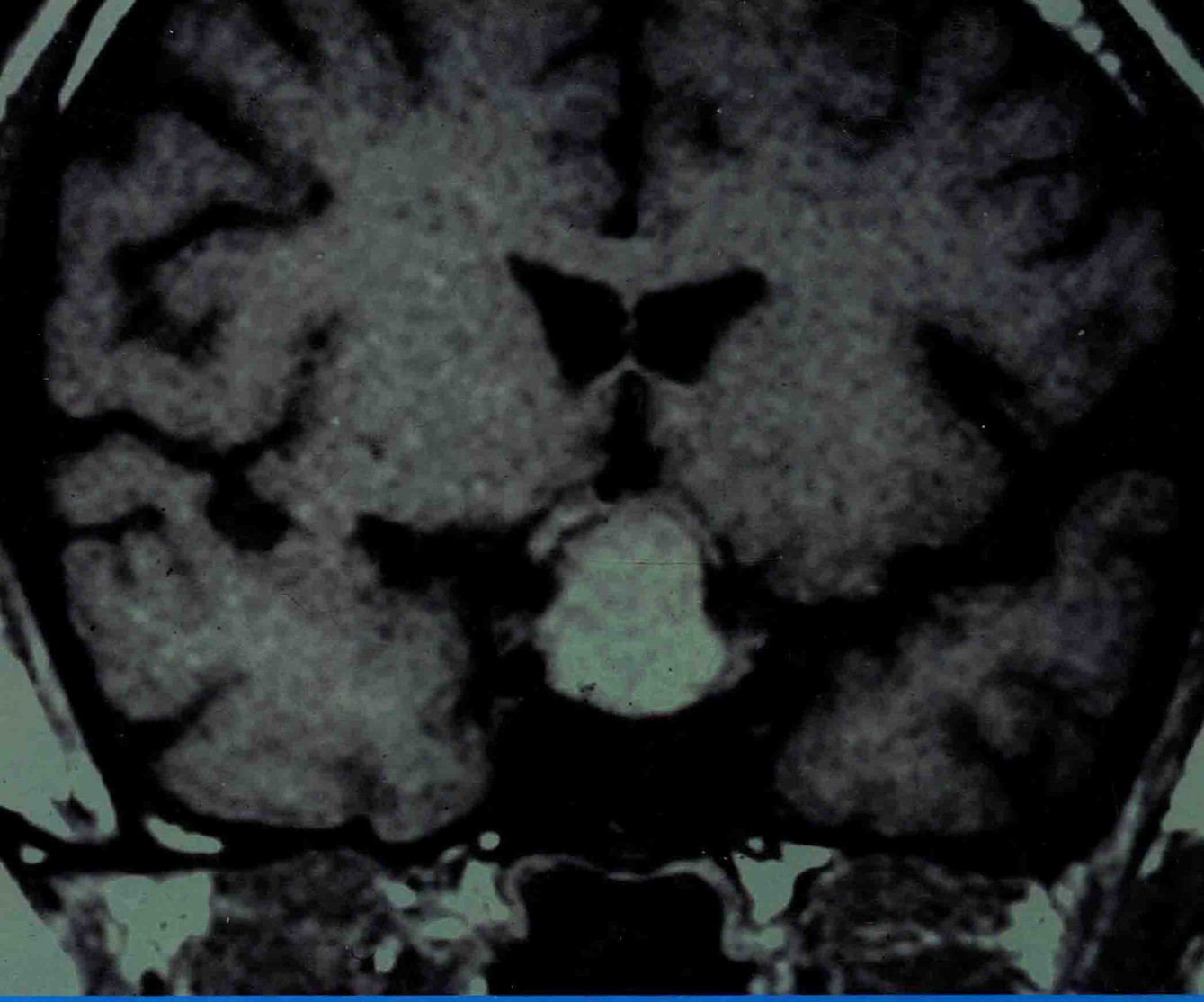

Endocrinology in Clinical Practice

Second Edition

Edited by
Philip E. Harris and
Pierre-Marc G. Bouloux

CRC Press
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Endocrinology in Clinical Practice

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Foreword by Dr. Ken Ho

Endocrinology is one of the most dynamic disciplines in biomedical science. It is among the most quantitative of the clinical specialties in which the marriage of basic and clinical sciences is very strong. The molecular revolution has led to an explosion of new information, bringing exciting insights and discoveries that have changed concepts of disease causation and treatment. How can all this information reach the practicing endocrinologist or trainee in a digestible form? What is required is a book that lays out the endocrine landscape, detailing where and how this is changing in ways that advance patient care.

It is this challenging confluence of research and patient care that has driven my work over 30 years as an endocrinologist and clinical scientist and now research director at a major teaching hospital in Australia, collaborating with likeminded colleagues internationally. My major area of interest is the neuroendocrine basis of metabolic disease with particular focus on the role of pituitary hormones.

I first met Philip and Pierre in London at the Clinical Endocrinology Trust Medallist of the British Endocrine Societies in 2000. We formed a strong bond through our shared fascination with, and commitment to, advancing the teaching, research, and management of endocrine disease. Philip and Pierre epitomize a rare breed: consultant endocrinologists with a passion to bring in advances to clinical practice. They are the beneficiaries of training at St. Bartholomew's Hospital, London, with Professor Michael Besser, and inspired by their mentor, they were drawn to neuroendocrinology, a field that demands a deep understanding of systems biology and its relevance to human disease. Together, they have made significant contributions: Philip in thyroid and pituitary disease, Pierre in reproductive endocrinology. Philip has carved a highly successful career for himself in the pharmaceutical industry while holding a consultant endocrinologist appointment at University Hospital Lewisham, London. As vice-president of Scientific Affairs at Ipsen, he provides strategic direction and opportunities in the development of new compounds, and he also takes collaborative opportunities to key opinion leaders at leading centers internationally. He brings an industry perspective to knowledge transfer in the advancement of patient care. Pierre, as Director of the Neuroendocrine Centre at the Royal Free Hospital, continues to advance research into the genetic basis of central hypogonadism. They both share a love of teaching and mentoring. Pierre brings in a particular brand of humor to teaching that is both memorable and highly engaging. Nothing stands clearer in my mind than the roars of laughter that interspersed a meet-the-professor delivery by Pierre at a 2007 meeting in Sao Paolo, Brazil. Together, they have assembled a distinguished authorship team from the United Kingdom, Europe, and the United States, the members of which, like themselves, are not only world leaders but also practicing endocrinologists.

In this second edition, Philip and Pierre have harnessed advances in clinical practice in a readable and succinct style by drawing on their considerable knowledge, experience, and network as leading consultant endocrinologists. This is a well-crafted compendium of practical information, invaluable for the clinical endocrine readership who will find relevant basic science covering the tenets of endocrine disease dovetailed to practical assessment, investigation, and management of the patient.

Buy it, read it, and keep it.

Ken Ho
Professor of Medicine, University of Queensland
Chair, Centres for Health Research, Princess Alexandra Hospital
Translation Research Institute, Brisbane, Australia
Past President, Growth Hormone Research Society
President, Pituitary Society

Preface

The objective of the first edition was to provide cutting-edge information on clinical practice for practicing endocrinologists and doctors training in endocrinology. The second edition retains this ethos, but it has been extensively updated and modified. Endocrinology is moving toward an increasingly personalized approach to patient management. This is reflected by the increased focus on mechanisms of disease and biomarkers.

Certain subjects, such as neuroendocrine disease (Chapter 1), take a more generalized approach to the field, before focusing on specific diseases. The chapter is supported by protocols for pituitary function testing in the appendix. Separate chapters have been assigned to pituitary radiotherapy and surgery. Other chapters are more specifically focused from the outset. There is a dedicated chapter for imaging, which has changed considerably in the past few years, particularly with the increasing use of positron emission tomography.

A major stride forward has been achieved in the field of pituitary disease with the identification of aryl hydrocarbon receptor–interacting protein mutations in a proportion of patients with familial isolated pituitary adenomas. Accordingly, there is a new chapter dedicated to this topic. Neuroendocrine tumors are included for the first time as a separate chapter, because the incidence of this disease is increasing rapidly, and endocrinologists frequently take a leading role in their management. Closely linked to neuroendocrine tumors, there is a new chapter on hereditary primary hyperparathyroidism and multiple endocrine neoplasia. New chapters on disorders in calcium regulation and genetics of infertility reflect the mechanistic and genomic advances that have been made in recent times. Finally, there is a new chapter on the endocrinology of aging, focusing on the highly relevant endocrinological changes that occur in this group of individuals, who form an increasing part of the clinician's responsibilities.

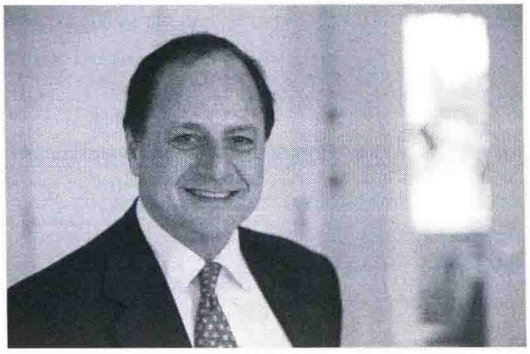
A separate pharmacopeia has not been included in this edition, because details of pharmacological treatments are included in each chapter where relevant.

We are most grateful to our colleagues who have kindly found the time to contribute to this book. Finally, as ever, our thanks to our families for their patience and support during this endeavor.

Philip E. Harris
Pierre-Marc G. Bouloux

Editor Biographies

Philip E. Harris trained in endocrinology as an MRC Training Fellow at the University of Wales College of Medicine, at St. Bartholomew's Hospital, London, and The University of Newcastle upon Tyne. In 1990–1991, Dr. Harris worked as an MRC Travelling Fellow at the Endocrine and Reproductive Endocrine units, Massachusetts General Hospital, Boston, USA. In 1994, he was appointed senior lecturer and consultant endocrinologist at King's College Hospital, London. His main clinical and research interest is in the field of endocrine oncology, in particular, pituitary disease. Dr. Harris is currently vice president for Scientific Affairs, Ipsen Biopharm Ltd. He is also an Honorary Consultant in Endocrinology at University Hospital Lewisham, London.



Pierre-Marc G. Bouloux is presently director of the Centre for Neuroendocrinology at the Royal Free and University College Medical School. He was an MRC Training Fellow under Michael Besser at St. Bartholomew's Hospital and was subsequently lecturer in medicine at the University Department of Medicine at St. Bartholomew's Hospital. He has held his present post since 1991. In addition to running a clinical service, he also has a special interest in neuroendocrinology. He has published more than 150 peer-reviewed publications.

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Contents

1

Neuroendocrine disease

Philip E. Harris

The normal hypothalamic–pituitary axis (see Chapter 5, Figure 5.1)

Normal anterior pituitary function is under the central control of the hypothalamus and higher centers. Hypothalamic releasing and inhibitory factors are secreted into the capillaries of the hypophysial portal circulation at the median eminence. The neurohypophysis consists of neurons arising from the magnocellular and parvocellular neurons of the supraoptic and paraventricular nuclei. The anatomical relationships of the hypothalamus and surrounding brain structures can be clearly demonstrated on magnetic resonance imaging (MRI) scan. The posterior pituitary (neurohypophysis) characteristically has a high signal on T1-weighted images that is lost in cranial diabetes insipidus (Figure 1.1).

Classification of hypothalamic–pituitary disease

Hypothalamic–pituitary disease is associated with increased mortality.[1] Endocrine dysfunction secondary to hypothalamic disease (Table 1.1) usually results in hypopituitarism. Rarely, activation of the hypothalamic–pituitary axis can occur. A well-recognized but rare example of this activation is precocious puberty, which may be associated with hypothalamic tumors such as neurofibromas, hamartomas, and pinealomas. Very rarely, hypothalamic tumors can produce releasing factors, resulting in pituitary hyperfunction. Acromegaly has been reported to occur as a result of the hypothalamic production of growth hormone–releasing hormone (GHRH) from hypothalamic tumors.[2] Similarly, Cushing's syndrome has been reported in association with the production of corticotropin-releasing hormone (CRH) by hypothalamic gangliocytomas.[3] Hyperprolactinemia is a frequent accompaniment of hypothalamic disease, secondary to damage of the dopaminergic (D2) neurons in the arcuate nucleus. Diabetes insipidus may complicate hypothalamic disease, in contrast to primary pituitary disease, where diabetes insipidus is almost never seen. There are certain clinical features that are indicative of hypothalamic disease rather than of pituitary disease. Obesity and hyperphagia pose major clinical problems for which there is, at present, no simple solution. Somnolence is also a characteristic feature that often occurs in conjunction with hyperphagia and obesity. Thermodysregulation and psychiatric disturbance can also occur[4] (Table 1.2).

Pituitary tumors are classified preoperatively in terms of function and size (Figures 1.2 through 1.5). There are several ways of classifying pituitary tumor size and invasion. In practice, most clinicians classify tumors on the basis of MRI or high-resolution computerized tomography (CT) imaging as grades 1–4 (Table 1.3). Postoperatively, tumors are routinely classified on the basis of histology and immunocytochemistry (Figure 1.6). The World Health Organization (WHO) 2004 classification of pituitary tumors describes typical adenoma; atypical adenoma with abnormal morphology: elevated proliferative indices (Ki-67 >3%, >2 mitoses/ 10 high power fields) and extensive nuclear p53 immunoreactivity; carcinoma. Functional classification is now well established but lacks predictive value[5] (Table 1.4). The identification and application of novel molecular markers is now being

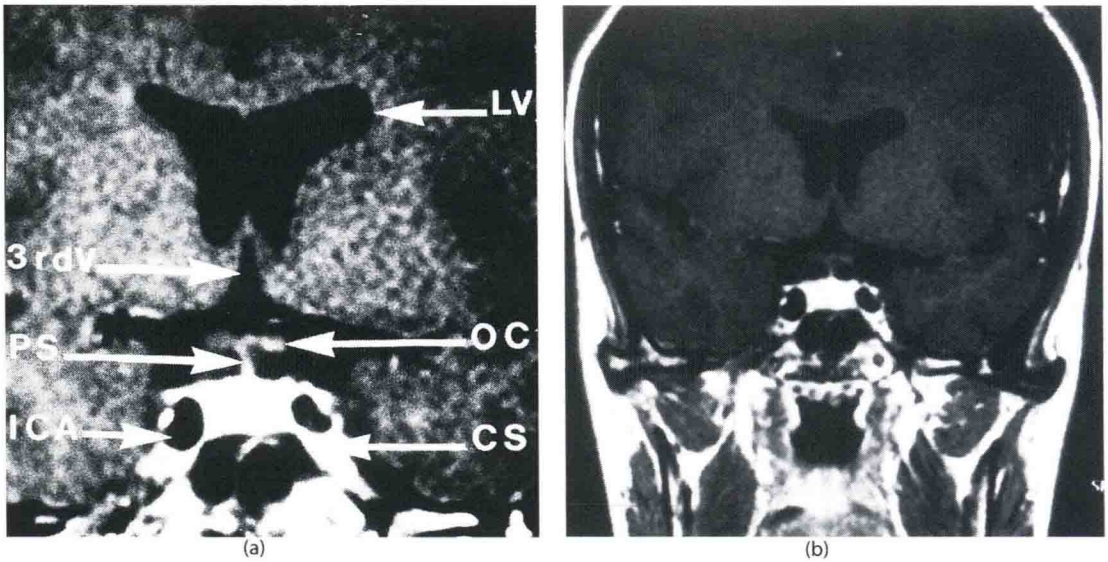

Figure 1.1
Coronal MRI scan (T1-weighted) demonstrating the pituitary gland, hypothalamus, and surrounding structures; scan a is an enlargement of scan b. LV, lateral ventricle; 3rd V, third ventricle; OC, optic chiasm; PS, pituitary stalk; ICA, internal carotid artery; CS, cavernous sinus (includes third, fourth, first and second divisions of fifth and sixth cranial nerves).

used to develop a more accurate prognostic classification of pituitary tumors, as clinical practice increasingly moves toward the personalized care of patients.[6] Pituitary carcinomas are very rare.[7]

Unlike hypothalamic disease that is usually manifested by hormone deficiency syndromes, pituitary tumors present with a wide variety of different features. In general, pituitary tumors can present with local pressure effects (Table 1.5), hypopituitarism, and/or syndromes of hormone excess.

An empty or partially empty sella on pituitary imaging (Figure 1.7) does not necessarily indicate an underlying pathology because this finding may represent a normal anatomical variant. Empty sella may also be seen in patients after pituitary surgery, radiotherapy, macroprolactinomas treated with dopamine (DA) agonists, and pituitary apoplexy.

Pituitary apoplexy usually occurs as a result of infarction of a pituitary tumor. It characteristically presents with a sudden onset of severe, debilitating headache that can last for several days, sometimes in association with cranial nerve lesions and acute onset of visual loss (Figure 1.8). Occasionally, patients may develop visual field defects, due to herniation of the optic chiasm into the fossa (see Chapter 24).

The optic chiasm is normally situated directly over the pituitary gland (80%), prefixed (15%), and postfixed (5%). The characteristic early field defect seen with a symmetrical suprasellar extension impinging on normally located chiasm is a bitemporal superior quadrantopia (Figure 1.9). This defect is due to the initial involvement of the decussating fibers originating from the inferior and nasal retinas. Further tumor growth involves the upper nasal fibers, with the development of the classical bitemporal hemianopia. Other patterns of visual disturbance are also frequently seen, depending upon the position of the chiasm and the site of suprasellar extension (Figure 1.10).

Principles of treatment

Pituitary surgery (see Chapter 3)

Neuroendocrine tumors should be managed in specialist centers. The management of these tumors requires a multidisciplinary approach involving specialists in endocrinology, neurosurgery, neuroradiology, radiotherapy, and neuropathology who have a particular interest in the subject. The cure of a pituitary tumor should aim for the complete removal of the tumor, with reversal of associated pressure effects such as visual field defects, the normalization of abnormal hormone secretion and

Congenital hypophysiotrophic hormone deficiencies
Isolated GnRH deficiency (olfactory–genital syndrome—Kallman's syndrome)
Isolated TRH deficiency
Isolated GHRH deficiency
Hypothalamic tumors
Craniopharyngioma
Arachnoid cyst
Hamartoma
Gangliocytoma
Glioma
Choristoma
Chordoma
Hypothalamic infiltration
Sarcoidosis
Histiocytosis X
Metastatic disease, e.g., breast
Infection
Tuberculosis
Meningitis
Viral encephalitis
Trauma
Stalk section, e.g., road traffic accident
Direct hypothalamic damage, e.g., surgery
Cranial irradiation
Vascular
Infarct
Aneurysm, subarachnoid hemorrhage
Arteriovenous malformation

GnRH, gonadotrophin-releasing hormone; TRH, thyrotropin-releasing hormone; GHRH, growth hormone–releasing hormone.

Table 1.1
Classification of hypothalamic diseases.

associated metabolic abnormalities, the reversal of abnormal pituitary function, or the retention of normal pituitary function.

Perioperative medical management (see also Appendix)

Patients undergoing pituitary surgery should be managed jointly by the neurosurgeon and the endocrinologist.

Disorders of food intake
Hyperphagia
Anorexia
Disorders of temperature regulation
Hyperthermia
Hypothermia
Poikilothermia
Disorders of drinking
Adipsia
Compulsive drinking
Disorders of sleep and consciousness
Somnolence
Altered sleeping patterns
Disorders of psychological functioning
Behavioral changes
Altered cognition
Disorders of neurological functioning
Raised intracranial pressure
Epilepsy
Impaired motor function
Impaired sensory function
Impaired autonomic function

Table 1.2
Non-endocrine manifestations of hypothalamic disease.

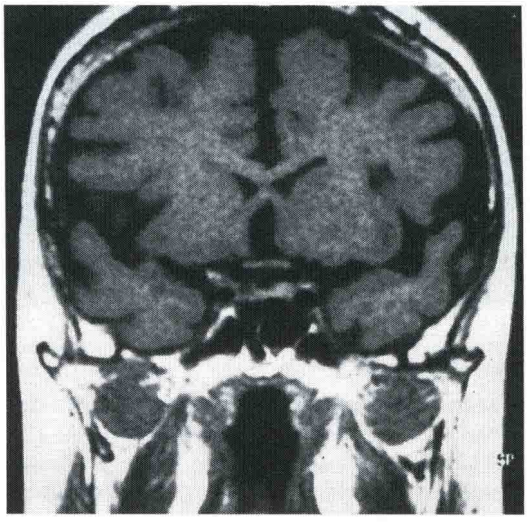

Figure 1.2
Coronal MRI scan (T1-weighted) demonstrating a pituitary microadenoma (hypodense area on the right).

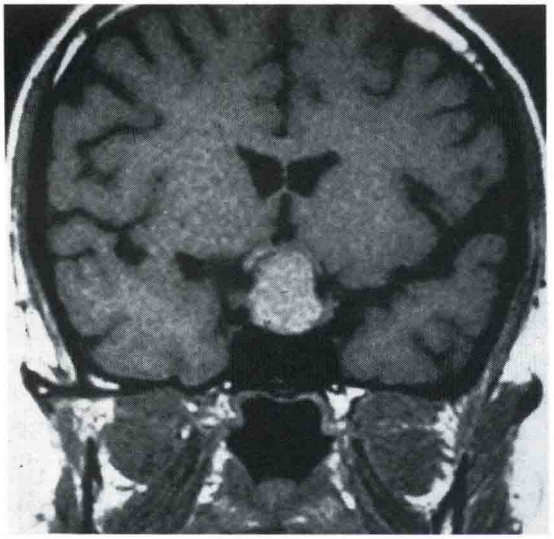

Figure 1.3
Coronal MRI scan (T1-weighted) demonstrating a pituitary macroadenoma with suprasellar extension, compressing the optic chiasm.

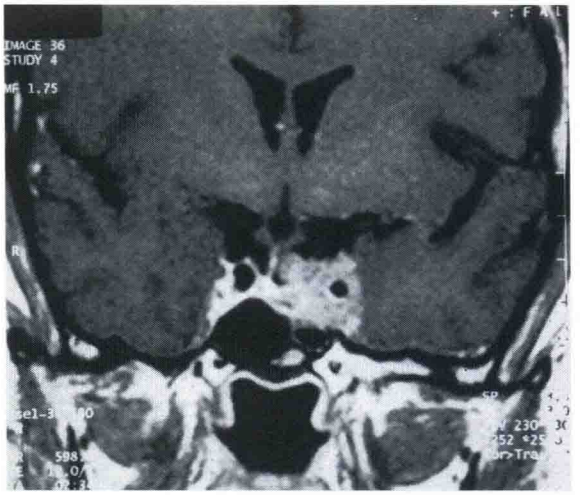

Figure 1.4
Coronal MRI scan demonstrating an invasive pituitary macroadenoma, extending into the left cavernous sinus, with suprasellar extension.

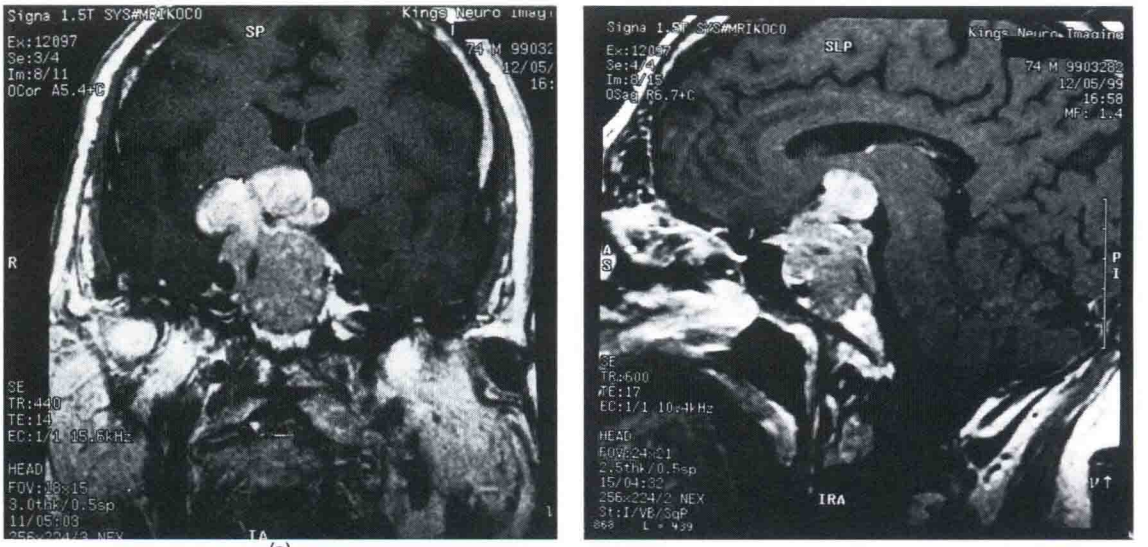

Figure 1.5
MRI scan (T1-weighted) demonstrating a giant invasive macroadenoma. (a) Coronal section. (b) Sagittal section.

Although some centers elect not to give glucocorticoid cover to patients with small microadenomas, it is certainly a safe policy to routinely provide all patients with perioperative glucocorticoid cover. Patients are frequently overtreated with glucocorticoids perioperatively, with consequent attendant risks of hypertension, glucose intolerance, poor wound healing, wound infections, and electrolyte disturbances. It is usually unnecessary to provide anything more than a modest increase in what would normally be replacement therapy. Patients with Cushing's