells, many of which arise from the primitive endoderm. Nevertheless, functionally they act as neuron-like cells; they secrete peptides that are often also produced by neurons. In fact, endocrine cells and neurons are like conventional and wireless communication: neurons produce messengers that are released at synapses and activate receptors in physically adjacent cells, rather like conventional wiring, whereas neuroendocrine cells produce the same types of messengers but release them into the bloodstream to activate cells throughout the body, analogous to wireless messages that do not rely on physical contact for communication.

These cells aggregate into classical endocrine organs, the pituitary, parathyroid, and adrenal medulla, and are also found singly and in small clusters of the dispersed endocrine system, scattered within other organs, such as the calcitonin-secreting C cells of the thyroid, and the endocrine cells of the lung, gut, and pancreas. The wide array of peptide hormones they produce is essential for regulation of most metabolic and reproductive functions.

Steroid Hormone-Producing Cells

Steroid hormone-producing cells are primarily found in the adrenal cortex and the gonads. They also have a distinct morphology that reflects their primary function of conversion of cholesterol into the various mineralocorticoid, glucocorticoid, androgenic, and estrogenic hormones. They are of mesodermal origin arising from the coelomic epithelium that gives rise to the adrenal and the genital ridge.

Thyroid Hormone-Producing Cells

Thyroid hormone-producing cells are modified epithelial cells derived from the oral endoderm that invaginate from the base of tongue. They are specifically involved in the synthesis of thyroglobulin and its iodination to form thyroid hormones.

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Endocrine Regulation

The endocrine system is tightly regulated by hormones that stimulate target endocrine cells and in turn respond to suppression by the products of their targets. The hypothalamic–pituitary axis is the central regulatory system (Figure 1.1, left). Through this axis, there is central regulation of growth, adrenal and thyroid metabolic function, reproduction, and breast development and function. Direct and indirect mechanisms involved in this system regulate immunity and emotional status (Figure 1.2). The hypothalamus and posterior pituitary also regulate salt and water homeostasis as well as lactation (Figure 1.1, right). A separate axis regulates nutrient metabolism through the pancreatic islets

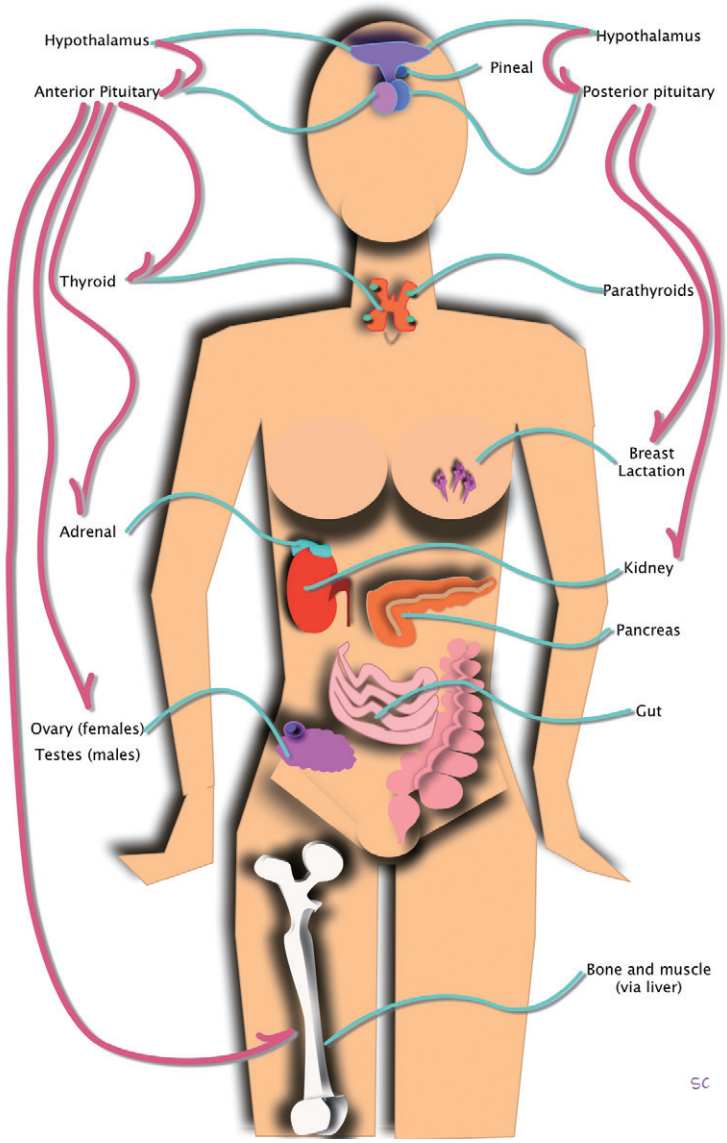

Figure 1.1. The endocrine system is composed of cells, groups of cells, and organs that have as their main function the production of hormones that regulate homeostasis throughout the body. The hypothalamus is the central mediator of the system where it integrates neuronal input with feedback from target organs. Via the posterior pituitary, the hypothalamus regulates salt and water resorption in the kidney through vasopressin; it also regulates breast lactation through oxytocin. Hypothalamic control of the anterior pituitary regulates thyroid, adrenal, and gonadal function, as well as growth of bone and muscle through growth hormone-mediated liver production of IGF-1. The pancreas and gut represent an independent endocrine regulatory system that modulates nutrient absorption and utilization. (Illustration by Sonia Chang.)

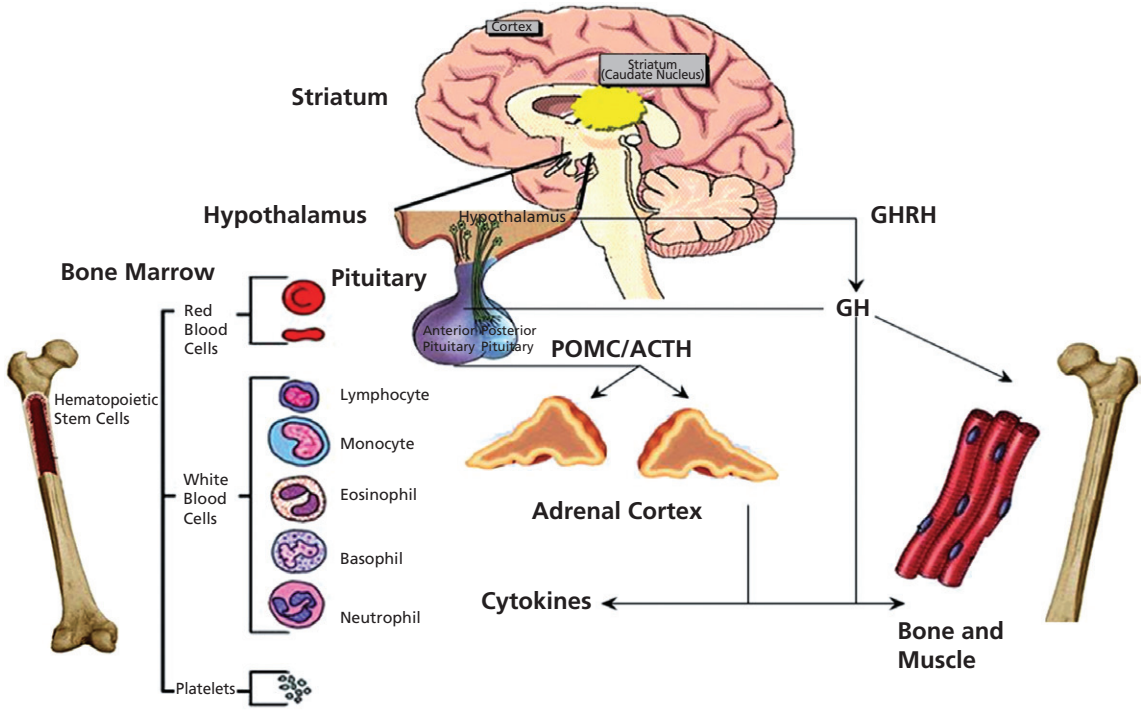

Figure 1.2. Ikaros is expressed in restricted sites throughout the neuroendocrine and hematopoietic systems. In the brain, the highest expression is in the medium spiny neurons of the striatum where the loss of function results in neurobehavioral changes characterized by an anti-depressant phenotype. In the hypothalamus, the median eminence of GHRH-containing neurons colocalize with Ikaros expression. Loss of Ikaros severely diminishes GHRH production and consequently GH and IGF-1 activation. In the anterior pituitary, Ikaros is expressed in POMC-producing corticotrophs that govern the ACTH/adrenocortical axis. Ikaros is also expressed in the somatotrophs where it plays a direct inhibitory role. In the hematopoietic system, peak expression of Ikaros is in stem cells where it directs lymphoid lineage commitment. The multidimensional actions of Ikaros serve to sort and integrate diverse signals to regulate neuroendocrine–immune interactions through direct and indirect mechanisms. (Source: Ezzat S, Asa SL. The emerging role of the Ikaros stem cell factor in the neuroendocrine system. *Journal of Molecular Endocrinology* 2008; **41**:45–51.)

and gut (Figure 1.1, right). There is evidence that this too is under central control, but mainly by regulation of appetite [2]. Finally, the sympathetic and parasympathetic nervous systems regulate endocrine function through the adrenal medulla and paraganglia [3].

Endocrine Pathology

This review will provide information on pathologies of the endocrine system with a focus on the role of the pituitary in endocrine homeostasis. In general, endocrine homeostasis is altered when there is hypofunction, resulting in hormone deficiencies, or hyperfunction, due to hormone excess. Endocrine deficiencies can result from many pathological processes, as discussed later. Hormone excess is almost always due to hyperplasia or neoplasia.

Endocrine Deficiencies

Deficiency of endocrine function can be attributed to several types of pathological processes.

Fortunately, most hormone deficiencies can be treated with hormone replacement regimens.

Isolated Hormonal Deficiencies or Resistance

These are usually caused by genetic mutations that interrupt the production of hormones, their receptors, or the enzymes required for their actions. The most common isolated hormone deficiency is congenital hypothyroidism [4], which can result in dyshormonogenetic goiter and cretinism, but in many countries complications are prevented by screening programs of neonates that lead to thyroid hormone replacement. Congenital adrenal hyperplasia is a spectrum of disorders due to a defect in one of the five enzymatic steps involved in steroid synthesis [5]; 90–95% of cases are caused by deficiency of 21-hydroxylase, resulting in marked elevation of 17-hydroxyprogesterone and male hormone excess at the price of diminished glucocorticoid reserves.

Isolated pituitary hormone deficiency most commonly involves growth hormone [6]. Rare examples of thyroid hormone receptor [7] or glucocorticoid receptor resistance [8] result in similar clinical manifestations as loss of hormone itself.

Tissue Destruction

Tissue destruction resulting in hormone deficiencies is another major cause of hormone deficiency. Tissue destruction can be the result of surgery, or may be caused by pressure or infiltration of the organ or cells by cancer or inflammation. There are many examples of each of these types of endocrine hypofunction. The most common iatrogenic hormone deficiency is hypoparathyroidism following thyroid surgery. In the pituitary, compression of normal tissue by cysts or tumors can result in hypopituitarism; tissue resection at the time of surgery can exacerbate hypopituitarism.

Inflammatory conditions can cause endocrine dysfunction, although acute and chronic infections rarely cause endocrine deficiencies in the Western world. In the sella turcica [9] this can happen in association with sphenoid sinus infection, cavernous sinus thrombosis, by spread of otitis media mastoiditis or peritonsillar abscess, or rarely by vascular seeding of distant or systemic infection by a wide variety of infectious agents, including fungi, mycobacteria, bacteria, and spirochetes. Other causes of secondary hypophysitis include sarcoidosis, vasculitides such as Takayasu's disease and Wegener's granulomatosis, Crohn's disease, Whipple's disease, ruptured Rathke's cleft cyst, necrotizing adenoma, and meningitis. Complications of AIDS may also involve endocrine tissues, including the pituitary gland; involvement is usually infectious in nature (including *Pneumocystis jirovecii*, toxoplasmosis, and cytomegalovirus) and results in acute or chronic inflammation with necrosis.

Autoimmune endocrine disorders are a significant cause of hormone deficiency. Examples include type 1 diabetes mellitus due to autoimmune destruction of insulin-producing cells of the pancreatic islets and hypothyroidism due to the various forms of chronic lymphocytic thyroiditis including Hashimoto's thyroiditis. Autoimmune inflammation has been described in almost every endocrine tissue. Most of the rare variants are associated with polyendocrine autoimmune syndromes that predispose individuals to immune destruction of endocrine and nonendocrine cells in multiple tissues, both endocrine and nonendocrine, the latter including melanocytes of the skin (resulting in vitiligo) and parietal cells of the stomach (resulting in pernicious anemia). The autoimmune polyendocrine syndrome type 1 (APS1) is the most well understood of these disorders, since its pathogenesis has been recently elucidated. This monogenic autoimmune syndrome is caused by mutations in the autoimmune regulator (*AIRE*) gene on chromosome 21 that encodes a nuclear protein involved in transcriptional processes and the regulation of self-antigen expression in thymus [10]. High-titer autoantibodies toward intracellular enzymes are a hallmark of APS1 and serve as diagnostic markers and predictors for disease manifestations.

In the pituitary, lymphocytic hypophysitis has been attributed to autoimmunity [9]. The disease is associated with other endocrine autoimmune phenomena and forms part of APS1; a tudor domain-containing protein 6 (TDRD6) was identified as the target of a putative autoantibody in APS1 patients and in patients with growth hormone (GH) deficiency, and is expressed in pituitary [11],

but it remains to be proven if this is the causative antigen. The association of the classical form of lymphocytic hypophysitis with pregnancy may be attributed to hyperplasia of lactotrophs that triggers the immune response, or may be because the precipitating antigen is α-enolase, a protein that is expressed by the placenta as well as pituitary [12,13]. Anti-pituitary antibodies have also been detected in patients with the "empty sella syndrome" [14], idiopathic GH deficiency [15, 16], idiopathic adrenocorticotropin (ACTH) deficiency [17], Cushing's syndrome [18], and different autoimmune isolated and polyendocrinopathies without hypophysitis [19]. In an isolated case of ACTH deficiency, antibodies to corticotrophs were thought to be directed against an antigen that represents a cell-specific factor required for pro-opiomelanocortin (POMC) processing [20].

Idiopathic Addison's disease has an autoimmune etiology in 75–90% of cases, with circulating autoantibodies to endocrine antigens (21-OH, P450 scc, and 17-OH).

Hormone Excess: Hyperplasia and Tumor Pathology

Tumors of the endocrine system reflect their origin in the three types of endocrine cells. Well-differentiated tumors can produce hormone excess syndromes when they are the source of hormone production that is dysregulated. They can also cause hormone deficiency when they destroy the normal tissue in which they arise.

Endocrine tumors can be benign or malignant. They can sometimes be associated with hyperplasia of endocrine cells. In some cases, the hyperplasia is a precursor of neoplasia. In some examples, tumors in one site can produce hormones that result in hyperplasia at a target site; for example, pituitary tumors producing ACTH can result in adrenal cortical hyperplasia, and when the pituitary tumor is small and undetectable on imaging, the pathology may appear to be a primary adrenal disorder. Such clinical scenarios illustrate the importance of understanding endocrine homeostasis and using biochemical localization tests to identify the true source of pathology.

Rarely, hormone excess and hyperplasia can be due to an immunologic alteration. The best example of this is Graves' disease, a diffuse hyperplastic and hyperfunctioning state of the thyroid due to autoantibodies that stimulate the thyroid stimulating hormone (TSH) receptor on thyroid follicular cells.

Tumors of Neuroendocrine Cells

Tumors can arise either in classical neuroendocrine tissues, like pituitary, parathyroid, or adrenal medulla, or in other tissues where the dispersed cells reside, such as thyroid, lung, gut, or pancreas. These lesions exhibit a wide spectrum of biological behaviors. They may be slowly growing well-differentiated neoplasms that are considered benign (adenomas), because they do not metastasize. This is the case in the pituitary where metastasis is rare but large tumors can still result in death due to mass effects and local invasion. The most aggressive neuroendocrine neoplasms are poorly differentiated (small-cell) carcinomas that are rapidly lethal. Many tumors fall into intermediate categories and the prediction of outcome can be very difficult. The term "carcinoid", meaning "carcinoma-like," was originally introduced by Oberndorfer in 1907 [21], and the terminology has been applied to well-differentiated neuroendocrine tumors as well as to tumors that result in the classical "carcinoid syndrome" that results from serotonin excess. The use of this terminology has, however, caused great confusion because of the wide diversity of hormone activity and biological behavior among these tumors that cannot all be conveyed by this classification. Since many of these ultimately prove to be malignant, this terminology has fallen out of favor [22]. These tumors may be clinically silent in terms of hormone function, but they are almost always found to produce and store hormones. Some elaborate hormones that give rise to colorful clinical syndromes of hormone excess; the pattern of hormone production may be eutopic to the tissue of origin or ectopic, reflecting derepression of genes that are expressed in related cells.

Tumors of Steroid Hormone-Secreting Cells

These usually arise in the adrenals or gonads and very rarely arise in other sites where embryologic remnants are found. They are generally classified

as benign adenomas or malignant carcinomas based on features of differentiation, hormone production, and invasion. Well-differentiated and generally benign tumors express mature steroid hormones. Tumors that are less well-differentiated and exhibit malignant behavior tend to lose the complex enzymatic pathways required for mature hormone production, but often produce hormone precursors of various types. Nevertheless, the functional behavior of these tumors is not strict enough to allow classification as benign or malignant. These tumors are usually limited to production of steroid hormones and almost never produce peptide hormones ectopically.

Tumors of Thyroid Follicular Cell Derivation

These are the most common neoplasms of the endocrine system. They include benign follicular adenomas, well-differentiated papillary or follicular carcinomas, poorly differentiated "insular" carcinomas, and dedifferentiated anaplastic carcinomas. Among human malignancies, they include the most benign and nonlethal occult papillary microcarcinomas that are found incidentally in up to 24% of the adult population, and one of the most rapidly lethal malignancies, the anaplastic carcinomas that frequently results in death by strangulation in less than 6 months.

Epidemiology

Tumors of endocrine differentiation are considered to be rare and the epidemiologic data are therefore limited. There are, however, several statistics of note.

Pituitary tumors are reported to be found in about 20% of the general population [23]. Many studies have reported the identification of these lesions as incidental findings at autopsy, or as radiologic findings in the asymptomatic "normal" population. The true incidence of clinically significant lesions is not known. Some forms of pituitary neoplasia, including corticotroph adenomas causing Cushing's disease and prolactinomas, are more common in women than in men, but overall there is no sex predilection of pituitary neoplasia. These lesions tend to increase with age and are rare in children [9].

Primary hyperparathyroidism is most often due to parathyroid neoplasia and is reported to occur in 1% of the adult population [24,25]. The true incidence of parathyroid adenomas is, however, not known. Parathyroid carcinomas are rare. Benign lesions are more common in women than in men and are primarily found in middle-aged to elderly women. In contrast, carcinoma does not have a predilection for women and some studies indicate onset about one decade earlier than benign parathyroid tumors.

Pheochromocytomas of the adrenal medulla have a reported incidence of 2–8 per million per year and extra-adrenal paragangliomas are even more rare. These lesions have no sex predilection and are rare in children [3,26].

Well-differentiated tumors of the dispersed endocrine system are rare. Tumors of thyroid C cells, medullary thyroid carcinomas, represent about 5% of thyroid cancers that predicts a prevalence of about 1–2 per 100 000 [27,28]. Tumors of the endocrine pancreas have an estimated prevalence of 1 in 100 000 [29]. These lesions show no sex predilection and are very rare in children. Small-cell carcinoma of the lung, the most poorly differentiated endocrine neoplasm of this type, represents one of the four major types of lung cancer, the second most common cancer in men and women and the number one cancer mortality site [30]; this variant has an annual incidence of almost 10 per 100 000 population.

Although adrenal cortical nodules are identified as incidental findings in 0.6–1.3% of asymptomatic individuals, clinically significant adrenal neoplasms are more rare and adrenal cortical carcinoma has an estimated incidence of only about 1 case per million population [26,31]. There is a slight female preponderance. The incidence has a bimodal distribution in the first and fifth decades.

As indicated above, thyroid cancer is the commonest endocrine malignancy, representing 1–2% of all cancers [28,32–34]. It is about three times more common in women than in men and currently represents the 10th most common malignancy in women [30].

Etiology

The etiology of most endocrine tumors is not known. A small minority are due to inherited genetic defects.

Multiple Endocrine Neoplasia Syndromes

The genes responsible for the two most common multiple endocrine neoplasia (MEN) syndromes, MEN-1 and MEN-2, have been cloned and characterized, and the mutations have clarified our understanding of mechanisms of disease. MEN-1 is a classic example of germline inheritance of a mutant tumor suppressor gene (TSG), menin [35]. It is an autosomal dominant disorder with variable penetrance; the variability of tumor development in pituitary, parathyroids, pancreas, and occasionally other sites of the dispersed endocrine system in individual patients is due to the requirement for loss of the intact allele encoding the tumor suppressor. In contrast, MEN-2 is the best example of inheritance of a mutant proto-oncogene. The gene responsible for this disease encodes the transmembrane receptor tyrosine kinase ret [36]. The identification of an activating ret mutation in members of kindreds is now accepted as an indication for prophylactic thyroidectomy in early childhood, since these individuals will develop medullary thyroid carcinoma that can metastasize and is lethal in more than half of patients. Moreover, distinct ret mutations are associated with distinct clinical phenotypes. Mutations in exons 10 and 11 that encode the extracellular domain of the ret protein are implicated as the cause of familial medullary thyroid carcinoma alone. Specific mutations, usually in exon 11 involving codon 634, are associated with MEN-2A and specifically codon 634 mutations replacing cysteine with arginine are more often associated with parathyroid disease and pheochromocytoma that characterize this disease complex. Activating mutations in exon 16 that replace a codon 918 methionine with threonine alter the tyrosine kinase domain of ret and result in MEN-2B, a more aggressive variant of MEN-2 with mucosal neuromas and a marfanoid habitus in addition to tumors of thyroid C cells, parathyroids and adrenal medulla.

Defects in cyclin-dependent kinase inhibitors (CDKIs) have been identified in a small number of families with multiple endocrine tumors similar to MEN-1; this syndrome has been classified as MEN-X or MEN-4. Reports include mutations of CDKNIB/p27Kip1 [37–39] and CDKN2C/p18INK4c [40].

Carney's Complex

Carney's complex (CNC) is an autosomal dominant disorder characterized by development of myxomas (mainly cardiac), spotty pigmentation due to lentigo or several types of nevi that affect mucosal surfaces and the lips, and endocrine tumors including pigmented nodular adrenocortical disease, thyroid and testicular tumors and pituitary adenomas with gigantism or acromegaly [41]. These lesions share cAMP signaling pathways and the disease has been associated with germline mutations in the PRKAR1A gene that encodes the PKA regulatory subunit 1Aα [42].

Isolated Familial Somatotropinoma and Familial Isolated Pituitary Adenoma Syndromes

The isolated familial somatotropinoma (IFS) and familial isolated pituitary adenoma (FIPA) syndromes involve families with pituitary GH-producing adenomas (IFS) [43] or nonsomatotroph lesions (FIPA); virtually all FIPA kindreds contain at least one prolactinoma or somatotropinoma [44]. Patients with FIPA are significantly younger at diagnosis and have larger tumors than sporadic counterparts. Germline mutations in the aryl hydrocarbon receptor-interacting protein (AIP) gene with loss of heterozygosity (LOH) of AIP is implicated [45] in about half of IFS kindreds and in about 15% of FIPA families. In families with AIP mutations, pituitary adenomas have a penetrance of over 50% [44]. In the pediatric population, where pituitary adenomas are rare, germline AIP mutations can be found in children and adolescents with GH-secreting tumors, even in the absence of family history [46].

Familial Paraganglioma Syndromes

Familial paraganglioma (PGL) syndromes are caused by mutations of succinate dehydrogenase genes SDHD (PGLl), SDHC (PGL3), and SDHB (PGL4),which also appear to function as TSGs. A novel aspect of PGLl is a mode of transmission that involves genomic imprinting, i.e., tumors occur only after paternal transmission of the mutated gene [47].

Von Hippel–Lindau Disease and Neurofibromatosis Type 1

von Hippel–Lindau disease (VHL) and neurofibromatosis type 1 (NFI), due, respectively, to mutations of the VHL and NFl TSGs, confer susceptibility to pheochromocytomas/paragangliomas and pancreatic endocrine tumors [22].

Familial Hyperaldosteronism Type 1

Familial hyperaldosteronism type 1 (glucocorticoid-remediable aldosteronism) is an autosomal dominant disorder caused by a hybrid gene formed by crossover between the ACTH-responsive regulatory portion of 11-β-hydroxylase (CYP11B1) gene and the coding region of the aldosterone synthase (CYP11B2) gene. It results in aldosterone-producing adenomas, together with micronodular and homogeneous hyperplasia of the adrenal cortex [48].

Cowden's Syndrome and Familial Adenomatous Polyposis Syndrome

Cowden's syndrome and the familial adenomatous polyposis (FAP) syndrome result from mutations of the PTEN and APC genes respectively; these genetic disorders result in tumors of the intestine and other sites, including endocrine tumors of the thyroid [22].

Hyperparathyroidism–Jaw Tumor Syndrome

The hyperparathyroidism–jaw tumor (HPT-JT) syndrome is caused by mutations of the parafibromin gene and, as the name implies, affected individuals develop hyperparathyroidism, with a high incidence of parathyroid carcinoma, as well as jaw tumors and renal cell carcinomas [49].

Li–Fraumeni Syndrome

The Li–Fraumeni syndrome, due to mutations of the *TP53* TSG, is associated with adrenocortical carcinoma [48].

The cause of sporadic endocrine tumors may be attributed to mutations of the genes implicated in familial disorders, but this is not always the case. The etiology of sporadic pituitary adenomas is largely unknown. Neuroendocrine tumors of other sites occasionally have mutations of the menin gene; others, such as the Daxx or ATRX genes in pancreatic neuroendocrine tumors, have also been implicated. The MEN2 gene, ret, is frequently mutated in sporadic medullary thyroid carcinomas.

Thyroid carcinomas of follicular epithelial derivation are the best characterized of endocrine tumors. The pathways of mutation that correlate with aggressive behavior have been elucidated [50]. Many of the early events underlying these tumors appear to be related to environmental mutagenesis, specifically radiation following atomic bomb and nuclear reactor exposures.

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