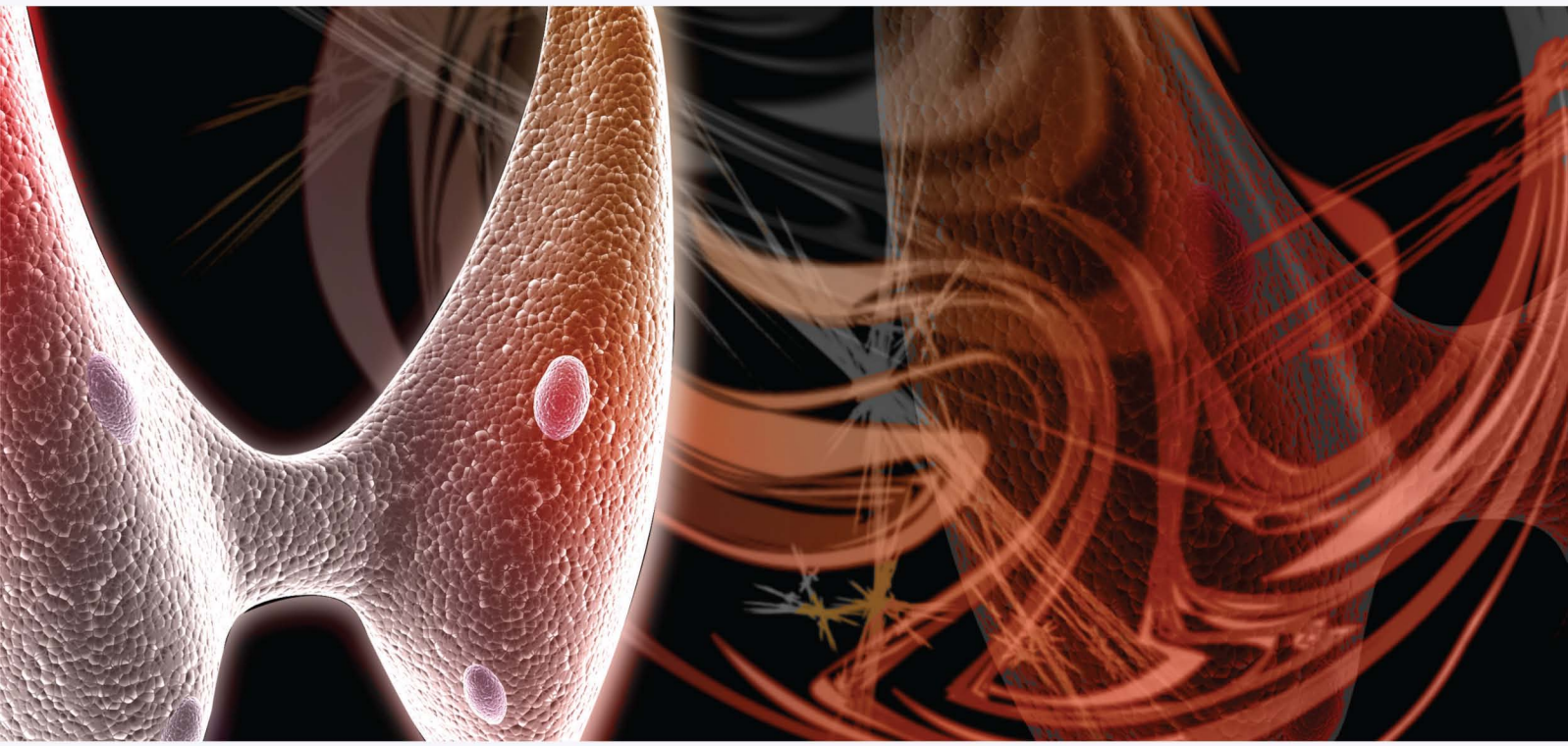
# ENDOCRINE SURGERY SECOND EDITION



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To Lois, my wife, sons Alexander and David, and grandchildren Sarah, Helen, and William.
In gratitude to Bradley H. Jack, philanthropist and friend, whose endowment has allowed continuation of my clinical and academic work.

*Demetrius Pertsemlidis*

To my wife, Kathleen, and children, Frances and William, whose unconditional support is a true blessing. And to my patients, who consistently put their genuine trust in me to shepherd them to improved health.

*William B. Inabnet III*

For France, who is always there, and sons Xavier, Guillaume, and Maxime

*Michel Gagner*

# Contents

# Foreword

Today's endocrine surgery is based on the ongoing efforts and contributions of many clinicians and scientists. The early luminaries in surgery, Billroth, Kocher, and Halsted, made important contributions not only to the technical development and performance of operative procedures on endocrine glands but also to the understanding of the pathophysiology of the underlying diseases and of the resulting effects of surgery. In 1902, Bayliss and Starling first discovered that a chemical messenger from one tissue could be transported in the bloodstream to affect the function of a different tissue or organ. Bayliss coined the term "hormone" to categorize this action of secretin. The subsequent identification of other hormones such as insulin by Banting and Best and gastrin by Gregory illustrate the profound impact that endocrinology and endocrine surgery have had on the course of medicine and the care of patients. Endocrinology has always been a dynamic field but now more than ever the pace of discovery and depth of understanding of the cellular and physiologic processes in this field has rapidly accelerated. This is especially true since the publication of the first edition of *Endocrine Surgery*.

Endocrine surgery is now a well recognized subspecialty with advanced training programs that develop the required expertise to deal with the technical and, most importantly, the intellectual aspects of the field. The complexities involved in the diagnosis, management, and treatment options of endocrine surgical disease necessitate a multidisciplinary approach to produce a comprehensive, up-to-date clinically relevant textbook, Drs. Pertsemlides, Inabnet, and Gagner have assembled a nationally and internationally recognized group of authors from the diverse fields that impact the care and management of the endocrine surgical patient. The depth of knowledge and experience of these experts in endocrinology, pathology, radiology, basic science, surgery and surgical subspecialties provides useful approaches for the reader in all areas of endocrine surgical disease. It emphasizes that a skilled team is needed to deal with the multi-faceted aspects of these problems if the best results are to be obtained. Drs. Pertsemlides, Inabnet, and Gagner have provided a clear and integrated presentation of the clinical signs and symptoms, diagnostic laboratory tests, imaging findings and methods of localization, medical and surgical treatment options and the steps involved in the operative procedures for both benign and malignant disease. By emphasizing the multispecialty aspects of endocrine surgery, the reader not only strengthens their knowledge and understanding in their area of interest but also becomes conversant in the scope of expertise that is the purview of their colleagues.

This textbook brings together much new information and knowledge that has expanded the understanding of endocrine and metabolic surgical disease. From the molecular biology that underpins these diseases to the newest technologies and techniques that are being applied to the diagnosis, imaging and treatment of endocrine problems, the text provides a very functional source of valuable information. This edition will serve as the go to reference for Endocrine Surgery. It has much to offer physicians, endocrinologists, endocrine surgery fellows, residents and students, and non-clinicians with research interests in the field. It elucidates the standard approaches to current endocrine surgical problems but also looks forward to developing techniques of endoscopic and robotic surgery. As specialization in medicine increases, it is very useful to have a comprehensive text that deals with all aspects of a field even though one's interest may be limited to a particular area of that field. I feel that anyone who deals with an endocrine surgical patient will find many areas of interest in this second edition of *Surgical Endocrinology*. I am sure that readers of this text will not be disappointed and will find a vast array of useful information in dealing with the clinical aspects of endocrine surgical disease.

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# Preface

This second edition of *Endocrine Surgery* provides the standard reference source for clinicians and scientists, house staff, and students. The textbook is contemporary, up to date, and complete, with its contents ranging from morphology and physiology to molecular and genetic aspects of endocrine diseases. An online version of the entire book is also available.

All chapters have been updated, extensively revised, or entirely rewritten. In addition, a new section on metabolic surgery, which includes four chapters, has been added.

The authors and their educational institutions come from across the world, making this book of universal relevance. The geographical locations are in North and South America, Europe, the Far East, the Near East, and Australia.

The goal of this book is to enhance the day-to-day practice of medical and surgical endocrinologists by including modern applications for the care of adults and, to some extent, adolescents and children as well.

Prominent contributing leaders in endocrinology and endocrine surgery and the well-known publishing house of CRC Press/Taylor & Francis Group have created this global anthology, which merits recognition by educational institutions and libraries, as well as by individual readers.

Our table of contents spans 10 parts and accommodates 57 chapters. The first two parts are devoted to pituitary, pulmonary, and thymic endocrine neoplasms. Parts 3 and 4 are dedicated to the thyroid and parathyroids. Eleven chapters on the adrenal glands and seven on the pancreas constitute Parts 5 and 6. Part 7 is a single but long contribution entitled "Inherited Syndromes," and the chapter title is "Multiple Endocrine Neoplasias." Nine chapters comprise Part 8, "Gastroenteropancreatic System." The new Part 9 is a constellation of four important chapters, including one on pancreas transplantation, and all welcome new additions to this edition. Finally, and looking to the future, the last single chapter, and Part 10, is entitled "Robotic Endocrine Surgery."

Demetrius Pertsemlidis
William B. Inabnet III
Michel Gagner
*New York*

# Landmarks in endocrinology and endocrine surgery

DEMETRIUS PERTSEMLIDIS

Endocrinology and endocrine surgery have advanced rapidly and rightfully gained stately recognition in the academic environment and the world of medicine. The first biochemical assay for a hormone, secretin, was achieved at the beginning of the last century [1]. In 1946, Ulf van Euler, a catecholamine physiologist at the Karolinska Institute in Sweden, discovered that norepinephrine had the properties of a neurotransmitter. In 1970, he shared the Nobel Prize with Sir Bernard Katz of Great Britain and Julius Axelrod of the United States for the recognition of adrenergic neurotransmitter function [2,3].

In 1954, Paul Wermer described the inherited constellation of pituitary, parathyroid, and pancreatic islet cell neoplasia and named it "familial adenomatosis of the endocrine glands", later defined as MEN 1. In 1961, John Sipple described the association of thyroid carcinoma and pheochromocytoma, later termed Sipple syndrome, or MEN 2 [4].

In 1956, vanillylmandelic acid (VMA), a urinary metabolite of catecholamines, was discovered by M.D. Armstrong; a second urinary metabolite, metanephrine, was discovered the following year by J. Axelrod. Until the early 1950s, about one-half of pheochromocytomas were discovered at autopsy. These biochemical discoveries have permitted early detection with high accuracy (up to 95%) and low surgical mortality (close to zero) in the past four decades [2].

In the 1960s, Rosalyn Yalow and Solomon Berson, then at the Bronx Veterans Administration Medical Center and later faculty members of the Mount Sinai Hospital in New York, developed radioimmunoassay (RIA) to identify and characterize peptides, hormones, and amines. Solomon Berson died prematurely, before the Nobel Prize was given to Dr Yalow in 1977. RIA and later immunohistochemistry revolutionized endocrinology and endocrine surgery through better diagnosis and surgical skills [2,3].

## MOLECULAR BIOLOGY

In the 1930s, macromolecules and their crystalline properties were studied using the technique of ultracentrifugation. In the 1950s, Linus Pauling (Nobel Prize 1954) discovered the three-dimensional structure of proteins, and the double helix of the DNA molecule was described by James Watson and Francis Crick (Nobel Prize laureates in 1962) [4,5].

By the 1980s, the landscapes of endocrinology and endocrine surgery benefited from the rapid scientific advances of molecular biology.

## MOLECULAR ENDOCRINOLOGY

Molecular and cellular endocrinology emerged in 1974, encompassing genetic, epigenetic, biochemical, molecular endocrine, and cell regulation. Hormones, neurotransmitters, interaction with receptors, intracellular signaling, hormone-regulated genes, gene structure or endocrine functions, and multiple endocrine neoplasia were integrated into molecular endocrinology. Concepts and techniques borrowed from molecular biology significantly expanded the field [6].

Autoimmune diseases, type I diabetes mellitus, autoimmune thyroid diseases, and genetic diseases all stemmed from deficiencies of hormones, binding proteins, or steroid enzymatic biosynthesis. Hormone resistance caused by mutations in the gene for hormone receptors; resistance to insulin, thyroid hormone, androgen, and vitamin D; and glucocorticoid resistance are included in molecular endocrinology [6].

## THE HUMAN GENOME

The Human Genome Project was launched in 1990, with the first "rough draft" of the genome completed in 2000, and final sequence mapping completed in 2003 [7–9]. The completed human genome and advances in molecular biology added better understanding of molecular physiology and diseases in all areas of medicine and endocrinology [5].

The 3.2 billion base pairs of DNA per haploid genome contain 22 autosomes and the X and Y sex chromosomes, coding for roughly 21,000 genes, which are transcribed into RNA, which is then translated into more than 250,000 proteins. The human genome contains 21,000 genes. Each chromosome contains many genes, the source of physical and functional units and heredity. Genes are located in specific

sequences of bases that encode the transition to proteins, performers of the function of life. Interestingly, genes make up only 1.5% of DNA. The remaining DNA consists of sequences—some repetitive and most not completely understood—that are transcribed into RNA but do not make proteins. A large portion of this noncoding DNA has biochemical activity, including regulating gene expression, organizing chromosomal architecture, and controlling epigenetic inheritance.

From prediction to reality, studies of the genome have led to diagnosis and treatment of diseases.

## EPIGENETIC SILENCING

Classical genetics cannot explain the entire spectrum of cancers [10]. There is no genetic explanation for how monozygotic twins with identical DNA can have different phenotypes and different susceptibilities to a disease. Epigenetic changes such as DNA methylation and histone modification can alter patterns of gene expression without changes in the underlying DNA sequence.

The best-known epigenetic inactivation (silencing) is through DNA methylation of tumor suppression genes, and plays a critical role in controlling gene activity and architecture of the nucleus. Epigenetic silencing has been observed in many cancers: breast, lung, prostate, kidney, glioma, esophagus, stomach, liver, ovaries, leukemia, and lymphoma. Unlike mutations, DNA methylation is reversible. Hypermethylated tumor suppressor genes can be reactivated with drugs. Demethylating agents, however, have not shown successful clinical antitumor activity.

## MICRORNAS

MicroRNAs (miRNAs) are 19- to 23-nucleotide-long noncoding RNAs that post-transcriptionally regulate gene expression by interacting with messenger RNAs, triggering degradation or translational repression [11–14]. They are involved in nearly every physiologic process, are critical to development, and play a significant role in cancer initiation and progression.

MiRNAs have been shown to regulate gene expression in metabolically active tissues, including the endocrine pancreas, liver, and adipose tissue; their expression has been implicated in the development of the endocrine pancreas and may regulate the progression of diabetes and metabolic syndrome. In the pancreas, miR-375 has been implicated in islet cell viability and function, with perturbations of intracellular levels of miR-375 having significant effects on glucose metabolism [11,12]. In the liver, miR-122 has been shown to be critical for normal lipid metabolism [13]. Specific patterns of tumor and serum miRNA expression have been associated with different types of thyroid tumors, including anaplastic, follicular, and papillary thyroid carcinomas, with variation in the sequence of a single miRNA associated with a familiar risk for papillary thyroid carcinoma (PTC) [14]. Thus, both variation in miRNA sequence and differences in miRNA expression add molecular tools to the diagnostic, prognostic, and therapeutic armamentarium of endocrinology.

## MOLECULAR ISOTOPIC IMAGING

Somatostatin is an anterior pituitary hormone and a regulatory peptide with receptors (somatostatin receptor (SSTR)) in numerous organs: the brain, thyroid, pancreas, gastrointestinal system, spleen, and kidney [15–19]. Somatostatin has a short half-life (3–4 minutes) and is susceptible to quick enzymatic degradation.

Somatostatin suppresses the secretion of hormones of numerous glands and has been used to treat diseases with hormonal hypersecretion by inhibiting adenylyl cyclase simultaneously with hormone binding.

$^{111}$Indium-DTPA (diethylenetriamine pentaacetic acid)-octreotide and $^{90}$Yttrium octreotide have been the most commonly used with somatostatin analog. $^{111}$In-DTPA-octreotide has a high affinity to somatostatin receptor type II (SSTR2).

Carcinoid tumors show higher sensitivity when octreotide is labeled with $^{111}$Indium compared with $^{123}$I-MIBG (methyl-iodo-benzylguanidine). $^{111}$In-octreotide is less sensitive in detecting pheochromocytoma (originating from the adrenal medulla or extra-adrenal) and medullary thyroid cancer.

$^{90}$Y-octreotide is very sensitive (80%–100%) in detecting carcinoid tumors. The sensitivity for gastrinoma is 60%–90% and for insulinoma is limited to 50%, due to low affinity and small tumor size.

In the search for better nuclear medicine molecular imaging for insulinoma, exendin-4, an analog of glucagon-like peptide (GLP-1), was discovered. Exendin-4 offers the highest affinity to the radiotracers $^{111}$Indium and $^{68}$Gallium, and strong conjugation with abundant receptors in pancreatic β-cells.

In recent years, peptide ligands DOTA, DOTATOC, and DOTANOC have been discovered to form complexes with the following metal tracers: $^{111}$In, $^{68}$Ga, $^{64}$Cu, $^{90}$Y, and $^{177}$Lu. DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTATOC (phenylalanine replaced by tyrosine at molecule position 3), and DOTANOC (DOTA-1-NaI-octreotide) have chemical purity and high affinity to neuroendocrine tumors. The phenylalanine replacement by tyrosine at position 3 in the molecule increases hydrophilia and offers stronger conjugation with SSTR2 in somatostatin-avid tumors.

$^{68}$Ga-DOTA-PET, a recent introduction for clinical research use, markedly improved nuclear medicine molecular imaging, especially in neuroendocrine tumors. The sensitivity of 97% and specificity of 92% reached an accuracy up to 96%. It has been a landmark discovery in neuroendocrinology.

Several therapeutic radiopharmaceuticals have been used in small nonrandomized trials, including

$^{111}$In-pentareotide, $^{90}$Y-DOTA-lanreotide, $^{90}$Y-DOTATOC, $^{177}$Lu-DOTATATE, $^{90}$Y-DOTANOC, $^{90}$Y-DTPA-D-Glu$^{1}$-minigastrin, $^{177}$Lu-AMBA, $^{90}$Y-DOTAGA-substance P, and $^{131}$I-MIBG.

## ENDOCRINE AND METABOLIC SURGERY

Metabolism and metabolic surgery have been ingredients of endocrinology and endocrine surgery [4,11]. The terms encompass changes in biosynthesis, enzymatic and biologic degradation, biochemical interactions, and energy storage.

The surgical interventions for endocrine disorders include modulation of hormones causing a physiologic or pathologic metabolic effect. Common disorders encompass thyrotoxicosis, hypothyroidism, goiter, pituitary and adrenal diseases, obesity, and diabetes mellitus and hyperlipidemia.

In recent years, the horizon of metabolic surgery has been expanded to integrate bariatric procedures for obesity, type II diabetes mellitus, post-gastric bypass nonpancreatogenous hyperinsulinemia, and nesidioblastosis in MEN 1 patients with diffuse multicentric insulinomas or hyperplasia/hypertrophy of the entire pancreas.

The enormities of endocrinology and metabolism have created complexities that at times make it difficult to distinguish malfunctions from diseases.

## THE ENDOCRINE PATIENT

The patient expressing hormonal hypersecretion, or suspected endocrinopathy, is initially directed to an endocrinologist by the clinician. The history, clinical findings, and family background are recorded in detail. Biochemical testing starts with a basal and, if needed, stimulated hormonal hypersecretion or antigenic profile in both functioning and silent neuroendocrine neoplasia.

Traditional imaging with ultrasound, computed helical tomography, and magnetic resonance are standard noninvasive, radioactive instruments.

Before exposure of a patient to nuclear medicine procedures, it is mandatory to explain in practical terms the events, the approximate times, and the instruments to be used. The patient preparation should include information about diet, hydration, medication needed or restricted, and the rationale for these requirements. The radiation risk must be explained to the patient in writing, and that possible consequences may occur over a long time period. The distinction between diagnostic and therapeutic radiopharmaceuticals should be clarified before the consent is signed.

The final interpretation of the results should be explained by placing them into clinical context. Interference with performance of the instruments or interpretation of the results should be revealed to the patient.

Genetic testing and counseling is essential for the patient if the family heredity is known, or in young patients with an unknown family link or skipped generations.

Every patient's case is reviewed by the multidisciplinary committee, where the discussions usually reach a maximum of indications and choice of procedures.

Current instruments, surgical techniques (endoscopy, laparoscopy, and robotic), molecular biochemistry, isotopic imaging, and genetic and genomic advancements offer unique diagnostic and therapeutic outcomes.

## CHANGES THAT IMPROVED OUTCOMES IN ADRENALECTOMIES

### Preoperative pharmacologic vasodilatation

It is common practice to start ambulatory preoperative adrenergic blockade for 4–6 weeks, expecting expansion of the circulating blood volume [20–22]. The described oral dose is usually designed to control the blood pressure, heart rate and rhythm, sweating, and metabolic activity under conditions without stress.

Physical trauma or emotional stress will most likely cause hypertensive or arrhythmic crisis due to insufficiency of drug concentration in the ambulatory state.

Phenoxybenzamine, a long-acting ($t½ = 2–3$ hours), nonselective oral α-adrenergic blocker is given orally three times a day (preferably every 6 hours) to a total dose of 40–100 mg/day. After α-adrenergic blockade, a β-blocker (metoprolol or atenolol) or calcium channel blocker (nicardipine) is added.

Plasma and erythrocyte volumes in pheochromocytoma have been proven to be within the normal range [20,21]. Preoperative attempts to create pharmacologic expansion of the circulating volume do not prevent cardiovascular intraoperative crises or hypotension after removal of pheochromocytoma [22]. The optimal time for volume restoration with isotonic crystalloid (rarely blood) is immediately after tumor removal.

### Unknown duality of the adrenergic system

We strictly separated paragangliomas from adrenomedullary pheochromocytomas in the adrenergic system. Common embryologic ancestry from the neural crest, secretion of norepinephrine, and potential production of ectopic hormones are the only similarities.

Paraganglioma patients are younger, the tumors are derived from sympathetic ganglia, genetics differ completely, tumor multiplicity is 30%, malignancy is more prominent, and the association with other neoplastic syndromes is not distinguishable. As a result, the preoperative radiologic detection, molecular imaging, intraoperative dissection, and postoperative surveillance are more difficult.

### Choice of adrenergic blockers

We have always used only intraoperative continuous intravenous short-acting α-1 blocker (phentolamine) and short-acting β-1 antiarrhythmic blocker (esmolol).

When phentolamine was no longer manufactured, we substituted the calcium channel blocker (nicardipine).

Long-acting adrenergic blockers are not suitable in the operating theater. They block the catecholamine receptors partially or completely, rendering them ineffective. Substitution of effective adrenergic blockers with less effective antihypertensive medications is a mistake. We have routinely stopped the long-acting adrenergic blockers the day before surgery and started intravenous short-acting blockade for 24 hours in a monitored bed.

The preoperative initiation of the continuous intravenous adrenergic blockade offers a high degree of receptor affinity and allows preparation of the appropriate concentration for controlling the intraoperative crisis.

## Experience in pheochromocytoma and adrenocortical neoplasia

We, Demetrius and David Pertsemlidis, performed 245 consecutive operations (87 laparoscopic) in 225 patients with pheochromocytomas (30 paragangliomas); there was zero surgical mortality over a period of 4½ decades in a single institution.

Early on, we created programmatic canons and applied them strictly by preparing a well-organized pharmacologic environment, working with highly skilled anesthesiologists, selecting an appropriate surgical approach conforming to tumor size or anatomic location, and continuing close monitoring during immediate postsurgical recovery, until normo-volemia is restored.

One hundred fifty adrenocortical neoplasms were treated by laparoscopy or open traditional methods: Cushing's adenomas, adrenocorticotropic hormone (ACTH)-dependent hypercortisolism, adrenocortical carcinoma, aldosteronoma, nonfunctioning adrenocortical adenomas, and metastases to adrenals. R0 resection margins are essential to avoid recurrent Cushing's hypercortisolism or tumor, if there is a millimeter fraction of cortex left behind. Restoration of function in the suppressed contralateral adrenal, following unilateral adrenalectomy for Cushing's adenoma, may be as long as 6 months.

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PART 1

# Pituitary Gland

1

# Selective sampling of petrosal veins

JUSTIN R. MASCITELLI AND AMAN B. PATEL



## INTRODUCTIONS AND RATIONALE

Cushing's syndrome (CS) describes the signs and symptoms that are secondary to persistent hypercortisolemia, including stigmata of hypertension, diabetes, truncal obesity, osteopenia, bruising, abdominal striae, moon facies, generalized malaise, fatigue, and emotional lability. Cushing's disease (CD) is restricted to hypercortisolemia secondary to an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma. CD accounts for approximately 70% of adult cases of CS [1]. The prompt identification and treatment of CD is paramount since CD left untreated can carry a high morbidity and mortality. Untreated CD has a 5-year survival rate of only 50% [2].

The differentiation of CD from CS secondary to an ectopic ACTH-producing tumor generally relies on a number of different biochemical tests, especially when MRI does not definitively demonstrate a pituitary adenoma as the cause. The three most commonly used tests to diagnose hypercortisolism are urinary free cortisol (UFC), low-dose dexamethasone suppression tests (DSTs), and midnight serum cortisol or late-night salivary cortisol, but these tests carry variable sensitivity and specificity. Tests to further differentiate CD and CS include serum ACTH, high-dose DST, corticotropin-releasing hormone (CRH) or desmopressin stimulation testing, and MRI of the brain [3]. The high-dose DST has been reported to have a sensitivity of only 80% [4]. MRI has been reported to have a false-negative rate of up to 50% [5]. This accuracy may be improved by using techniques such as dynamic contrast spin echo (DC-SE) and volume-interpolated three-dimensional spoiled gradient echo (VI-SGE) MR sequences [6], as well as 3 T MRI [7].

Inferior petrosal sinus sampling (IPSS) was first reported in 1981 to differentiate CD and CS due to an ectopic ACTH-producing tumor [8]. IPSS with CRH stimulation is currently considered to be the gold standard in diagnosing CD when all other methods have failed, with sensitivity and specificity rates in the range of 96% and 100%, respectively [9]. Although IPSS was traditionally advocated for all cases with negative imaging [10], it is currently considered in selected cases with hypercortisolemia when both laboratory and radiographic tests fail to make the diagnosis with a high degree of certainty or in cases of persistent hypercortisolemia after hypophysectomy if not previously performed [11,12]. In these cases, a preoperative positive MRI scan may have represented a nonsecreting pituitary adenoma.

The rationale for IPSS is that a large proportion of the venous drainage of the pituitary gland is via the IPSs, allowing for analysis of blood samples uncontaminated from other sources. Therefore, in CD the concentration of ACTH is expected to be higher in the IPS draining the hemihypophysis bearing the tumor than in the contralateral IPS or in the peripheral blood [10,13]. CRH is released from the paraventricular nucleus of the hypothalamus into the hypophyseal portal system and stimulates the release of ACTH from the anterior pituitary. CRH stimulation has long been known to increase sensitivity and specificity of IPSS [10].

## ANATOMY AND SAMPLING TECHNIQUE

Venous sampling must be obtained from a source that represents the venous drainage of the pituitary gland. The venous drainage of the pituitary gland is via the cavernous sinus. The cavernous sinus then usually drains into the IPSs,

superior petrosal sinuses (SPSs), and basilar venous plexus. These all have variable drainage courses into the internal jugular vein (IJV) and paraspinal venous plexus. There are as many as four intercavernous venous connections (the largest of which is the basilar plexus located along the dorsum sellae). Despite these connections, pituitary venous drainage is unilateral under normal circumstances [14,15]. Therefore, bilateral simultaneous sampling is required to evaluate the side of possible pituitary microadenoma. The IPSs are usually the best sites to obtain venous samples from, since they usually capture a large portion of the cavernous sinus drainage from their respective side.

It is important to ensure that the patient is hypercortisolemic at the time of IPSS; otherwise, the test may yield a false-negative result. Midnight salivary cortisol the night before the procedure [16] and 24-hour urinary cortisol the day before (our protocol), and same-day analysis of the samples, offer assurance.

## Anticoagulation

Venous thrombosis of the IPS, cavernous sinus, basilar venous plexus, or IJV is an undesired event that can potentially have severe consequences. Therefore, systemic anticoagulation is maintained during the procedure [10] with a bolus of 4000 units of intravenous heparin followed by 1000 units intravenously every hour thereafter. Alternatively, the dosage of heparin can be titrated to maintain an activated clotting time (ACT) of greater than 200. At the minimum, the catheters will be in place for 30 minutes, and in cases of difficult catheterization, it is not unusual to have a catheter in place for a longer period of time.

## Jugular vein catheterization

Bilateral venous access is established by the standard transfemoral approach. On one side, a 5 French (Fr.) sheath is placed, so that concomitant peripheral venous sampling can be obtained during the procedure. A 4 Fr. sheath is placed into the contralateral femoral vein. The IJVs and, subsequently, the IPSs are catheterized with 4 Fr. catheters. The catheter used should have a 20°–30° angled tip, followed by a 2 cm straight segment. Occasionally, a different angle or shape may be necessary depending upon the specific anatomy. When sampling, each side should be accessed with the respective IPS to match sampling sides and catheters [10].

On the left, the junction of the innominate vein and the superior vena cava (SVC) is relatively large. Once the catheter is aimed in the correct direction, a hydrophilic-coated guidewire should allow easy passage from the SVC to the left subclavian vein. Catheterization of the left IJV can be challenging, usually because of a valve located at the thoracic inlet. Getting the wire to enter the IJV is usually a matter of chance with repetitive prodding during various phases of respiration. A forceful contrast injection into the subclavian vein will often show the location of various inflow veins as stumps, due to the venous valve system, which can then be used as guides.

Accessing the right IJV is usually more straightforward than the left, as the course is relatively straight. There can be variations that make the catheterization more difficult, but access can usually be achieved with a small amount of searching. The valve is usually not as much of a problem on the left.

## Inferior petrosal sinus catheterization

The venous drainage of the skull base is variable [17], making entry of the IPSs into the jugular system more difficult to find. In fact, advancing the catheter into the IPS is often the most challenging aspect of the procedure. The most common site of IPS entrance is at the apex of the jugular/sigmoid sinus curve and is typically located anterior and medial. Careful probing with a hydrophilic guidewire aimed in the appropriate direction will allow one to the find the IPS. Occasionally, a contrast injection will be needed to identify the location of the IPS. Once the guidewire is positioned in the IPS, the catheter can be passed into the distal aspect of the IPS. Once the catheter is within the IPS, anteroposterior (AP) and lateral venograms are performed to confirm the position and to assess the venous drainage. With good positioning, retrograde filling of both cavernous sinuses, the contralateral IPS and basilar venous plexus, is commonly seen (Figures 1.1 and 1.2). Occasionally, the IPS will be too small for a 4 Fr. catheter, in which case a microcatheter and microwire can be used.

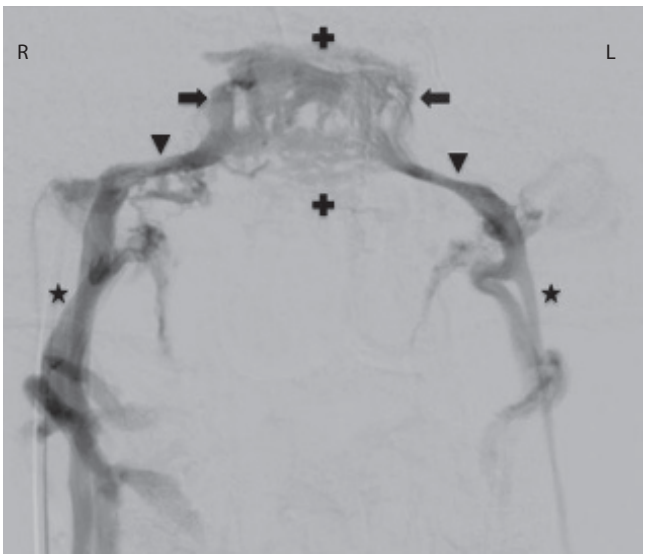


Figure 1.1 Right IPS injection, AP view. Normal symmetric IPSs. Note that the right-sided injection opacifies the bilateral IPSs (arrowheads), the bilateral cavernous sinuses (arrows), the intercavernous sinus (plus signs), and the bilateral IJVs (stars). The catheter is well positioned in the right IPS (arrowhead). Note that the IPS arises medially from the IJV.

Normal lateral

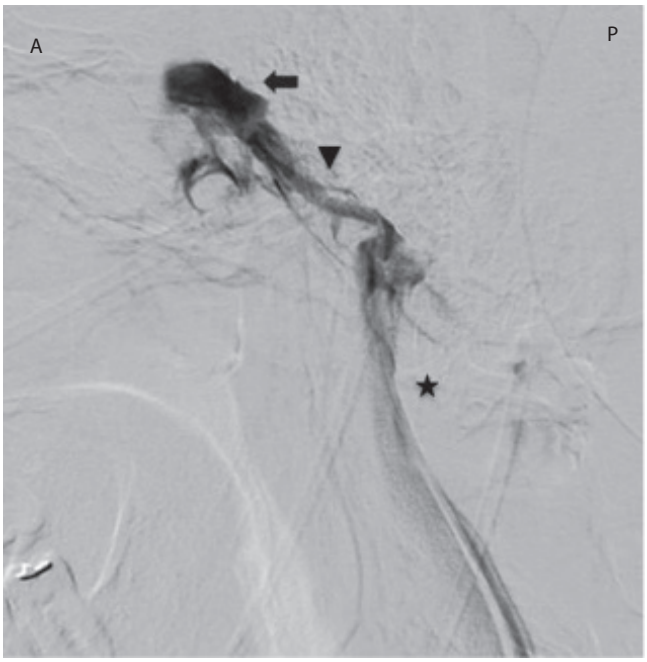


Figure 1.2 Right IPS injection, lateral view. Lateral venogram in the same patient as shown in Figure 1.1. The cavernous sinus (arrow), IPS (arrowhead), and IJV (star) can be seen well. Note that the IPS arises anteriorly from the IJV.

There are some variable anatomical patterns to consider. Small venous channels originating in the cerebellopontomedullary angle can infrequently drain into the IPS. Additionally, small bridging veins can also be found connecting the IPS with the transverse pontine vein, the vein of the pontomedullary sulcus, or the lateral medullary vein near the jugular bulb [18]. The anterior condylar vein is an important tributary vein that can dilute the sample if the catheter is not positioned distal to its junction with the IPS [19]. Occasionally, the IPS drains into the IJV as a plexus of veins, leading to difficult catheterization and reduced accuracy of the test (Figure 1.3). Even less commonly, the IPS drains directly into the vertebral venous plexus and does not connect to the IJV, which could potentially lead to false-negative results [9]. There also may be an absent IJV (Figure 1.4) that precludes lateralization. In addition, it is possible to have an abnormally located junction between the IPS and the IJV (Figure 1.5) that, if not appreciated, may make catheterization of the IPS difficult and possibly even dangerous due to repetitive unsuccessful attempts via the normal anatomic configuration.

Anomalous venous anatomy can make catheterization of the IPS difficult for even the most skilled practitioners. If difficulty is encountered, the interventionalist should suspect a duplicated IJV or anomalous drainage of the IPS. In these circumstances, venography of the other IPS would invariably fill across the midline, clearly demonstrating the contralateral IPS. It is then possible to locate the exact entry point of the IPS into the opposite IJV. In the most difficult cases,

Plexiform IPS

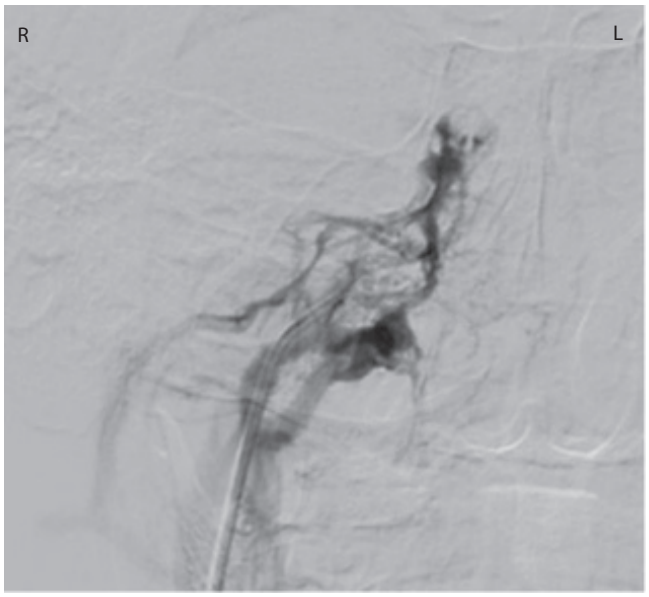


Figure 1.3 Right IPS plexus injection, AP view. This injection reveals a plexus of veins representing the right IJV, which could make catheterization difficult and decrease the accuracy of the test. Options include sampling from the right IJV or attempting to place a microcatheter into one of the smaller plexiform veins. There is risk of obtaining a false-negative result.

No IJV

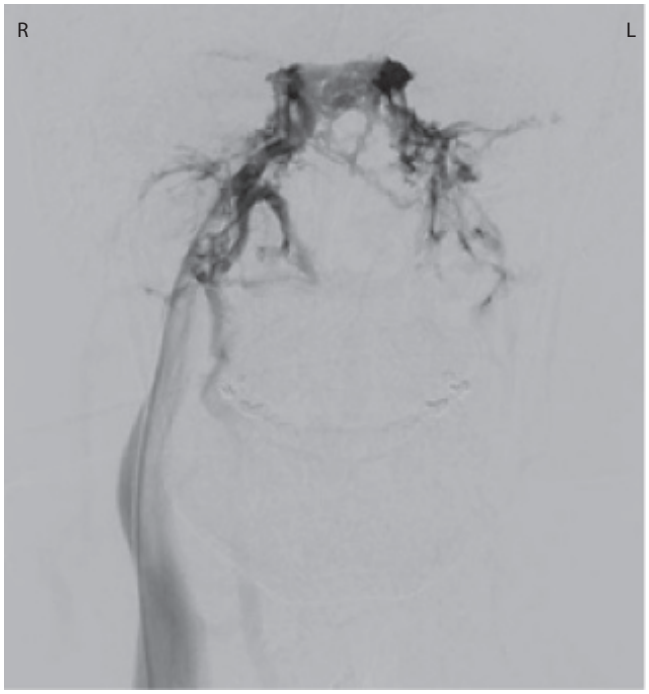


Figure 1.4 Right IPS injection, AP view. This injection reveals complete absence of the left IJV after many attempts at catheterization on the left. Although testing can be performed from the right IPS and compared with peripheral blood, this variant precludes tumor lateralization.

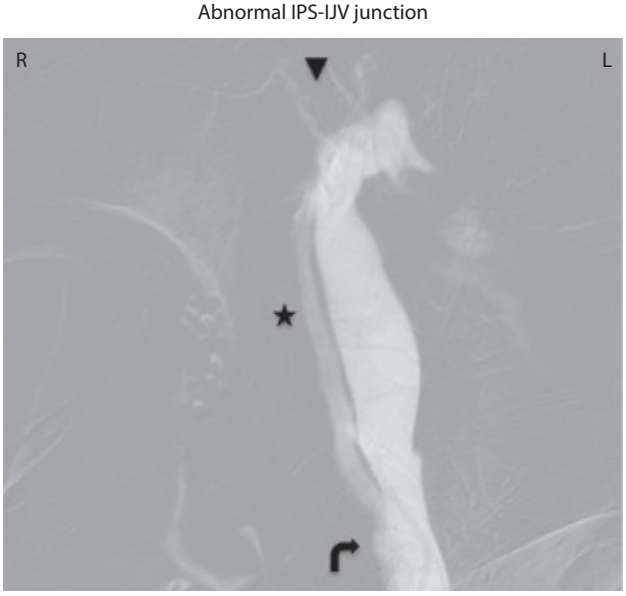


Figure 1.5 Left IJV injection, oblique view. This injection reveals that the IPS (arrowhead) enters the IJV in the mid-cervical region (curved arrow), which is a rare variant of this anatomy. There is a small vein (star) that lies anterior and slightly medial to the IJV that connects the IPS to the IJV. If this variable anatomy is not appreciated, catheterization of the IPS will be impossible and potentially dangerous due to persistent attempts to catheterize via the normal anatomic configuration.

it is necessary to catheterize the arterial system, select the internal carotid artery, and perform a standard angiogram to locate the cavernous sinuses and visualize their drainage.

### Venous sampling procedure

After the catheters are in position bilaterally, baseline samples are taken from each IPS catheter and the peripheral 5 Fr. sheath simultaneously. One must take care to place samples in the appropriate specimen tubes. For ACTH analysis, samples are placed in the same tubes used for complete blood counts (usually "lavender top") and kept on ice. Prolactin and growth hormone samples are placed in serum chemistry (usually "red top") tubes. These are guidelines, and for each institution, prior contact with the appropriate laboratory should be made for confirmation of these instructions and coordination of handling.

After the baseline samples are collected, challenge or stimulation testing should be performed. This is most commonly performed for the workup of CS. For ACTH testing, CRH or Acthrel (ovine CRH) is administered in a 1 μg/kg (up to a maximum of 100 μg) intravenous bolus peripherally. After administration, samples are obtained simultaneously from IPSs and peripheral blood at 2, 5, 10, and 15 minutes. These samples are then placed in the appropriate tubes, labeled, placed on ice, and then sent to the laboratory for the appropriate analysis.

After the samples have been obtained, the IPS catheters are removed, heparin is reversed using protamine, and the sheaths are withdrawn. Pressure is applied to the femoral veins for approximately 10 minutes or until hemostasis is obtained. The patient is then observed for 2 hours with the head of the bed flat and then discharged.

A ratio between IPS and peripheral ACTH concentrations of 2:1 or greater at baseline or 3:1 after administration of CRH has been classically considered a positive test and indicative of CD. In addition, a ratio of 1.4:1 or greater in the detected ACTH concentration of one IPS versus the other can suggest the laterality of the tumor [10]. It has been reported that prolactin measurement during IPSS can improve the accuracy of IPSS [20]. A baseline ratio of prolactin IPS to peripheral of 1.8 or more suggests successful catheterization of the IPS. In addition, ratios of prolactin-normalized ACTH IPS to peripheral can then be used to differentiate between a pituitary and ectopic source of ACTH. Prolactin measurement has not been used at our institution.

## PITFALLS AND COMPLICATIONS

### Pitfalls

The false-negative rate has been reported as 1%–10% [9]. Doppman et al. reviewed the venograms of patients in a large series of surgically proven CD and negative MRI and found that all patients with false-negative results had either hypoplastic or plexiform IPS ipsilateral to the adenoma [21]. Another explanation for a false-negative result is a potential additional drainage through the portal sinuses, ascending through the pituitary stalk into the hypothalamus. Sampling errors may also occur secondary to dilution of pituitary blood from nonpituitary sources secondary to extensive anastomoses between the IPS and the basilar venous plexus, retrograde drainage of the SPSs, or misplaced catheters [22]. Presampling visualization of anatomical variants may give an indication of the possibility of a false-negative result. However, even when venograms show correct position of the catheter, there is no definitive proof of correct sampling of pituitary blood from both IPSs.

Additionally, the ability for IPSS to lateralize the tumor is not as good as its ability to identify the pituitary as the overall source of hypercortisolemia. A recent analysis of more than 500 patients found IPSS to have a positive predictive value of 69% in its ability to lateralize the tumor [23]. Asymmetric IPSs or the complete absence of one IPS can confuse or preclude lateralization.

The high frequency of incidentalomas raises the questions of the reliability of an abnormal MRI to confirm CD [24]. If transphenoidal surgery is performed based upon the endocrine data and an abnormal MRI and an ACTH-staining tumor is not found, we also then perform IPSS, if not previously performed.

## Complications

IPSS is a safe and reliable procedure, but it is nonetheless an invasive test and should be used with caution. Although extremely rare, brainstem vascular damage and transient or permanent neurological deficit can occur [25–28]. In most cases, however, IPSS causes only minor complications, such as groin hematomas, vasovagal reaction, or transient ear discomfort. Due to vascular fragility and hypercoagulability of patients with CS, heparin should be given to prevent thrombotic events. Injury to the vascular wall with subsequent thrombosis is the presumed cause of venous thromboembolism after IPSS [29,30]. Although severe adverse events are rare, IPSS should be performed only in specialized referral centers, where safety of the procedure is a high standard. IPSS is acceptable when imaging fails to demonstrate a well-defined lesion or when biochemical or clinical findings are inconsistent with CD [11].

## The Mount Sinai Hospital experience

At Mount Sinai Hospital, from 2001 to 2007, the major complication rate was reported to be 1 in 44 (2.3%) [27]. This patient sustained a brainstem stroke from the procedure. From 2007 to 2014, 76 additional IPSS procedures were performed and there were no additional major complications. Therefore, the major complication rate at Mount Sinai from 2001 to 2014 was 1 in 120 (0.8%). Additionally, at Mount Sinai, from 1987 to 2005, the false-negative rate was reported to be 2 in 105 (1.9%) and there were no false positives (0%) [11]. Furthermore, in the 1987–2005 cohort, lateralization was only possible in 66% of patients.

# CONCLUSIONS

Bilateral IPSS with CRH stimulation is the procedure of choice in confirming the diagnosis of CD. It should be considered in cases when the laboratory tests are discordant with MRI of the brain or when a patient remains hypercortisolemic following transphenoidal surgery. IPSS is safe and accurate, but it is important to remember that rare and serious complications such as brainstem strokes can occur.

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# 2

# Pituitary tumors and their management

CHRISTOPHER A. SARKISS, RAJ K. SHRIVASTAVA, AND KALMON D. POST



## INTRODUCTION TO THE HYPOTHALAMIC–PITUITARY UNIT

The anterior pituitary gland is under predominantly stimulatory control by the hypothalamus. The function of the normal pituitary gland depends on the integrity of the hypothalamus, the portal circulation, and the pituitary stalk. Portal vessels originate in a capillary bed in the median eminence and extend through long portal vessels into the pituitary stalk and to the adenohypophysis. The pituitary hormones adrenocorticotropic hormone (ACTH), growth hormone (GH), prolactin, thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) are controlled by the hypothalamic hormones corticotropin-releasing factor (CRF), dopamine (aka prolactin inhibitory factor [PIF]), thyroid-releasing hormone (TRH), and gonadotropin-releasing hormone (Gn-RH), respectively. This is efficiently accomplished via a portal vascular system connecting the hypothalamus with the anterior pituitary gland. These hypothalamic releasing factors are then under negative feedback control from the end-organ products, i.e., adrenal gland products, thyroid hormone, etc., thereby completing the axis loop [1]. The predominant net hypothalamic regulatory influence is stimulatory for all pituitary hormones except prolactin, which is under dominant inhibitory control [2]. Any interruption or compression of the network of portal vessels as a result of pressure or invasion by any perisellar mass can alter the delivery of these hypothalamic factors to the anterior pituitary and cause impairment in its function.

The anterior pituitary gland is responsible for the secretion and regulation of a variety of peptide hormones and regulating factors. Tumors originating in the anterior pituitary gland may therefore produce excess quantities of a particular peptide hormone. Pituitary adenomas are benign monoclonal tumors that arise from the cells comprising the anterior pituitary gland. They account for approximately 15% of all intracranial tumors. When a pituitary adenoma secretes one or more hormones, the resulting adenoma is classified as a functioning or secretory adenoma. Tumors without hormonal activity are logically classified as nonfunctioning or nonsecretory adenomas. In this chapter, we briefly review the different types of functioning pituitary tumors. To this end, we first review the hypothalamic–pituitary organ axis to help understand the diagnosis and treatment of patients with functioning pituitary tumors.

Anterior pituitary gland adenomas are identified pathologically both by their *in vivo* endocrine activity and by

their *in vitro* immunohistochemical staining characteristics. The advent of immunohistochemical staining for the various peptide hormones has revealed the fact that many adenomas once thought to be nonsecretory actually secrete endocrinologically inactive peptides [3]. The alpha-subunit, which has no known systemic effects, is one of the commonly found peptides.

Adenomas may be further subdivided into micro- or macroadenomas based upon size [4] (Figure 2.1). Tumors less than 1 cm in diamter are considered microadenomas and are predictably located solely within the sella turcica. They characteristically do not invade neighboring structures such as the sphenoid and cavernous sinuses. Macroadenomas, by definition greater than 1 cm, typically enlarge the sella turcica and frequently invade neighboring structures (Figure 2.2). Microadenomas usually are discovered either incidentally or because of an endocrinopathy, whereas macroadenomas present with compressive effects of the tumor, i.e., bitemporal hemianopsia, as well as endocrinopathy. The endocrinopathy may be one of either oversecretion or undersecretion.

The evaluation of a patient with a suspected functioning pituitary tumor will be discussed in relation to each tumor type; however, because of the protean and often subtle manifestations of these endocrinopathies, a detailed history and physical examination are mandatory in guiding the rest of the workup. Subtle changes in hair growth, skin texture or color, and body mass may be the only heralds of early endocrine dysfunction. MRI technology has dramatically changed the radiographic evaluation of pituitary adenomas. MRI with and without gadolinium enhancement is now considered the study of choice in evaluating patients with suspected pituitary abnormalities [5–8]. The normal pituitary gland will enhance within 5 minutes of contrast

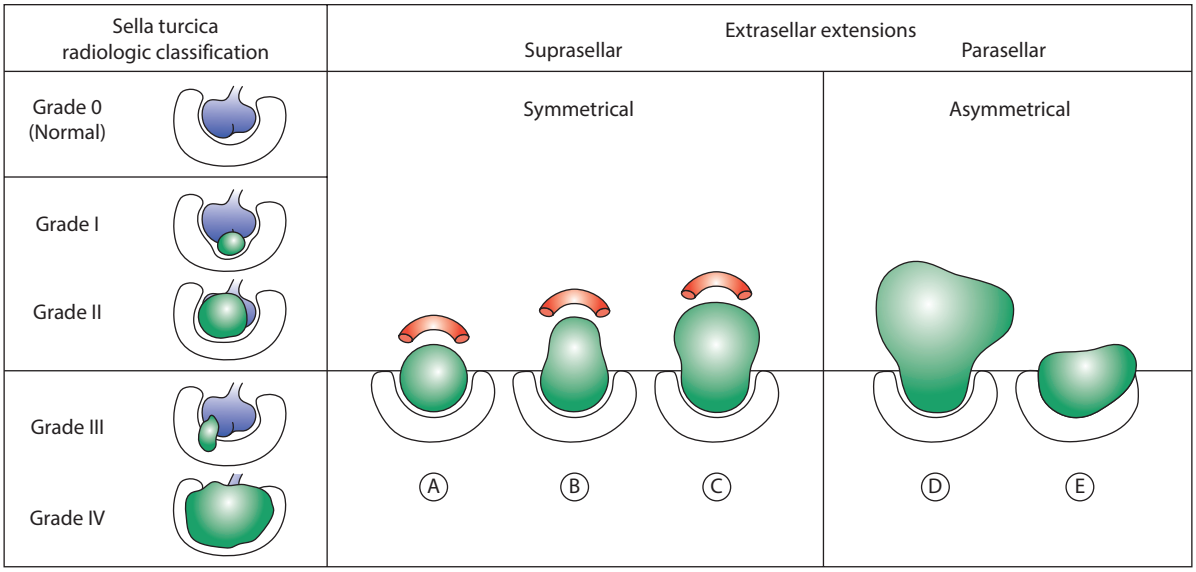


Figure 2.1 Radiograpic/imaging classfication of pituitary adenomas. Grades I and II are enclosed adenomas. Grades III and IV are invasive adenomas. Extensions A, B, C are directly suprasellar, while D is asymmetric intracranial and E is asymmetric into the cavernous sinus. (Adapted from Post K, Shrivastava R. Functioning pituitary tumors. In: Rengachary S, Ellenbogen R, eds., *Principles of Neurosurgery*. New York: Elsevier Mosby, 2005:603–20.)

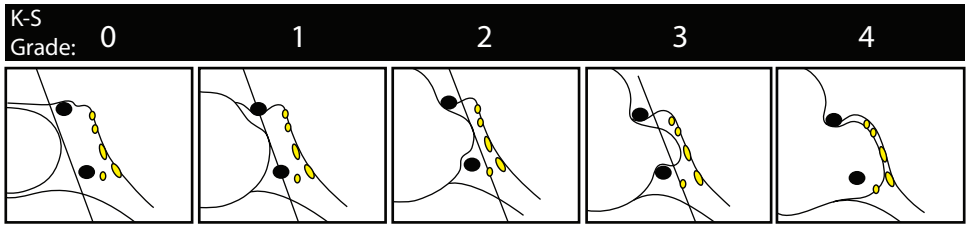


Figure 2.2 Knosp-Steiner classification scheme: Grade 0, no invasion, the lesion does not reach the medical aspect of the CCA; Grade 1, invasion extending to, but not past, the intercarotid line; Grade 2, invassion extending to, but not past, the lateral aspect of the CCA; Grade 3, invasion past the lateral aspect of the CCA but not completely filling the CS; and Grade 4, completely filling the CS both medial and lateral to the CCA. (Adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: *Neurosurgery.* Knosp et al.: Pituitary adenomas with invasion of the cavernous sinus space: a magnetic resonance imaging classification compared with surgical findings. *Neurosurgery* 33(4):610–618, copyright 1993.)

administration, leaving the adenoma hypointense compared with the surrounding pituitary (Figures 2.3 through 2.5). If the study is performed more than 5 minutes after contrast administration, the tumor will appear enhanced while the normal gland will appear unenhanced. It is therefore necessary that the neuroradiologist indicate the timing of the study in relation to contrast enhancement. Findings on high-resolution MRI studies are highly sensitive, with a 60%–70% sensitivity on unenhanced studies and increasing by 10% on postcontrast studies. CT scans are helpful in evaluating bony changes in the sella and surrounding structures, but they are much less sensitive than MRI in detecting small adenomas [9–12]. All patients with pituitary adenomas ought to undergo detailed visual field testing; however, this is most important in those patients with macroadenomas.

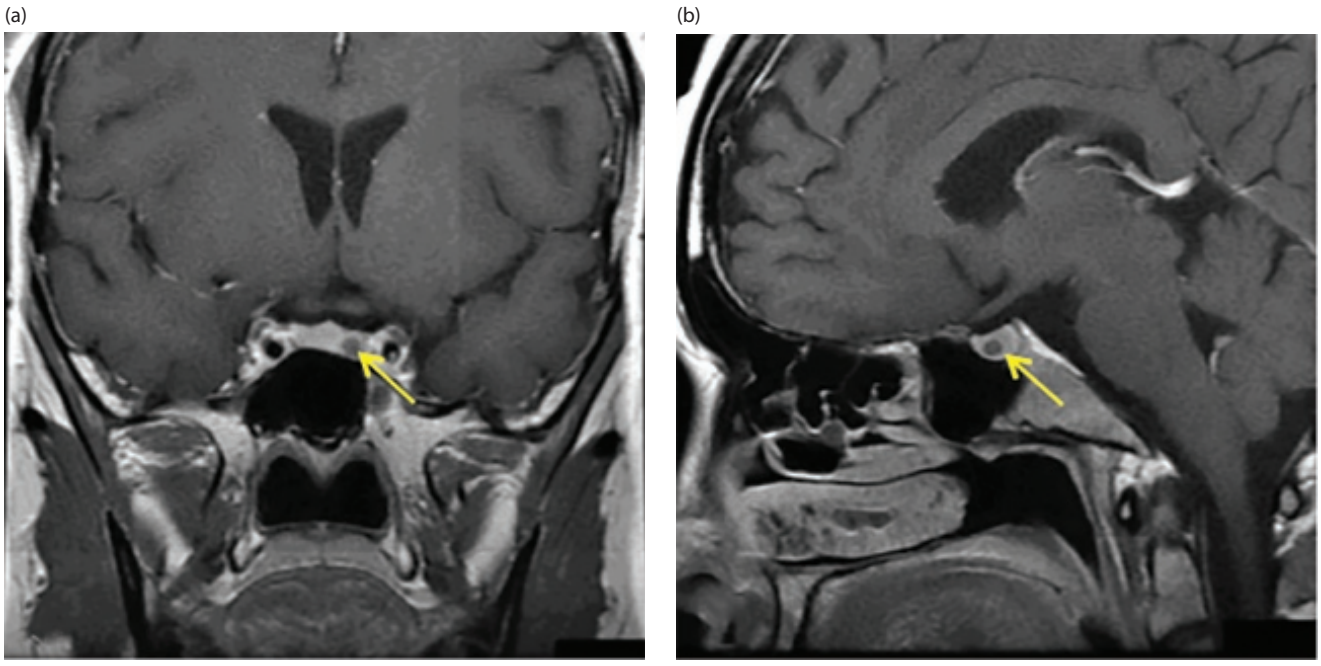


Figure 2.3 Coronal **(a)** and sagittal **(b)** post contrast MRI showing a non-functioning microadenoma.

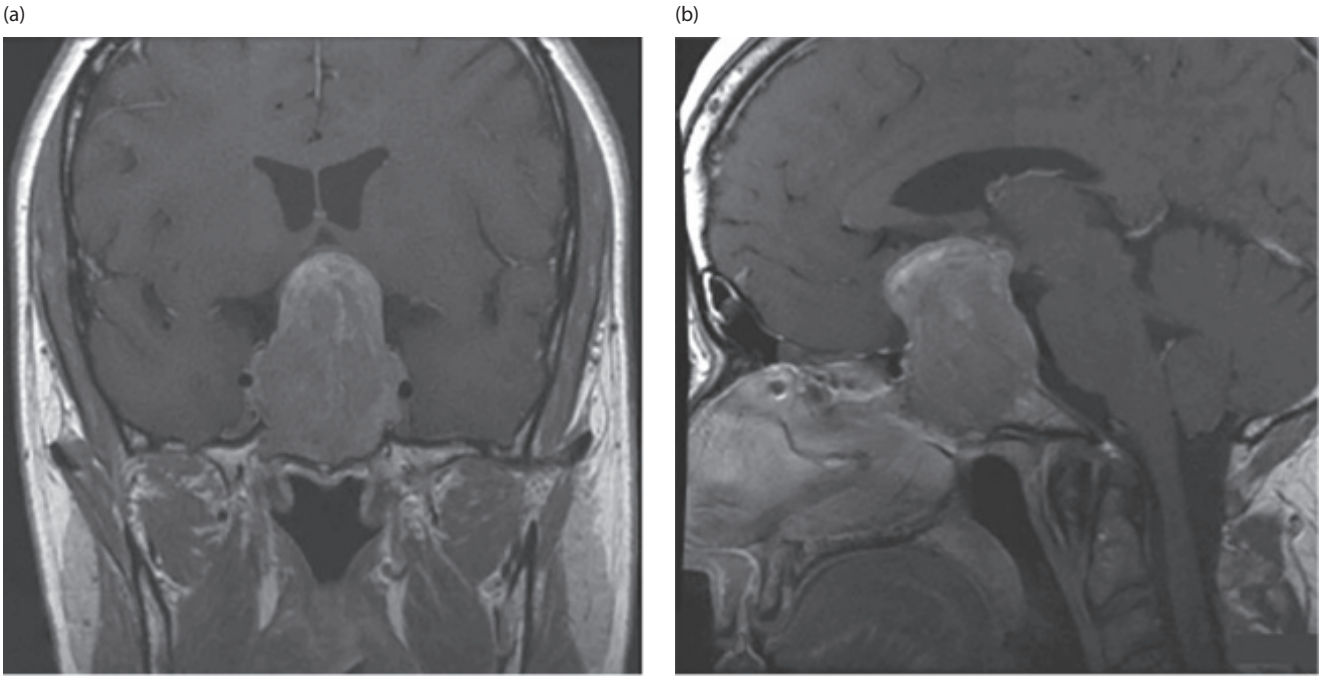


Figure 2.4 Coronal **(a)** and sagittal **(b)** post contrast MRI showing a large sellar–suprasellar non-functioning pituitary adenoma that is abutting both the right and left cavernous sinus.

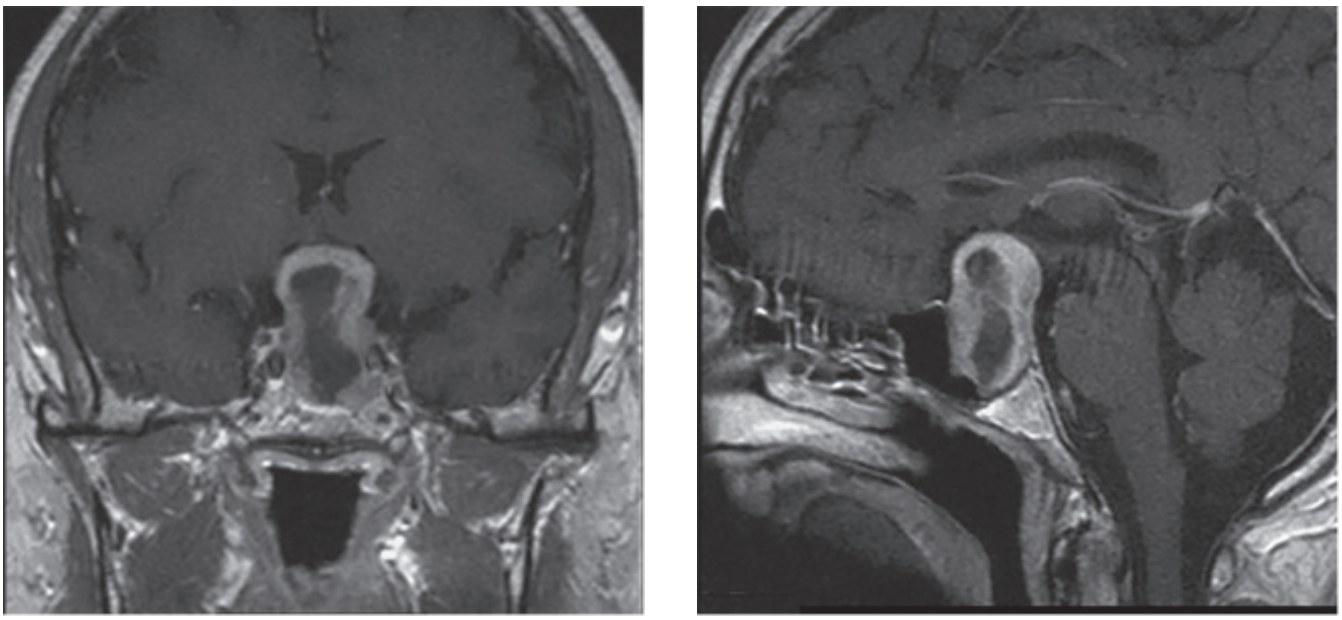


Figure 2.5 Coronal **(a)** and sagittal **(b)** post contrast MRI showing a large sellar–suprasellar non-functioning pituitary adenoma that has a solid and cystic portion.

## PITUITARY TUMORS AND NEUROSURGERY

### Prolactin-secreting adenomas

Prolactin-secreting pituitary adenomas are the most common form of pituitary tumor and represent the most common cause of hyperprolactinemia. Prolactin is classified as a somatomammotropic hormone along with GH and chorionic somatomammotropin [13]. It is a peptide chain that is 198 amino acids long, necessary for the normal lactation in postpartum women. Prolactin levels begin to rise shortly after conception and reach levels of 150–200 ng/mL at term; however, it is not until the postpartum decline in estrogen is complete that lactation may occur. Stimulation of tactile receptors on the nipple and areola of the breast leads to prolactin secretion that in the postpartum estrogen-primed breast results in lactation. Hyperprolactinemia disrupts normal reproductive function by altering the pulsatile gonadotropin secretion, interfering with sex steroid feedback at the level of the hypothalamus, and inhibiting gonadal steroidogenesis. TRH and vasoactive intestinal peptide (VIP) both appear to have minor prolactin-releasing activity, although their significance is presently unclear. Although the above stimuli lead to increases in prolactin secretion, the overwhelming control of prolactin release is inhibitory in nature, via dopamine. Dopamine, also known as a PIF, is released by the hypothalamus and leads to a decrease in prolactin secretion. As mentioned earlier, this inhibitory control becomes vitally important in the medical management of prolactinomas [14,15]. Normal prolactin levels are less than 15 ng/mL in men and less than 20 ng/mL in nonpregnant women. Causes of hyperprolactinemia other than a pituitary adenoma include pregnancy, stress, hypoglycemia, renal failure, hypothyroidism, and phenothiazine-like medications. These, as well as several other etiologies, must be considered prior to a detailed investigation of a patient's pituitary gland [16].

#### SIGNS AND SYMPTOMS

Prolactin-secreting tumors represent 40% of all pituitary adenomas and are typically more symptomatic in women. Hyperprolactinemia in women leads to amenorrhea, galactorrhea, and osteoporosis, while in men it may result in diminished sexual drive and impotence, or it may be asymptomatic. The menstrual disturbances are present in 93% of premenopausal women with prolactinomas. Because of this difference, men are not usually diagnosed until the tumor has reached a size sufficient to cause compressive effects on neighboring structures [17].

#### DIAGNOSIS

Random measurements of the serum prolactin level are reliable to establish the diagnosis of hyperprolactinemia. In the absence of the other above-mentioned disorders, investigation of the pituitary gland is necessary. This should begin with an MRI with contrast, which often discloses a pituitary macroadenoma. Hyperprolactinemia in the presence of a macroadenoma does not mean *a priori* that the tumor is a prolactinoma. The degree of prolactin elevation is believed to be directly related to the functionality of the tumor. Serum prolactin levels greater than 250 ng/mL correlate well with the presence of a prolactinoma; however, milder elevations may be due to stalk compression leading to interference with the inhibitory effects of dopamine [18].

## TREATMENT

The dopamine agonists bromocriptine and cabergoline have fundamentally changed the treatment of symptomatic prolactinomas [19–33]. Other than selected indications, dopamine agonist therapy has virtually replaced trans-sphenoidal resection as the therapy of choice. They directly stimulate the dopamine receptors located on lactotrophs (prolactin-secreting cells). Response to medical therapy can be dramatic. Prolactin levels begin to decrease in a matter of hours following the first dose, and tumor size often diminishes within a few days. Patients with visual field deficits may begin to improve after a few days of treatment. Other than a rapidly deteriorating visual or neurological function, there are virtually no contraindications to an initial trial of dopamine agonist therapy. Follow-up with periodic serum prolactin measurements and imaging studies of the sella is necessary to ensure that therapy is effective. In approximately 66% of patients, tumor size will be reduced by as much as 75%, with the best response seen in patients with large tumors [22] (Figure 2.6). Endocrine

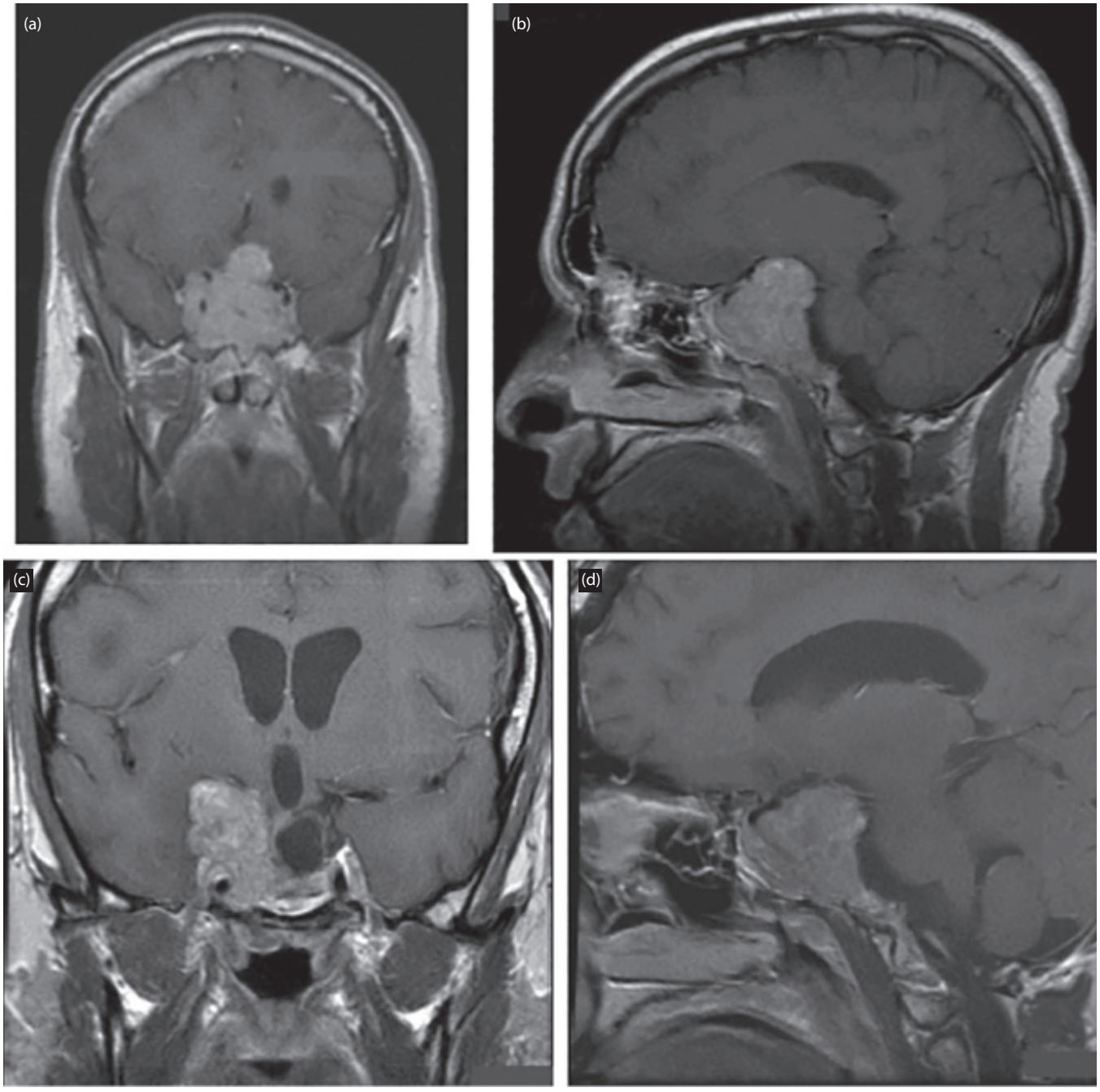


Figure 2.6 Coronal **(a)** and sagittal **(b)** post contrast MRI showing a large sellar–suprasellar prolactinoma pre medical therapy and coronal **(c)** and sagittal **(d)** post contrast MRI 3 months after initiating medical therapy with significant decrease in left side of the tumor.

functions often return to normal with establishment of cyclic menses in women and return of libido in men. Many previously infertile women have, in fact, been able to conceive while on bromocriptine therapy. The side effects, if present, usually consist of nausea, vomiting, headache, and dizziness, which do not occur as frequently with cabergoline therapy [34]. There are no known teratogenic effects from dopamine agonists, and they are therefore safe during pregnancy [35]. Women with tumors larger than 12 mm who wish to conceive either must remain on the medication or are referred for surgery prior to pregnancy to avoid the pregnancy-induced enlargement of the tumor and its secondary neurological symptoms. For women with tumors less than 12 mm, there is a less than 1% risk of neurological dysfunction [36]. A recently published systematic review has shown that cabergoline carries fewer side effects and is more effective in normalizing serum prolactin levels, thereby surpassing bromocriptine as the first choice in treatment of prolactinomas [34,37].

Since dopamine agonists are not tumoricidal, it is said that tumor re-expansion will occur when therapy is stopped [38]. There is, however, a subset of patients in which neither discontinuation of therapy nor microdosage leads to a return of symptoms [22,39]. Since there is no way of knowing which patients will have a continued need for medical therapy, it is prudent to stop therapy every few years and determine if there is a current need for treatment [40]. There now exists newer nonergot dopamine agonists, such as CV 502-205, which has shown promise in a once-daily administration.

The indications for surgery in patients with prolactinomas are for those who either are completely intolerant or show minimal response to medical therapy, as well as for patients with a severe or worsening visual field deficit. Surgery is also recommended for those patients who do not show a response after 3 months of medical therapy [41], those who desire pregnancy and prefer not to continue medication, and those on certain psychotropic medications where dopaminergic drugs are contraindicated.

The role of radiation therapy in prolactinomas is limited. Primary radiation therapy is reserved for elderly or debilitated patients who have large tumors and who are not helped by medical therapy. Radiation therapy is mostly used as an adjunctive to surgery in those patients with residual tumor who are unresponsive to medical therapy.

The role of pretreatment with bromocriptine prior to surgery to "shrink" the tumor has been suggested to increase the cure rate [42,43]. Since long-term treatment with bromocriptine has been associated with tumor fibrosis, if surgery is indicated, it is best performed within a year of therapy [44,45].

There exists a subset of patients with so-called asymptomatic microprolactinomas whose tumor size and serum prolactin levels remain unchanged or even decrease over many years in follow-up. For this population, regular surveillance without treatment may be sufficient [46,47]. It still remains to be determined whether there are any beneficial effects to normalizing prolactin levels in this population [48,49]. However, if hyperprolactinemia leads to amenorrhea, treatment is advised even if pregnancy is no longer a concern to prevent osteoporosis.

## Growth hormone-secreting adenomas (acromegaly)

Acromegaly or gigantism results from the hypersecretion of GH. The term *acromegaly*, derived from the Greek *akron* (extremity) and *megale* (large), describes only one aspect of the clinical features of the disease process. Harvey Cushing is credited with relating the overproduction of GH from a pituitary source [50]. GH is a polypeptide, 191 amino acids long, normally produced and released by the somatotropic cells found in the anterior pituitary in response to hypothalamic GH-releasing factor (GRF) [51]. Somatostatin is a 14-amino acid cyclic peptide-releasing factor that inhibits GH release [52]. Three or four bursts of GH secretions occur per day, punctuating a basal state of minimal activity [53]. Sleep, physical exertion or stress, hyper- and hypoglycemia, and a variety of pharmacologic agents can also precipitate GH release. Circulating GH results in the secretion from the liver of a family of peptides called somatomedins. Somatomedin-C (insulin-like growth factor 1 [IGF-1]) is the most familiar somatomedin measured. These secondary hormones, in turn, produce a variety of anabolic effects throughout the body and mediate the effects of GH at the end-organ level. Unlike GH, the somatomedins do not exhibit significant diurnal variation in serum levels, and therefore may be a better means of evaluating patients [54].

Hypersecretion of GH can result from a number of conditions. The most common, and the focus of this section, is a pituitary adenoma. GH may also be produced by ectopic adenomas derived from remnants of the embryonic pituitary diverticulum or from tumors of the breast, lung, or ovary [55]. Acromegaly may rarely be caused be excessive production of GRF by a hypothalamic tumor or from peripheral sources, such as carcinoid tumors of the abdomen [56].

### SIGNS AND SYMPTOMS

Acromegaly affects males and females equally in the fifth decade [57]. The effects of chronically elevated GH are gradual and will result in gigantism in a child whose epiphyseal plates have not yet closed or in classic acromegalic features in an adult. Typically, there is an insidious coarsening of the facial features and an increase in the soft tissues. A significant number of patients present not because of somatic disturbances, but because of local compressive effects of the pituitary tumor. The somatic changes may be so insidious as to go unnoticed until old photographs are used for comparison. Classically, patients first note an increase in shoe size or an inability to wear rings that previously fit well. Later in the disease process, patients may develop visceromegaly, arthralgias, nerve entrapment syndromes, hyperhydrosis, prognathism, and acrochordon (skin tags) (Figure 2.7).

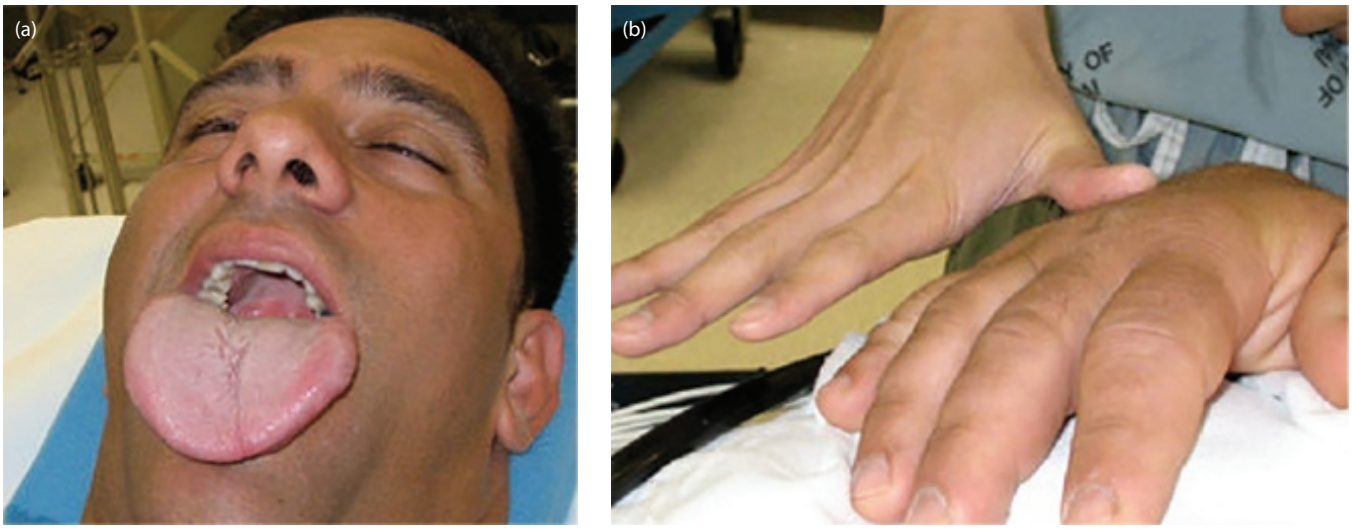


Figure 2.7 Patient demonstrating acromegalic features with soft tissue swelling causing **(a)** enlargement of the nose, macroglossia and **(b)** enlargement of hands compared to a healthy adult female hand.

The development of skin tags is interesting and deserves some comment because of its relationship to potentially malignant colonic polyps. It has been noted in several studies that as many as 46% of patients will have colonic polyps, of which more than 50% are adenomatous [58]. Some studies have also shown that the incidence of true colon carcinoma in acromegalics may be higher than in the general population. Because of this relationship, it has been recommended that acromegalic patients older than 50 years, patients with more than a 10-year history of acromegaly, or patients with more than three skin tags should have careful screening for colonic disease [59].

## DIAGNOSIS

The laboratory diagnosis of acromegaly is hampered by the normally wide daily variations in serum GH levels. In fact, the daily bursts of secretion are maintained even in the presence of oversecretion of GH from an adenoma. Unlike the other secretory adenomas, static measurements of serum GH are therefore unreliable in establishing the diagnosis of acromegaly. Normal basal GH levels are generally below 1 ng/mL, with several secretory bursts seen throughout the day [60]. In acromegaly, the basal level is often elevated to levels above 5 ng/mL, although some patients may have normal basal levels with elevations only during the daily secretory burst.

Fortunately, IGF-1 (somatomedin-C) levels not only are even throughout the day, but also are consistently elevated in acromegaly. Static measurements of IGF-1 are an effective and reliable method for confirming the diagnosis of acromegaly [61,62]. Additionally, a glucose tolerance test can be performed. Normally, GH is suppressed to levels below 1 ng/mL 2 hours after an oral glucose load (75 g). Failure of this normal suppression is consistent with hypersecretion of GH. In addition, infusions of either GRF or TRH will lead to increased GH in affected individuals but not in normal subjects.

Once a patient is confirmed as having a hypersecretory state, the goal is to discover the source. The overwhelming majority of patients will have an anterior pituitary adenoma, and therefore the radiographic workup should begin with a contrast MRI. Only in the few cases where no pituitary mass is demonstrated should a search be made for ectopic sources of GH. When discovered on MRI, about 25% are microadenomas and 75% are macroadenomas. In studies done by our team, the typical latency of diagnosis can be 8 years.

## TREATMENT

The effects of untreated acromegaly can eventually be fatal. Patients will develop cardiac failure, diabetes, disfigurement, and possibly blindness, leading to a markedly shortened life expectancy [63]. The goal of treatment, therefore, is the safe and rapid reduction of GH levels, elimination of any mass effect, and preservation of normal hormonal balance. The type of treatment must be judged by its ability to normalize GH levels and thereby to eliminate the development of the various metabolic derangements associated with hypersecretory states. The criteria for successful treatment of acromegaly are controversial. The accepted postoperative levels of GH that are indicative of a remission have declined in recent years. The current standard for clinical remission is a postoperative GH level of <1 ng/mL with a normal IGF-1 level [64]. GH levels may return to normal in hours or days, but it has been our experience that IGF-1 levels may take weeks or months to normalize. Also, a return to normal oral glucose tolerance test (OGTT) is required. Postoperative adjuvant therapy should be reserved for patients that do not meet these criteria.

Trans-sphenoidal resection remains the primary treatment modality for acromegaly. Successful resection results in a rapid reduction in GH levels, and can be achieved with very low morbidity and mortality, even in older patients [4,65–70]. In addition, the preservation of pituitary function

has been reported to be as high as 95%, avoiding the need for lifelong hormone replacement. For larger tumors not amenable to curative resection, surgery still plays a significant role in reducing tumor load prior to any adjuvant therapy.

While trans-sphenoidal resection of pituitary adenomas is a safe and well-tolerated procedure, there are still many patients who are not surgical candidates. In those cases, medical therapy and radiotherapy have therapeutic importance. The medical treatment of acromegalics has undergone considerable change in the past 10–15 years. Medical therapy that included estrogens, chlorpromazine, and antiserotonergic agents, had met with only limited success. Bromocriptine therapy, then used for its dopaminergic effects, was able to reduce GH levels to 5–10 ng/mL in more than 20% of patients [71–75]. Cabergoline may be far more effective, as it has been shown to achieve hormonal control in 15%–40% of patients [34,76,77]. Most patients did achieve some relief of their somatic symptomatology, with reduced soft tissue swelling and decreased perspiration, even though GH levels were still elevated. The dosages necessary to achieve these effects are much higher than the dosages needed to control a prolactinoma, and the consequent incidence of side effects and drug intolerance is much higher.

Since somatostatin naturally suppresses GH production, the ideal medication would be somatostatin; however, this would require multiple administrations each day for life because of somatostain's short half-life (2 minutes). A somatostatin analogue named octreotide has a longer half-life and has been shown to be very effective [78–86]. It must be administered three times each day as a subcutaneous injection or as a continuous subcutaneous infusion. The most common side effects reported include diarrhea and cholelithiasis [87], and the incidence of these side effects increases the longer the drug is administered. Some recent studies have shown dramatic reductions in GH levels and moderate tumor shrinkage. The perioperative period may be significantly improved by using octreotide for 3–4 months preoperatively. The soft tissue changes in the tongue and throat may lessen the risks of anesthesia. Long-acting Sandostatin analogs are used now far more effectively, administered by deep intramuscular injection once each month. A long-term study spanning 9 years demonstrated that approximately 70% of patients treated with long-acting octreotide had normal IGF-1 levels and GH levels of <2.5 μg/L [88]. Moreover, a multicenter trial investigating the effect of long-acting lanreotide demonstrated a 62.9% rate of clinically significant tumor volume reduction (≥20%) with significant improvements in GH and IGF-1 levels, as well as quality of life [89]. Additionally, a study comparing pasireotide, a multi-receptor-targeted somatostatin analogue, and octreotide demonstrated greater biochemical control (GH < 2.5 μg/L and normal IGF-1) with pasireotide [90]. Recently, GH receptor antagonists such as pegvisomant (Somavert) given 15–20 mg daily have been shown to reduce production of IGF-1, with normalization of values in up to 63% of patients, with up to 90% radiographic stability or decrease in size of tumors after treatment, thereby halting the symptoms of acromegaly. In addition, it has a high safety profile with a reported low incidence of tumor size increase, elevated liver enzymes, and injection site reactions seen [91,92].

The only other treatment option for patients is radiation therapy. Not only is this treatment fraught with difficulties, but it has not been shown to be uniformly effective [93]. Many patients will have persistently elevated GH levels for years following radiation therapy and may never reach normal levels, resulting in delayed or incomplete remission [94]. There is an approximate 60%–65% remission rate (IGF-1 normalization) with radiotherapy, combined with a 30%–35% pituitary hormone deficiency rate, and therefore, it should only be employed in postsurgical patients not tolerating medical therapy or in patients with recurrent, aggressive tumors [34,95]. The longer the follow-up, the higher the rate of recurrence and hypopituitarism.

## Glycoprotein-secreting adenomas (TSH, FSH, LH)

The glycoprotein hormones produced in the mammalian pituitary gland are TSH, LH, and FSH. Although these hormones are clearly related structurally, their roles are markedly different. TSH, as its name implies, regulates the metabolic rate via thyroid hormones, while the gonadotropic hormones LH and FSH are responsible for sexual maturation and play pivotal roles in reproduction. Structurally, all three are composed of a common alpha-subunit bonded to a beta-subunit that is unique to each hormone.

A number of laboratory advances have changed our understanding of glycoprotein-secreting adenomas. Two in particular were the development of specific immunohistochemical techniques for looking at tumor specimens and the improved techniques of measuring hormone and subunit levels *in vivo*. It has always been taught that glycoprotein-secreting adenomas represent a very small percentage of all pituitary tumors (approximately 1%). These improved techniques are revealing that many so-called "nonfunctioning" adenomas have evidence of glycoprotein production by immunohistochemical staining and serum radioimmunoassay techniques.

### SIGNS AND SYMPTOMS

Except for TSH-secreting tumors, which may present as hyperthyroidism, the glycoprotein-secreting adenomas do not produce any specific clinical syndrome. Consequentially, these adenomas are not diagnosed until they produce compressive effects with visual change or hypopituitarism. This unfortunately means that many of these tumors will grow to a size and extent that precludes any curative resection.

Hyperthyroidism caused by a TSH adenoma differs significantly from Graves' disease, for which it is very often mistaken [96,97]. The typical features of Graves' disease, including ophthalmopathy, pretibial edema, female preponderance, and serum thyroid-stimulating immunoglobin,

are lacking in hyperthyroidism of pituitary origin. While these differences are not usually enough to make a clear distinction, they should raise questions as to the accuracy of the diagnosis of Graves' disease. Of note is a rare inherited disorder (autosomal dominant) designated as "selective pituitary resistance to thyroid hormone," in which the normal feedback effect of thyroid hormone upon TSH secretion is defective. This leads to TSH hypersecretion and continued production of active thyroid hormone, resulting in clinical hyperthyroidism. The TSH levels increase with TRH simulation, and this disorder is often associated with deaf–mutism, stippled epiphyses, and goiter, distinguishing it from a pituitary adenoma.

### DIAGNOSIS

As mentioned above, these tumors do not typically present with symptoms of hormone hypersecretion. As a result, the determination that a pituitary tumor is secreting one of the glycoproteins is usually made after the tumor itself is discovered. Each of the hormones is composed of an alpha and beta subunit. Although the alpha-subunit is the same for all three hormones, the beta-subunit is specific to each type. We are currently only able to measure serum intact hormone levels (alpha + beta), or alpha-subunit levels alone. The measurement of beta-subunit levels is possible, but is only available in some research laboratories. We have learned that not all patients will have an elevated intact hormone level, and some may in fact have low intact hormone levels with evidence of hormone production seen on pathologic examinations [98]. Fortunately, alpha-subunit levels are elevated consistently in these tumors, decrease after successful treatment, and rise with tumor recurrence, although 22% of truly nonfunctional adenomas will have an associated alpha-subunit association [99,100]. Even with this small false-positive rate, alpha-subunit measurements serve as reliable guides to tumor therapy and recurrence. Ultrasensitive assays for TSH measurement have led to faster discoveries of hyperthyroid states with inappropriate TSH secretion, thereby lending a clue to investigate for a potential TSHoma [101].

As with all other pituitary adenomas, MRI with contrast has replaced all other imaging modalities for evaluation of tumor anatomy. Specific to glycoprotein-secreting adenomas is the tendency to be larger and involve adjacent structures more often [102]. Aside from this, there is no way to distinguish these adenomas from any other pituitary adenoma based on radiographic studies alone.

### TREATMENT

The treatment of patients with glycoprotein-secreting adeomas is often difficult. Because of the delay in clinical presentation, these tumors usually have suprasellar extension and involvement of the cavernous sinuses, lowering the chances for a surgical cure. Trans-sphenoidal resection is necessary for tissue diagnosis as well as decompression of the optic chiasm. Most patients have adequate symptomatic relief postoperatively; however, surgery is very often combined with radiotherapy or adjuvant medical therapy. Since the response of the tumor to radiation has not been impressive, the indications for it remain controversial [103]. Trials with a somatostatin analogue and bromocritpine in the treatment of these tumors have met with some success, but not as much as in the treatment of acromegaly and prolactinomas, respectively [104]. At our institution, these patients are managed with trans-sphenoidal adenomectomy, followed by radiation therapy if residual tumor is seen on postoperative scans and enlarges on follow-up. If the postoperative studies suggest a "cure," they are repeated every 12 months. A recent study of 70 patients demonstrated a 75% rate of normalized thyroid function, with an approximate 60% rate of normalized pituitary imaging and hormone profile. In those patients in whom surgery was unsuccessful, radiotherapy and somatostatin analogues were used to control hyperthyroidism and tumor growth [101].

## ACTH-secreting adenomas (Cushing's disease)

Cushing's syndrome was first described by Harvey Cushing in 1912. Cushing's syndrome is a condition of hypercortisolemia from any source, while the term *Cushing's disease* refers exclusively to an ACTH-secreting pituitary adenoma. Cushing's disease, more than any other pituitary tumor, remains the most diagnostically and therapeutically challenging. Hypercortisolemia can cause a myriad of clinically significant problems. In general, patients tend to feel poorly and have diffuse muscle weakness and pain, emotional lability, and profound fatigue. The presence of cortisol-induced or accelerated atherosclerosis, hypertension, diabetes, osteoporosis, obesity, susceptibility to infections, and perhaps peptic ulcer disease and thrombosis provides compelling evidence to identify the diagnosis.

The usefulness of standard radiologic imaging in Cushing's disease has been either negative or nonspecifically (thereby misleadingly) positive [105–113]. More recent advances in high-resolution 3 T MRI with contrast may change this [114,115].

Most cases of hypercortisolemia seen in the adult population are caused by microadenomas of the anterior pituitary gland [116]. Other sources that are less common include ectopic overproduction of ACTH [117,118] or corticotropin-releasing hormone (CRH) [119,120]; benign or malignant adrenal tumors; iatrogenic or exogenous hypercortisolemia; and alcoholic, depressive, or obese "pseudo-Cushing's" states. The presence of neural tissue within an adenoma and either a distinct adenoma or diffuse or nodular hyperplasia may support the concept that pituitary Cushing's disease is actually a heterogeneous disorder [112,121].

The implications of this pathological finding are important in the clinical management. Primary pituitary Cushing's (with a single adenoma) might be curable by selective adenomectomy. Hyperplasia (perhaps from central overstimulation of the pituitary) might best be treated by complete hypophysectomy or medication aimed at modulating that stimulation [122]. Intermediate-lobe Cushing's,

on the other hand, may be responsive to bromocriptine or pasireotide, a medication that normally has no effect in other types of Cushing's [123].

## SIGNS AND SYMPTOMS

There is a female preponderance with a median age of approximately 40 years. All patients present clinically with varying degrees of hypercortisolemia. Typically, patients will have truncal obesity, hypertension, easy bruisability, abdominal striae, and plethoric or moon facies. Because of this impressive clinical picture, patients generally present early in terms of tumor growth, making detection and identification of a source challenging (Figure 2.8).

## DIAGNOSIS

The diagnosis of Cushing's disease is linked to the complex endocrine pathway involved with ACTH action. ACTH, stimulated by CRH, increases the production and secretion of cortisol from the adrenal cortex. There is a normal diurnal pattern to cortisol release, with the highest level seen in the morning and lowest seen in the evening. Cortisol negatively feeds back to reduce ACTH secretion. Circulating levels of cortisol or its urinary metabolites are used for diagnosis.

While Cushing's syndrome is easy to recognize clinically, its etiology is difficult to determine. Various diagnostic protocols have been developed; however, no main paradigm has emerged [116,117,124–137]. Measurements of midnight salivary cortisol, plasma, and urinary cortisol and its derivatives, basally and in response to dexamethasone or metyrapone, as well as determination of plasma ACTH, may suggest a primary adrenal, pituitary, or ectopic neoplastic source of disease [132,138,139]. If these data are equivocal, CRH measurements [119,120,128,140] and CRH stimulation testing with measurement of ACTH or cortisol [115,125,126,130,131,136], peripherally or in the bilateral venous effluent from the petrosal sinuses [129,133,135,137], are now frequently employed to provide additional biochemical evidence for the diagnosis of Cushing's disease in the clear state of hypercortisolemia.

Once it has been determined that a patient has a pituitary source of ACTH hypersecretion (Cushing's disease), it can be extremely difficult to identify the pituitary source. Since most ACTH-producing adenomas are small, their radiographic detection is difficult at best. Improvements in MRI with contrast have identified many microadenomas that would be radiographically invisible. Because many cases have no evidence of tumor on MRI, the technique of petrosal sinus sampling has been developed to confirm the diagnosis and guide the surgical resection (Figures 2.9 through 2.11). The rationale behind this technique, described in detail elsewhere, is straightforward [135]. Patients with Cushing's disease should have high (or inappropriately high) levels of ACTH production coming directly from the pituitary gland [129], and the levels may lateralize [135–137] to the side containing the adenoma. Comparison of pituitary to peripheral ACTH levels should demonstrate a gradient.

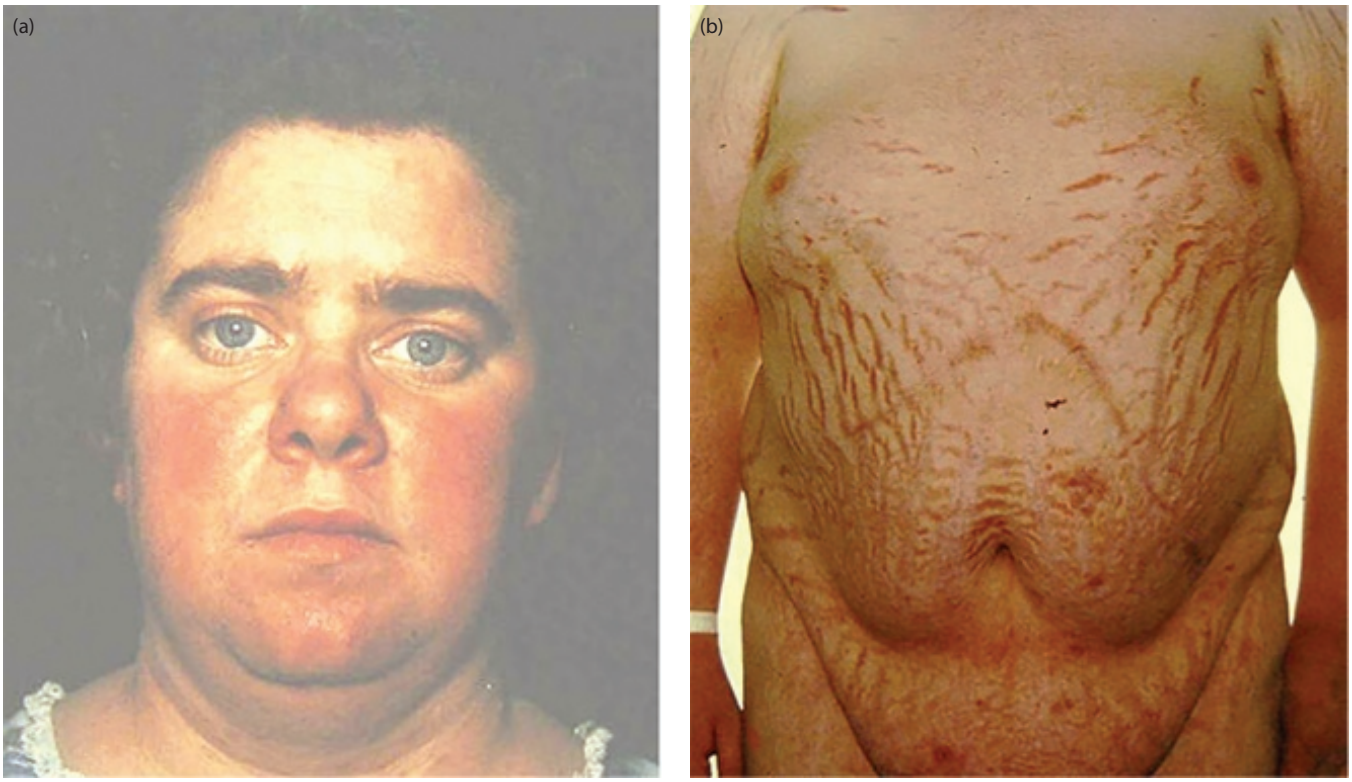


Figure 2.8 Patient demonstrating cushingoid changes with facial fullness **(a)** and central obesity along with atrophic red striae **(b)**.

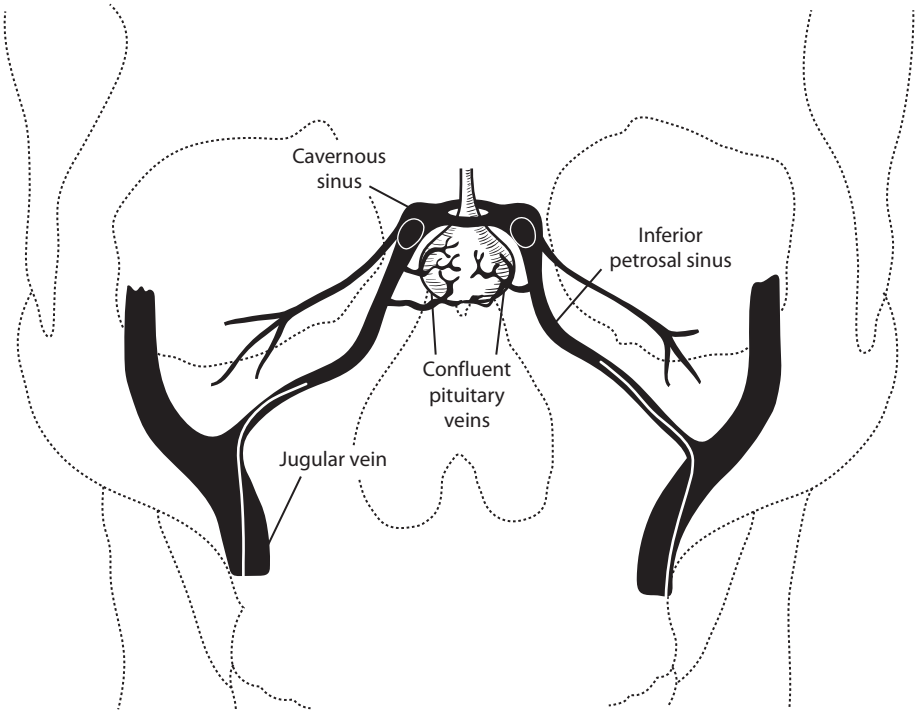


Figure 2.9 Catheter placement for bilateral simultaneous blood sampling of the inferior petrosal sinuses. Confluent pituitary veins empty laterally into the cavernous sinuses, which drain into the inferior petrosal sinuses. (Adapted from Oldfield EH et al. *N Engl J Med* 1985;312:101.)

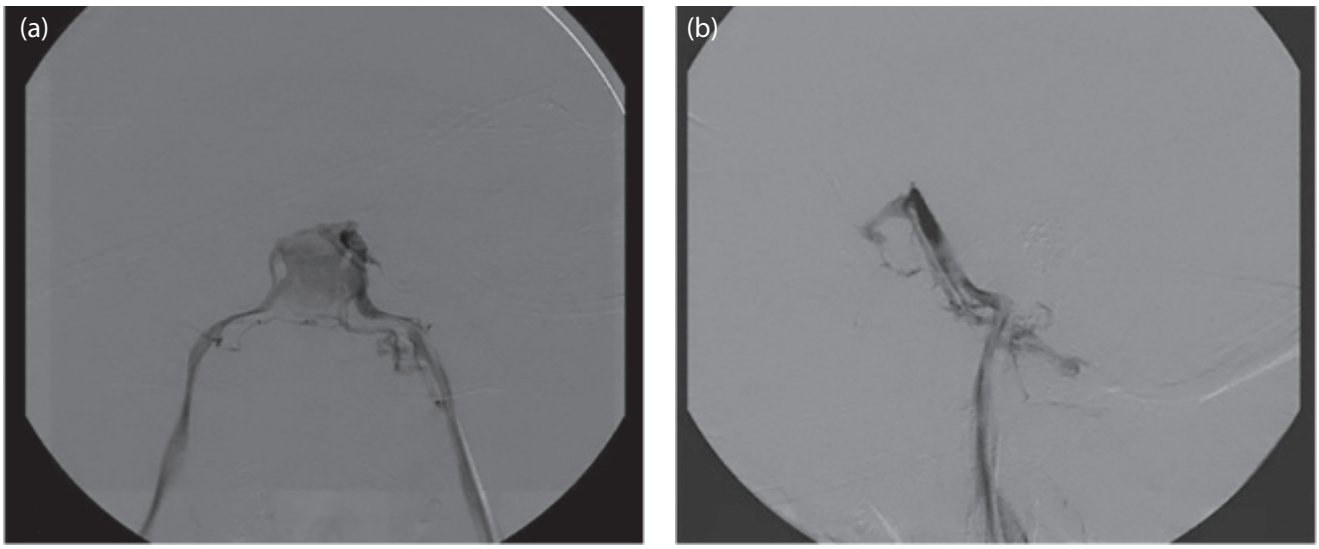


Figure 2.10 Angiogram of bilateral inferior petrosal sinus AP **(a)** and lateral **(b)** view venogram.

Those with ectopic ACTH secretion whose pituitary glands are suppressed should have neither an elevated pituitary-to-peripheral gradient nor a difference between sides. Patients without a discrete pituitary tumor (i.e., with hyperplasia of the corticotrophs) may have an increased central level of ACTH that is equal in blood from both sides of the gland. Some have advocated petrosal sinus sampling in all patients with ACTH-dependent disease, either to supplement or to supplant the conventional methods for establishing the etiology of the hypercortisolism [125,133,138]. Published series indicate that the usefulness and reliability of this technique may be variable.

In Mampalam et al.'s series [111], 39 of 116 subjects (34%) had selective venous sampling of ACTH. A gradient of inferior petrosal sinus to peripheral was seen in 36. Of these 36, 31 (86%) were found to have adenomas. In three patients without a significant gradient, two had adenomas. Nine percent had false localization as to the site

Inferior petrosal sinus sampling with CRH stimulation

| | | ACTH (pg/mL) | | |
|---|---|---|---|---|
| | | Peripheral | Right IPS | Left IPS |
| Time (minutes) | 0 | 29 | 60 | 449 |
| | 2 | 30 | 323 | 5809 |
| | 5 | 56 | 992 | 8733 |
| | 10 | 119 | 305 | 4936 |
| | 15 | 130 | 947 | 3225 |

Figure 2.11 Positive IPSS results noting a greater than 2–3 fold step up from peripheral to central sampling. IPS, inferior petrosal sinus.

of the adenoma. In Ludecke's series [134], 6 of 19 (31%) had incorrect lateralization of the adenoma by inferior petrosal sinus sampling. Ludecke recommended intraoperative measurement of ACTH in the perpituitary blood as a means of lateralizing the adenoma. A recent series of 501 patients with confirmed ACTH adenomas underwent sampling, which demonstrated a 98% confirmation rate. Increased accuracy was seen with left-sided lateralization and consistent lateralization prior to and after CRH administration [141]. In our institution, we use the technique in the following situations:

1. Patients with clear hypercortisolemia but doubt exists as to the source of the ACTH overproduction with unhelpful radiographic studies.
2. Patients with laboratory data clearly pointing to the pituitary gland but with normal radiographic studies. A petrosal sinus-directed hemihypophysectomy is done if an adenoma is not seen at surgery.
3. Young patients, especially women, for whom preservation of fertility is an important consideration and whose radiological studies are not grossly abnormal. Even when the lab studies clearly indicate pituitary-dependent disease, we routinely study these patients to try to lateralize the tumor. If nothing is found at the time of surgery, hemihypophysectomy on the side with the higher CRH-stimulated ACTH levels would then be done. However, there is a 40% incidence of incorrect lateralization.
4. Patients who have not been cured following transsphenoidal surgery. In these patients, the question to be answered is whether the diagnosis of Cushing's disease was truly correct.

In the most skilled hands, this sampling of venous effluent from the petrosal sinuses appears to be reliable and safe, although there is a 1.5% incidence of complications, some of which can be very serious, such as posterior reversible encephalopathy syndrome (PRES) [142].

## TREATMENT

The treatment of Cushing's disease has advanced by the development of microsurgical transsphenoidal surgery. Successful surgery can cause reversal of hypercortisolism and eventual return of normal pituitary cortitroph function.

Most cases of Cushing's disease are caused by isolated adenomas of the anterior gland. The treatment of choice for Cushing's disease is transsphenoidal surgery with either selective adenomectomy or partial or hemihypophysectomy [108–112,143,144]. For those patients with very large tumors, surgery followed by conventional radiation therapy would be indicated and, very rarely, adrenalectomy. The surgical treatment paradigm remains controversial. The cure rate for this illness in all series remains under 90%. The surgical options for initial intervention include visual exploration of the gland, with removal of abnormal tissue [111], petrosal sinus-directed hemihypophysectomy [110], and total hypophysectomy [145]. Complications arise because incidental adenomas or small inhomogeneities in the gland are common, and the surgeon may be guided toward an abnormal part of the gland that is not responsible for the disease. Recurrence rates from 4% to 14% have been reported [108,110–112,144,146]. Many of these patients have been re-explored. According to Nakane et al. [112], verification of all pituitary adenomas was done by reoperation, during which time no corticotroph cell hyperplasia was found. It was concluded that late recurrence of Cushing's disease may follow adenomectomy due to regrowth of adenoma cells not removed from peritumoral tissue during the original surgery. The alternative explanation is that the primary etiology was not an isolated pituitary tumor but rather overstimulation; thus, as remaining pituitary tissue continues to be overstimulated, relapse is inevitable. In Friedman et al.'s study [147] of the efficacy of repeat surgery for recurrent Cushing's disease, the incidence of remission of hypercortisolism was highest if an adenoma was identified at surgery and the patient received selective adenomectomy.

Patients who are not cured by selective resection fall into several groups: (1) those with invasive adenomas, (2) those with unidentified microadenomas, (3) those with corticotroph hyperplasia without a discrete adenoma, and (4) those with ectopic secretion of ACTH or CRH. Those with lateral invasive extension will not be cured by any surgical procedure, and therefore hypophysectomy is not a consideration. Patients with microadenomas that are unidentified preoperatively are often cured by partial or total hypophysectomy; the microadenomas may be discovered within the excised tissue. If surgery has completely removed the tumor, the patient will be hypocorticsolemic for 6–12 months. Patients who are eucortisolemic immediately postoperatively have a high incidence of recurrence [148,149]. A study of 55 patients demonstrated that an ACTH level of >20 ng/L perioperatively is predictive of recurrence [150].

While transsphenoidal resection remains the primary procedure of choice, it does not obtain a 100% success rate. There are other treatment modalities available for use as adjuvants for those cases in which initial or repeat surgical therapy has failed.