Endocrine, *vol. 28, no. 1, 101–110, October 2005* 0969–711X/05/28:101–110/$30.00

Treatment of Pituitary Tumors

Dopamine Agonists

Gabriella Iván,[1] Nikoletta Szigeti-Csúcs,[1] Márk Oláh,[2] György M. Nagy,[2] and Miklós I. Góth[1]

[1]Division of Endocrinology, Department of Medicine, National Medical Center, Budapest; and [2]Neuroendocrine Research Laboratory, Department of Human Morphology, Hungarian Academy of Sciences-Semmelweis University, Budapest, Hungary

The neurotransmitter/neuromodulator dopamine plays an important role in both the central nervous system and the periphery. In the hypothalamopituitary system its function is a dominant and tonic inhibitory regulation of pituitary hormone secretion including prolactin- and proopiomelanocortin-derived hormones. It is well known that dopamine agonists, such as bromocriptine, pergolide, quinagolide, cabergoline, and lisuride, can inhibit PRL secretion by binding to the D_2 dopamine receptors located on normal as well as tumorous pituitary cells. Moreover, they can effectively decrease excessive PRL secretion as well as the size of the tumor in patients having prolactinoma. Furthermore, dopamine agonists can also be used in other pituitary tumors. The major requirement for its use is that the tumor cells should express D_2 receptors. Therefore, in addition to prolactinomas, targets of dopamine agonist therapy are somatotroph tumors, nonfunctioning pituitary tumors, corticotroph pituitary tumors, Nelson's syndrome, gonadotropinomas, and thyrotropin-secreting pituitary tumors. It is also an option for the treatment of pituitary disease during pregnancy. Differences between the effectiveness and the resistance of different dopaminergic agents as well as the future perspectives of them in the therapy of pituitary tumors are discussed.

Key Words: Pituitary tumors; dopamine agonists; management.

Introduction

Although pituitary disorders are considered relatively uncommon, it might be surprising that pituitary adenomas are found in 10–25% of unselected autopsy series *(13,29)*. Diagnosis of an altered pituitary function, i.e., elevated or reduced hormone secretion, has been traditionally based on clinical symptoms and confirmed by blood tests. However, nowadays, pituitary tumors are more and more often discovered incidentally in the process of trying to diagnose unrelated conditions using high-resolution imaging techniques. Therefore, there is a significant chance that medical professionals, who are not endocrine specialists, may discover clinically significant pituitary lesions. Confirming the data obtained from autopsy series, magnetic resonance imaging (MRI) reveals pituitary lesions in about 10% of normal individuals *(29,38)*. A frequently mentioned statement is that both the diagnosis and the treatment of patients with pituitary tumors require teamwork, involving endocrinologist, neurosurgeon, ophthalmologist, and radiologist. Based on the above-mentioned changes in the processes of diagnosis, this view has gained even wider acceptance.

It is generally agreed that the successful treatment of pituitary tumors depends on the specific therapy directed against the type and the etiology of the lesion *(32,66,68)*. According to the current view, the monoclonal origin of most adenomas makes it unlikely that lack or significant change (decrease or increase) of the hypophysiotrophic function of one particular hypothalamic releasing–inhibiting factor could itself initiate transformation of the appropriate cell type *(43)*. However, it may be able to create a circumstance where the chance is higher for proliferation of an already transformed cell. Among of various hypophysiotrophic factors and their receptors, the physiological function, pathological role, as well as therapeutic features and significance of the predominant hypophysiotrophic hypothalamic cathecholamine, dopamine (DA), is the best characterized. Therefore, it is not surprising that in addition to the surgical procedure and among various drugs having been employed in the management of pituitary diseases, DA and several structurally related compounds of it, called DA agonists, are the most frequently used. In this paper, following a brief summary of our knowledge about DA, its receptors, and their physiological role in the regulatory processes, we focus on practical clinical aspects and areas of pituitary tumors in which DA agonists, at least partially, are a usual treatment of choice.

DA and DA Receptors

DA is an important catecholamine neurotransmitter/neuromodulator that has various functions within the body

Received June 2, 2005; Accepted July 14, 2005.

Author to whom all correspondence and reprint requests should be addressed: Miklós I. Góth, Division of Endocrinology, Department of Medicine, National Medical Center, 33 Szabolcs, Street, 1135 Budapest, Hungary. E-mail: goth@ogyik.hu

(51). In the central nervous system, DA is involved in the control of a variety of functions including cognition, emotion, positive reinforcement, locomotor activity, food intake, endocrine regulations, and retinal cells function. In the periphery, this catecholamine plays multiple roles in the regulation of the homeostasis as a modulator of cardiovascular function, hormone secretion, vascular tone, renal function, and gastrointestinal motility. Nowadays, it is generally accepted that several pathological situations such as Parkinson's disease, schizophrenia, or hyperprolactinemia (HPRL) have been linked to a dysregulation of DAergic transmission; therefore, finding more or less selective agonists and/or antagonists of DAergic systems has been the focus of research over the past 35 yr. For example, DA receptor antagonists have been developed to block hallucinations and delusions that occur in schizophrenic patients. At the same time, DA receptor agonists are effective in alleviating the hypokinesia of Parkinson's disease. However, blockade of DA receptors can induce extrapyramidal side effects similar to those resulting from DA depletion, and high doses of DA agonists can cause psychoses. It was well known from the beginning that the DAergic therapies were associated with severe side effects; therefore, during the last decade, much effort has been made to discover selective DAergic drugs devoid of adverse effects. This effort has led to the development of a number of new therapeutic agents.

The family of DA receptors includes five different receptor subtypes, D_1–D_5, which are classified as two subgroups on the basis of their molecular, biochemical, and pharmacological characteristics: D_1-receptor subgroup includes D_1 and D_5 receptors, and D_2 subgroup includes D_2, D_3, and D_4 receptors *(39)*. Cloning of the D_2 receptor cDNA has shown that a single gene gives rise to two different mRNA transcripts that result from alternative splicing of a separate 87 nucleotide exon *(12,36,52,62)*. This directs the expression of a long (D_2-L) and a short (D_2-S) mRNA variant that encode two distinct receptors that differ only by a 29-amino-acid insert in the putative third cytoplasmatic loop *(12,36,52,62)*.

For a long time, the general and well-accepted view about pituitary prolactin (PRL) secretion is that it is under a predominant inhibition exercised by the medial–basal hypothalamus, namely, it is severely and tonically restrained in vivo by the action of hypothalamic PRL inhibiting factor (PIF). Based on several observations that drugs affecting biosynthesis and metabolism of catecholamines can significantly alter PRL secretion *(33)*, and that DA is present in high concentration in both the median eminence and the hypophyseal stalk plasma *(33)*, several investigators have concluded that DA is the hypothalamic PIF. Experimental evidence provided by MacLeod *(48)*, that DA inhibits PRL release from pituitary mammotropes in vitro, has strongly supported this conclusion *(33,48)*. Subsequently, high-affinity DA binding sites have been identified on rat, bovine, as well as human pituitary tissues *(39)*. It has been designated as a D_2 receptor *(14,39)*, which is expressed in both the anterior and intermediate lobes of the pituitary gland, where it participates in the tonic inhibitory control on PRL and proopiomelanocortin-derived hormone secretion, respectively. The ratio of D_2-L and D_2-S expression in the anterior lobe *(17,65)* of different strains of rat is not much different. The vast majority of D_2 receptors are the longer version (D_2-L) and 8–10% of the expressed D_2 receptors belong to the D_2-S variant *(4,65)*. Physiological or possible pathological significance of D_2-L and D_2-S in the anterior lobe is still an opened question.

Recently the importance of D_2 DA receptors in maintaining normal pituitary lactotroph function has been clearly demonstrated in mice lacking D_2 receptors. These mice display chronic HPRL and lactotroph hyperplasia *(41,59)*. Aged D_2 receptor deficient females develop macroadenomas and D_2 receptor–deficient males eventually develop microadenomas without concomitant hyperplasia *(3)*. However, in both male and female mice, there is a surprisingly long latency to the appearance of lactotroph adenomas. It must be emphasized that there is no evidence yet for similar pathogenetic background of prolactinoma in humans.

DA Receptor Agonists

As a consequence of the well-defined hypophysiotrophic inhibitory role of DA, it is not surprising that structurally and chemically similar compounds to DA, i.e., DA agonists (Table 1), can inhibit PRL secretion by binding to the cell-surface D_2 DA receptors located on mammotropes. Interestingly enough, DA agonists can also reduce tumor size in prolactinoma by both inducing a reduction in cell volume via an early inhibition of the secretory mechanism and a late inhibition of gene transcription, consequently, PRL synthesis *(2)*. It has also been shown that DA agonist treatment causes a perivascular fibrosis and partial cell necrosis that may explain why some PRL-producing adenomas do not recur after withdrawal of dopamine agonist treatment *(44)*. Moreover, DA agonists can also be used in other pituitary tumors in which cells express D_2 DA receptors, and, as described in the case of prolactinoma, they are able to decrease hormone secretion and reduce tumor size as well.

Currently, the most commonly used DA agonists are bromocriptine, pergolide, quinagolide, cabergoline, and occasionally lisuride. Table 1 summarizes the most important biochemical, phamakodynamic, and pharmacokinetic data of the above-mentioned DA agonists.

Bromocriptine (BRC)

BRC mesylate is an ergot derivative with potent DA receptor agonist activity. It was the first DAergic drug to be introduced, and it has been used for the treatment of prolactinoma and/or HPRL during the last 20 yr. Therefore, it is not surprising that it is considered to be the "gold stan-

Table 1
Biochemical, Pharmakodynamic, and Pharmacokinetic Data of DA Agonists

DA agonist	BRC-mesylate	Pergolide-mesylate	Quinagolide	Cabergoline	Lisuride-maleate
Derivative	Ergot alkaloid	Ergot alkaloid	Non-ergot, octahydrobenzyl(g)-quinagolide	Synthetic ergot alkaloid	Ergot alkaloid
Trade name	Parlodel Parlodel SRO Parlodel LA	Permax	Norprolac	Dostinex	Dopergin
R	D2: ++; D1: – ; D3: +; 5HT: ++; α_1: +++; α_2: ++	D2: ++++; D1: 0/+; D3: +++; 5HT: 0/+; α_1: ++; α_2: ++	D2: 1×; D1: 0; 5HT: 0.01× (as compared to D2)	D2: +++; D1: 0/+; D3: +++; 5HT: ++; α_1: ++; α_2: ++	D2: ++++; D1: 0/+; D3: NA; 5HT: +++; α_1: +++; α_2: ++++
C_{max} (μg/L)	1.3–6.5 (12.5–100)	1.8 (0.14)	NA	0.03–0.07 (0.5–1.5)	0.2–3.3 (0.3)
t_{max}	0.25–2.5 h	1–3 h	4–6 h	0.5–4 h	0.2–1.2 h
F	6%	20–60%	–	50–80%	10–20% (higher with higher doses)
A	28%	55%	High	High	Approx 100%, high interindividual variability
P	90–96%	95–96%	90%	40%	70%
M	Hepatic High first pass	Hepatic Inactive metabolites Inhibition of CYP 3A4 Interact with CYP 2D6	High first pass One active metabolite Mostly inactive metabolites	Hepatic	Dose-dependent first pass Inactive metabolites High interindividual variability
Exc	94–96% in bile-faeces 2–6% in urine 3–6% unchanged in urine	45% in feces 55% in urine	50% in bile-feces 50% in urine	Mostly in bile-feces 1% in urine	100% in urine 0.05% unchanged in urine
$t_{1/2\beta}$	3–7 h	12–27 h	22 h	63–110 h	1.3–2.5 h
Dose	1.25–10 mg/d	50 μg–5 mg/d	25–300 μg/d	0.5–4.5 mg/wk	0.2–0.6 mg/d
Dosing	2–3× daily	1–3× daily	1× daily	1–2× weekly	1–3× daily
Remarks	Experience > 20 yr Experience in pregnancy		Specific D2 R activity Effecive in 50% of BRC resistent cases	D2 receptor binding is long-lasting (up to 72 h)	

R, receptor affinity; 0/+, partial agonist on the receptor; C_{max}, peak plasma concentration (μg/L) for dose (mg); t_{max}, time to C_{max}; F, oral bioavailability; A, gut absorption; P, protein binding in plasma; M, metabolization; Exc, excretion; CYP, Cytochrome P450; $t_{1/2\beta}$, elimination half life; CL, clearance (mL/min), NA, information not available *(5,27)*.

dard" treatment of choice (Table 1). As is expected from the wide distribution of D_2 DA receptors in the central and peripheral central nervous system as well as in different peripheral organs, BRC is associated with several side effects such as nausea, dizziness, and postural hypotension. It may exacerbate preexisting schizophrenia. Milder side effects include nasal stuffiness and constipation. They can be avoided by a gradual escalation of the dose because desensitization and tolerance develop at the majority of the DA receptor sites but fortunately not on those that locate on the pituitary mammotropes. BRC pills should always be taken with food, because this delays its absorption and reduces or obviates unwanted side effects. It should be mentioned that long-acting BRC preparations such as BRC-LAR or BRC-SRO have fewer side effects *(23)*. Intravaginal administration is associated with diminished gastrointestinal side effects, and the effect of the drug lasts for 24 h. Occasionally, vaginal irritation may occur, but this approach is generally well tolerated *(42)*.

Pergolide

Pergolide mesylate, which is also an ergot derivative, can effectively inhibit PRL secretion. This drug was originally approved for the treatment of Parkinson's disease, because it has agonist effect at D_1, D_2, and D_3 DA receptor sites. As far as its D_2 agonist feature, it gives an option for the therapy of prolactinomas. Moreover, it is able to suppress PRL secretion for up to 24 h following a single dose *(21,28,31)*, and it is several times more potent than BRC on a milligram per milligram basis. Therefore, it allows an

effective control of HPRL when taking the appropriate dose once a day (Table 1). Side effects of pergolide are also similar to BRC, but fibrotic and serosal inflammatory disorders warrant special attention.

Quinagolide

Quinagolide is a non-ergot DA agonist with a selective D_2 receptor agonist activity (Table 1). The most important features of quinagolide are its selectivity and its prolonged duration of action *(23)*. The most common undesirable effects are nausea, vomiting, headache, dizziness, and fatigue, but they usually occur during the first few days of treatment, and are mostly transient events.

Cabergoline

Cabergoline is a synthetic ergoline type of DA agonist with high affinity to D_2 receptors. Based on the pharmacokinetic properties of cabergoline (Table 1) patients having prolactinoma should take the appropriate dose once or twice a week, making this drug highly advantageous over other DAergic agents in terms of both therapeutic compliance and better control of the symptoms. It has been shown in a large double-blind comparison of the two drugs that cabergoline is better tolerated than BRC *(70)*. According to this study, 3% of patients discontinued cabergoline because of drug intolerance compared to 12% of patients taking BRC. In addition, prolactinomas resistant to other DA agonists have been shown to respond to cabergoline *(11,19)*. In a recent retrospective study involving 452 patients with pathological HPRL, most of them having pituitary tumors, cabergoline was shown to be effective in many patients who were previously BRC intolerant or resistant *(69)*. Cabergoline is much less likely to cause nausea than other DA agonists, and is more likely to be effective for treatment of lactotroph adenomas that are resistant to BRC *(24,35)*. For all these reasons, cabergoline is often the best, consequently, the first, choice of treatment, except for a woman who is going to be pregnant *(18,19)*.

Lisuride

Lisuride, an ergot derivative DA agonist, is one of the most potent DA agonist displaying high affinity for both D_1 and D_2 receptors. However, it has been also shown to interact with peripheral (as an antagonist) and with central (as an agonist) serotoninergic systems. It is not only effective in suppressing PRL secretion, but it is able to reduce tumor size. It has several side effects (nausea, dizziness, and depression) that significantly limit its use in the treatment of pituitary tumors *(16)*.

Pituitary Tumors and DA Agonist Therapy

Prolactinoma

Prolactinoma is the most common hormone-secreting pituitary tumor. It accounts for about 30–40% of all pituitary tumors, and up to about 60% of the functioning pituitary tumors *(64)*. Prolactinomas are generally divided into three categories: microprolactinomas (<10 mm in diameter), macroprolactinomas (≥10 mm in diameter), and macroprolactinomas with extrasellar invasion.

Clinical Features

PRL is a polypeptide hormone, which is synthesized in and secreted from specialized cells of the anterior pituitary gland, called lactotrophs. The hormone was given its name based on the fact that an extract of bovine pituitary gland would cause growth of the crop sac and stimulate the elaboration of crop milk in pigeons or *pro*mote *lact*ation in rabbits *(33)*. However, we now know that PRL has over 300 separate biological activities *(33)* not represented by its name. Indeed, not only does PRL serve multiple roles in reproduction other than lactation, but it also plays multiple homeostatic roles in the organism. From the diagnostic point of view, the role of PRL on gonadal function warrants significant clinical attention. Hypersecretion of PRL leads to infertility and gonadal dysfunction by interrupting physiological secretion of GnRH, inhibiting the release of LH and FSH, and impairing gonadal steroidogenesis. Therefore, it is well established that women having prolactinoma typically present a history of oligomenorrhea, amenorrhea, or infertility. However, men can also complain about sexual dysfunction including the loss of libido, impotence, and disturbances in fertility. Galactorrhea is also a common symptom. It is due to HPRL-induced activation of PRL receptors located on epithelial cells of the mammary gland. Visual problems and/or headache are also important symptoms in the evaluation process. Osteopenia can be detected in both sexes. HPRL-induced gonadal dysfunction has been found to affect both cortical and trabecular bone compartments and a progressive loss in both of them has already been demonstrated in untreated hyperprolactinemic patients. Restoration of normal gonadal function by DA agonist treatment of HPRL might have a beneficial effect on bone loss as well. The trabecular bone density in a woman having oligomenorrhea is between the values detected in hyperprolactinemic amenorrheic patients and the normal controls. Therefore, estrogen deficiency with chronic amenorrhea leads to progressive osteopenia in such women. Data indicate that, as in other hypogonadal states, the trabecular bone compartment may be primarily affected by hyperprolactinemic amenorrhea and may be less likely to show improvement following restoration of normal function of the gonads. It must be emphasized that hyperprolactinemic amenorrheic women, who have had a sustained period of estrogen deficiency, may have a permanent decline in bone density, which persists until the menopause. Surprisingly, according to several literature data, osteopenia is probably not associated with fracture of the bones *(37)*. In hyperprolactinemic women, microadenomas with lower PRL levels predominate (it is about 90% of women having prolactinomas). In contrast, men usu-

ally have macroadenomas with higher PRL levels as much as in 60% of the cases. This may be due, at least in part, to the fact that men with this tumor usually present clinical symptoms of HPRL much later compared with women. Serum PRL levels generally are in good correlation with the size of the tumor. Macroadenomas are typically associated with serum levels of PRL over 250 ng/mL, and in some cases even higher (exceeding 1000 μg/L). In case of moderate elevation of PRL level (<100 ng/mL) in the presence of a macroadenoma, discrepancy can be due to either a compression of the pituitary stalk by the tumor itself, or to an artifact in the immunoassay for serum PRL, namely, the so-called "hook effect" *(34)*. It can be eliminated by serial dilution of the serum samples. Up to 10% of cases of elevated serum PRL are caused by the presence of circulating antibody–PRL complexes (macroprolactinemia), which have uncertain physiological significance. Macroprolactinemia can be detected by laboratory test and should be taken into consideration in hyperprolactinemic patients without having the typical clinical signs of HPRL *(67)*. DA agonist therapy is the treatment of choice for both micro- and macroprolactinomas. It is based on the size of the tumor and the presence of clinical symptoms, but the patient's desires with respect to fertility can also be considered *(56,61)*.

Microprolactinoma

Microadenomas can occur at any time in adults; however, prevalence increases with the advance of age. The natural history of untreated microprolactinoma is not completely understood. Although macroprolactinomas must begin as small tumors, most microadenomas do not progress to macroadenomas. Micro- and macroprolactinomas seem to be two distinct diseases. Patients diagnosed with PRL-secreting microadenomas and observed for a long period of time (even 10 yr) without any treatment have shown low risk of progression to macroadenoma with an exception of 5–10%. It must be emphasized that, in few cases, serum PRL can return to normal levels with an intermittent or even without any DA agonist treatment. Women with PRL-secreting micro-adenomas, who become pregnant during this interval, have a higher rate of remission than women who do not become pregnant (35% vs 14%) *(63)*.

Macroprolactinoma

For macroprolactinoma in addition to elimination of the symptoms of HPRL, an equally important indication for therapy is suppression of tumor growth, even its shrinkage. Normalized PRL levels and tumor shrinkage (by ≥50%) can be achieved in 60–75% of patients. At the same time, abnormal visual fields improve in most cases. Symptoms of mass effect, including headache and other visual disorders, can also be dramatically improved within a few days following initiation of the treatment. Sexual function can also be better even before the complete normalization of serum PRL levels.

Management

In 90–95% of patients having microadenomas, the size of the tumors does not progressively increase; therefore, suppression of tumor growth is not an indication for therapy. Because the natural history of untreated PRL-secreting microadenomas is quite benign, indications for treatment depend on the patient's symptoms. In contrast, in the case of macroadenoma the aim of therapy is to eliminate the symptoms and to restore normal pituitary functions, but also, to decrease the size of the tumor mass, and to eliminate visual-field abnormalities or other neurological complications. The main objective of treatment in the case of microadenoma associated with HPRL is the restoration and the maintenance of normal gonadal function, including elimination of galactorrhea and the restoration of normal fertility. While the restoration of fertility is the major goal, it would mean the attenuation or prevention of osteoporosis as well. It is also important to note that hyperprolactinemic women, who have regular menstrual periods, do not appear to have evidence of osteopenia. Therefore, PRL does not have an independent, deleterious effect on bone density, and osteopenia is only an important consideration in those women who have associated menstrual disturbances. In women with documented HPRL together with mild signs of androgen excess, treatment of HPRL with DA agonist therapy may result in normalization of serum androgens *(10)*.

Starting, Monitoring, and Follow-up DA Agonist Treatment

The starting dose of BRC should be determined on the basis of the initial serum PRL level. Two times 1.25 mg is usually suggested when serum PRL level is less then 40 ng/mL, two times 2.5 mg, if the PRL level is between 40 and 60 ng/mL. When serum PRL is very high, 10–15 mg BRC may be required, but in some cases the higher doses are not necessarily more effective. According to our practice, BRC treatment of prolactinoma is started by taking a quarter of a 2.5 mg tablet of BRC with a snack at night or upon retiring to bed. After 3 d, the dose should be increased to a quarter of a tablet with breakfast and a quarter at bedtime. After three more days, half a tablet should be taken twice a day, and 3 d later, one tablet at night and half with breakfast. Finally, the dose should be increased to one tablet twice a day. If PRL is still high, half a tablet should be added with lunch. If the medication is well tolerated, the dose can be increased to a full tablet. In the case of side effects at any time during the escalation of dose, patients should be advised to back off to the previous regimen where they were free of side effects. Side effects usually disappear with time, while the drug continues to lower serum PRL levels. Large tumors are responsive to the same dose of BRC as small tumors because the affinity of the DA receptors is irrespective of the size of the lesion. However, all patients have to be treated individually according to the clinical response, serum PRL levels, and tolerability. If serum PRL concen-

tration decreases to normal or close to normal, the consequences of the elevated PRL are usually reversed. For example, in premenopausal women, ovarian cycle and menses return, with a concomittant increase of estrogen secretion and restoration of fertility. In men, testicular function returns, with a consistent increase in energy, sex drive, muscle mass, blood count, and bone density. The reduced sexual activity and the breast enlargement can also be improved. Hypoprolactinemia should be avoided. In microprolactinoma serum PRL level should be checked in the 1st, 3rd, 6th, and 12th mo after the beginning of DA agonist therapy and yearly afterward. Pituitary MRI should be performed prior to and 1 yr after the initiation of DA agonist therapy. In the case of macroprolactinoma, serum PRL, visual field, and pituitary MRI have to be checked more often, taking into consideration the clinical symptoms. Pituitary MRI should be performed after 6 mo, 1, 2, 4, and 8 yr even if the patient has no clinical symptoms. Women should be advised to use a mechanical form of contraception until the occurrence of two regular menstrual periods, and BRC should be stopped when one menstrual cycle has been missed. When fertility is not desired, an oral contraceptive is not contraindicated in the case of prolactinoma. Although estrogen can induce lactotroph hyperplasia, short-term use of oral contraceptives does not appear to be associated with tumor growth. However, woman having microadenoma and taking estrogen will need to have their PRL levels measured more regularly *(25,30)*.

Pregnancy

The pituitary gland normaly increases in size during pregnancy, reflecting the stimulatory effects of estrogen and perhaps other growth factors on lactotrophs. Microprolactinomas rarely cause complications during pregnancy. About 5% of microadenomas increase significantly in size. In contrast, 15–30% of macroadenomas enlarge sufficiently enough to threaten vision. BRC has been used for over 25 yr to restore fertility in women with HPRL, without having evidence of teratogenic effects; nonetheless, most authors recommend strategies to minimize fetal exposure to this drug. When pregnancy is confirmed, BRC should be discontinued. In case of DA agonist–induced fertility and pregnancy, the clinical status of patients needs to be carefully monitored. More frequent measurement of serum PRL is not necessary because an increased level does not reliably correlate with tumor enlargement. Periodic visual field testing and MRI are also not necessary in microprolactinomas. For women harboring macroadenomas, monthly visual field testing is recommended, and the drug should be reinstituted if tumor growth is apparent. Although MRI of the sella may be safe during pregnancy, this procedure should be reserved for patients having severe headache and/or visual field defects. MRI scan is suggested on early postpartum state to detect any asymptomatic tumor enlargement. Alternatively, surgical decompression may be indicated if vision is threatened. Evidence to date suggests that cabergoline and quinagolide appear to have a good safety profile for women who wish to conceive, but evidence for not causing congenital malformations, when it is taken during early pregnancy, is currently only available for BRC. As cabergoline is long acting with a high D_2-receptor selectivity and affinity, it is not approved for routine use when fertility is desired. Lactation is not associated with tumor growth. Women wishing to breast-feed their infants, should not be given BRC.

Is DA Agonist Treatment Lifelong?

One of the most important disadvantages of DA agonist treatment of prolactinomas is that it is theoretically required to be continue for life. Previous morphological studies of tumor specimens obtained following long-term treatment with BRC have shown atrophic tumor-cell nests, pyknosis, and cytolysis, as well as karyorrhexis, necrosis, fibrosis, hyalinosis, and inflammatory-cell infiltration, suggesting a cytocidal effect of the drug *(44)*. According to the natural history of microprolactinoma the possibility of inducing long-lasting control of HPRL without continuing pharmacologic treatment, periodic withdrawal of DA agonist therapy can be considered after 2–5 yr. If PRL levels are well controlled with a DA agonist, gradual tapering of the dose to the lowest effective amount is highly recommended, and in a number of cases medication can be stopped after several years. Following a complete discontinuation of the treatment, regular monitoring of clinical symptoms and of serum PRL levels is recommended. It is particularly important in patients with macroprolactinomas, because tumor growth may compromise vision. Given the propensity for early recurrence of pituitary disease, plasma PRL levels should be measured monthly for the first 3 mo, then 3 mo later, and every 6 mo thereafter. As far as the cabergoline withdrawal is concerned, remission of HPRL can persist after withdrawal of the drug without having any evidence of re-newed tumor growth in about 57% of patients having macroprolactinomas *(18)*. This proportion is higher than those generally reported in the case of spontaneous regression that has also been described as part of the natural history of untreated tumors *(18)*. If a DA agonist drug is stopped after only a short-term treatment (weeks or months), HPRL generally recurs within a few weeks. According to clinical practice, discontinuation of DA agonist therapy will result in the recurrence of HPRL and tumor growth in a very high proportion of patients when the duration of treatment has been less than 2 yr. Female patients with HPRL who pass through the menopause have a significant chance of normalizing their PRL levels. The menopause is an indication for reassessment of the need to continue to treat HPRL and/or microprolactinoma with DA agonists. Several studies reported a decrease (or even normalization) of PRL after pregnancies in women having prolactinomas and treated with DA agonists *(18,55)*.

Effectiveness of DA Agonist Therapy

These drugs are very effective for decreasing both the hormone production and the size of most lactotroph adenomas. DA agonists lower PRL levels in about 80% of patients having lactotroph adenomas and in about 70% of those having macroadenomas. PRL levels usually fall within the first 2–3 wk of treatment, but detectable decreases in tumor size take longer (usually 6 wk to 6 mo). Most shrinkage occurs during the first 3 mo of treatment, although in a minority of patients tumor shrinkage is delayed. In about 40% of tumors its size decreases by more than 50% during the first 3 mo. After a longer period of time, DA agonists decrease tumor size in about 90% of patients *(9)*. When vision is affected, it usually begins to improve within days of starting the treatment.

Resistance to DA Agonists

Five to fifteen percent of tumors that do not respond to DA agonists appear to be due to low expression of DA D_2 receptors. Several defects in the dopaminergic transduction pathways participate in this bromocriptine resistance. The mean D_2-binding site density is decreased to 50% compared with responsive tumors. This loss of D_2 receptors can account for a lower transcription level of its gene and/or is accompanied by modifications in the messenger alternative splicing; the D_2 short isoform receptor expression decreases preferentially *(6)*. A reduction in $G_{i2\text{-}\alpha}$ protein expression can also be observed. Finally, the pituitary-specific transcription factor Pit-1 expression is affected. A highly significant correlation has been detected between the D_2 receptor mRNA and Pit-1 mRNA levels. These defects observed on many levels of the dopaminergic transduction cascade can explain DA resistance, and it may be an important step in the loss of the functional features of pituitary lactotrophs *(6)*. Resistance to DA agonists can be defined with respect to failure to normalize PRL levels after at least 3 mo of treatment with BRC at the dose of 15 mg daily and, in the case of macroprolactinoma, failure to decrease tumor size by at least 50%. It should be noted that according to the clinical practice the majority of the so-called "resistant" patients can still respond to a progressive increase of the dose of BRC or cabergoline, even if it can usually be able to induce normoprolactinemia. On a practical basis, if normal PRL level cannot be achieved, but the symptoms of HPRL are reduced or disappear, the treatment can be considered to be useful. Similarly, as long as there is no mass effect, or no evidence of tumor growth, treatment is adequate. Pretreatment level of serum PRL or the size of the tumor is not predictive for the success of treatment. Quinagolide and especially cabergoline have been shown to be significantly more effective than BRC in inducing a complete biochemical response and clinical efficacy in resistant tumors *(11)*. They are also better tolerated than BRC in the majority of cases. It was also proven effective in patients resistant to or with a poor response to BRC *(19,22,28)*.

Acromegaly

The aim of treatment is the suppression of circulating growth hormone (GH) and insulin-like growth factor-1 (IGF-1) concentrations, to achieve a remission of clinical signs and symptoms of the disease, and tumor shrinkage. DA agonist drugs, in particular BRC, have been used for over 20 yr in the medical therapy of acromegaly. It should be mentioned that DA agonists are usually not effective at reducing the size of a pure GH-secreting pituitary tumor *(40)*. Transsphenoidal surgery is the first choice of therapy in the majority of the patients. For those patients who do not show remission following surgery, even after repeated surgery or use of adjuvant therapy, the options are radiotherapy and medical therapy. The most effective medical therapy is long-acting analogs of somatostatin (SS). A novel therapeutic opening is pegvisomant, a GH receptor antagonist. Another possibility is the administration of a DA agonist. DA agonist therapy is much less effective but offers two main advantages: the oral administration that may help to improve patients' compliance and a much lower cost compared with SS analogs *(49)*. It has been widely shown that DA agonists suppress GH and IGF-1 secretion in 10–15% of acromegalics. Significant improvement of symptoms is slightly more frequent *(7,9,54)*. BRC in doses up to 20 mg/d (every 6 h) is needed for optimum treatment efficacy. It has not been shown that an increase in the dose of BRC to more than 20 mg/d has any clinical advantages *(8)*. Cabergoline seems to be the most efficacious of DA agonists for the treatment of acromegaly *(1)*. The dose of cabergoline is 1–1.75 mg/wk. Higher doses, up to 3.5 mg/wk, have been tried in some resistant patients without significant benefit *(1)*. As expected, the efficacy of DA agonist therapy is greater in patients whose tumor co-secrets GH/PRL. Pituitary scintigraphy with ^{123}I-iodobenzamide (^{123}I-IBZM) and ^{123}I-epidepride can be considered as a useful tool to study the expression of functioning D_2 DA receptors in the adenomas. Combined treatment, the addition of cabergoline together with a depot SS analog to treatment-resistant acromegalic patients, may give success, irrespective of PRL levels *(26)*. Recently, a chimeric molecule, BIM-23A387, has been created that contains structural elements of both SS and DA. The hybrid molecule retains potent, selective agonist activity at both the SS subtype 2 receptor (sst2) and the DA D_2 receptor *(60)*. Perhaps this new chimeric molecule may gain a more significant role in the treatment of all pituitary tumors that express both sst2 and DA D_2 receptor.

Non-Functioning Pituitary Adenomas (NFPA)

Clinically, NFPA are a category of pituitary tumors that are not associated with specific clinical or biochemical features of pituitary hormone hypersecretion. However, they represent a very heterogeneous group of tumors, because a consistent proportion of them have been shown to secrete small amounts of intact FSH and LH or their α and β sub-

units. Usually NFPAs are macroadenomas, often causing hypopituitarism and/or mass effects. The first choice for treatment is the surgical removal of the adenoma, which can result in an improvement in neurological symptoms, defects of visual field, and, in some cases, recovery in pituitary functions. However, owing to their size, surgery alone is not curative in all cases; therefore, radiotherapy is often recommended in order to prevent tumor re-growth. Considering medical therapy using DA agonists in NFPA is based on the observation that DA D_2 receptors are commonly expressed in nearly 70% NFPA *(57)*. Controversial results have been reported with the use of DA agonists in NFPA. In clinically NFPA, DA D_2 receptor expression was lower than in the normal pituitary, and the ratio between D_2-L and D_2-S was heterogeneous, with only D_2-L or D_2-S expressed in some cases. This evidence suggests that changes in the mechanism of alternative DA_2 splicing may occur during tumorigenesis of these tumors. D_2-S isoform plays a pivotal role in the control of hormone secretion and cell growth inhibition and that the lack of D_2-S isoform expression or an increased D_2-L/D_2-S ratio may contribute to DA agonist resistance of clinically NFPAs.

DA D_2 receptor imaging such as pituitary ^{123}I-IBZM and ^{123}I-epidepride scintigraphy can help to select a patient who will respond to DA agonist therapy *(20,47)*. An intense ^{123}I-IBZM uptake and ^{123}I-epidepride in patients with nonfunctioning adenomas are predictive of a good response to a chronic treatment with DA agonists. Comparing the two scintigraphies ^{123}I-epidepride has much higher affinity for striatal uptake than ^{123}I-IBZM *(47)*. Cabergoline seems to be more effective and better tolerated than BRC in the management of clinically NFPA. The reasons for the superiority of cabergoline compared with BRC have not been completely clarified. The majority of the studies comparing the behavior of the two drugs found that the differences in the pharmacokinetic and pharmacodynamic characteristics may explain the difference in their effectiveness and tolerability. However, other explanations could also be postulated. For example, the possible key role of D_2 receptor isoforms ratio in the expression pattern of these tumors can be hypothesized. Cabergoline might activate D_2-S isoform more than BRC. This seems to be supported by the evidence that in tumors expressing D_2-S isoform are associated with a better clinical response to cabergoline. Secondly, it has been demonstrated that D_4 DA receptors may be coexpressed with D_2 DA receptors and cabergoline might be able to activate D_4 receptor more efficiently than BRC, therefore, additive or synergistic effect on these two DA receptors may benefit the management of these tumors. This seems to be supported by the evidence that cases expressing D_4 receptor have a significant clinical response to cabergoline. Moreover, the possibility cannot be ruled out that cabergoline induces cell apoptosis more than does BRC through the activation of D_2-S and/or D_4 receptor *(58)*. Cabergoline improves clinical symptoms in about 70% of the cases. It induces tumor shrinkage in nearly 60% of cases and improves visual field impairment in 80% of NFPA. These data give strong support for the use of cabergoline in the therapy of residual clinically NFPA, especially following unsuccessful surgery *(58)*.

ACTH-Secreting Pituitary Tumors

Treatment of ACTH-secreting or corticotroph pituitary tumors with BRC has been already investigated, although with controversial results *(51,64)*. The usual occurrence of corticotroph tumors in the intermediate lobe of the pituitary gland is frequently associated with the rise in plasma PRL and responsiveness to DA agonists in animal model of Cushing's disease *(45)*. Moreover, the high incidence of corticotroph adenomas in the neurointermediate region of the human pituitary *(46)* led to the suggestion that hypophysiotrophic DA may have some pathogenetic and/or therapeutic role in ACTH-producing pituitary tumors. Therefore, it is not surprising that the DA agonist treatment of corticotroph pituitary tumors has still not yet been clearly established. Therefore, transsphenoidal pituitary surgery is the suggested treatment of choice for patients diagnosed with Cushing's disease. Because, in a recent study DA D_2 receptor expression has been approved in some corticotroph pituitary tumors, it seems to be logical to try DA agonists in ACTH-secreting pituitary tumors. Medical therapy with DA agonists has only been used as adjunctive therapy to lower cortisol levels in special cases. Interestingly enough, normalization of cortisol secretion and/or shrinking of tumor size have been reported after long-term DA agonist treatment *(57)*. There are also sporadic observations that long-term cabergoline treatment of patients having Nelson's syndrome resulted in a complete remission *(15)*. In a recent study, the expression of functioning D_2 receptors have been found in 80% of ACTH-secreting pituitary tumors. Moreover, a short-term treatment with cabergoline has been reported to be able to normalize ACTH as well as cortisol secretion in 40% of cases. *(57)*. This study represents the first clear demonstration of both receptor expression and receptor function in corticotroph pituitary tumors; therefore, it provides a rationale for its therapeutic use in the management of recurrent or persistent Cushing's disease.

Gonadotropinoma

Gonadotropinomas most often are asymptomatic and usually secrete inactive FSH- and LH-like molecule and/or excessive amounts of α-subunit of the glycoprotein pituitary hormones (LH, FSH, and TSH). They often are macroadenomas and usually result in hypopituitarism. Rarely, they can lead to testicular enlargement in men and ovarian hyperstimulation in women. Gonadotropin-producing pituitary

adenomas are extremely rare in women of reproductive age. In a case report, gonadotropin microadenoma with ovarian hyperstimulation has been successfully treated with BRC when D_2 type DA receptor is expressed in the adenoma. *(53)* Gonadotropin-secreting macroadenomas have to be treated surgically, followed by radiation. Medical therapy is reserved for those patients who decline definitive treatment or as adjunctive therapy following surgery and radiotherapy. DA agonists or SS analogs may also be used, GnRH antagonists may decrease hormone levels but do not affect the tumor size. In a case report a patient who refused surgery, BRC was administered and plasma FSH and α-subunit rapidly decreased; on MRI the tumor size was gradually reduced *(71)*.

Thyrotropin (TSH)-Secreting Pituitary Tumors

TSH-secreting pituitary adenomas represent about 1–2% of all pituitary adenomas and cause central hyperthyroidism. Most of the cases are macroadenomas, while microadenomas may exceptionally also occur. Pituitary surgery is the treatment of choice for TSHomas. When surgery fails or it is contraindicated, radiotherapy and SS analogs are therapeutic alternatives. In fact, administration of DA agonists failed to persistently block TSH secretion in almost all patients and caused tumor shrinkage only in those with combined hypersecretion of TSH and PRL *(64)*.

Summary

As a consequence of the well-defined hypophysiotrophic role of DA, it is not surprising that structurally and chemically similar compounds to DA, i.e., DA agonists, are frequently used in the clinical practice. In this article we have focused on practical aspects and areas in which there have been significant recent developments. Dopamine agonists are the preferred treatment for both symptomatic microprolactinomas and macroprolactinomas; these drugs result in normalization of hormone levels and tumor shrinkage in most treated patients. New DA agonists (such as cabergoline and parenteral bromocriptine) with prolonged duration of action offer improved compliance in the treatment of pituitary tumors. Besides prolactinomas, DA agonist therapy is more and more often a treatment of choise for acromegaly, adrenocorticotropin hormone (ACTH)-secreting, thyroid-stimulating hormone (TSH)-secreting, and nonfunctional pituitary adenomas.

Acknowledgments

Financial support for the present work was provided by OTKA T 035216 and ETT 022/2003 to MIG and OTKA T 043370 to NGM.

References

1. Abs, R., Verhelst, J., Maiter, D., et al. (1998). *J. Clin. Endocrinol. Metab.* **83,** 374–378.
2. Arita, J., Hashi, A., Hoshi, K., Mazawa, S., and Suzuki, S. (1998). *Neuroendocrinology* **68,** 163–171.
3. Asa, S. L., Kelly, M. A., Grandy, D. K., and Low, M. J. (1999). *Endocrinology* **140,** 5348–5355.
4. Autelitano, D. J., Snyder, L., Sealfon, S. C., and Roberts, J. L. (1989). *Mol. Cell. Endocrinol.* **67,** 101–105.
5. Bankowski, B. J. and Zacur, H. A. (2003). *Clin. Obstet. Gynecol.* **46,** 349–362.
6. Barlier, A., Pellegrini-Bouiller, I., Caccavelli, L., et al. (1997). *Horm. Res.* **47,** 227–234.
7. Bell, P. M., Atkinson, A. B., Hadden, D. R., et al. (1986). *Arch. Intern. Med.* **146,** 1145–1149.
8. Besser, G. M. and Wass, J. A. (1978). *Med. J. Aust.* **2,** 31–33.
9. Bevan, J. S., Webster, J., Burke, C. W., and Scanlon, M. F. (1992). *Endocr. Rev.* **13,** 220–240.
10. Biller, B. M. and Daniels, G. (1998). In: *Harrison's principles of internal medicine.* Fauci, A. S., Braunwald, E., Isselbach, K., et al. (eds.). McGraw-Hill: New York.
11. Biller, B. M., Molitch, M. E., Vance, M. L., et al. (1996). *J. Clin. Endocrinol. Metab.* **81,** 2338–2343.
12. Bunzow, J. R., Van Tol, H. H., Grandy, D. K., et al. (1988). *Nature* **336,** 783–787.
13. Burrow, G. N., Wortzman, G., Rewcastle, N. B., Holgate, R. C., and Kovacs, K. (1981). *N. Engl. J. Med.* **304,** 156–158.
14. Caron, M. G., Amlaiky, N., and Kilpatrick, B. F. (1986). In: *Frontiers in neuroendocrinology.* Ganong, W. F. and Martini, L. (eds.). Raven Press: New York.
15. Casulari, L. A., Naves, L. A., Mello, P. A., Pereira Neto, A., and Papadia, C. (2004). *Horm. Res.* **62,** 300–305.
16. Ciccarelli, E. and Camanni, F. (1996). *Drugs* **51,** 954–965.
17. Civelli, O., Bunzow, J. R., Grandy, D. K., Zhou, Q. Y., and Van Tol, H. H. (1991). *Eur. J. Pharmacol.* **207,** 277–286.
18. Colao, A., Di Sarno, A., Cappabianca, P., Di Somma, C., Pivonello, R., and Lombardi, G. (2003). *N. Engl. J. Med.* **349,** 2023–2033.
19. Colao, A., Di Sarno, A., Sarnacchiaro, F., et al. (1997). *J. Clin. Endocrinol. Metab.* **82,** 876–883.
20. Colao, A., Ferone, D., Lastoria, S., et al. (2000). *Clin. Endocrinol.* **52,** 437–445.
21. Colao, A., Loche, S., Cappa, M., et al. (1998). *J. Clin. Endocrinol. Metab.* **83,** 2777–2780.
22. Colao, A. and Lombardi, G. (1997). *J. Clin. Endocrinol. Metab.* **82,** 2755–2756.
23. Colao, A., Merola, B., Sarnacchiaro, F., et al. (1995). *Horm. Res.* **44,** 222–228.
24. Colao, A., Vitale, G., Cappabianca, P., et al. (2004). *J. Clin. Endocrinol. Metab.* **89,** 1704–1711.
25. Corenblum, B. and Donovan, L. (1993). *Fertil. Steril.* **59,** 671–673.
26. Cozzi, R., Attanasio, R., Lodrini, S., and Lasio, G. (2004). *Clin. Endocrinol.* **61,** 209–215.
27. Deleu, D., Northway, M. G., and Hanssens, Y. (2002). *Clin. Pharmacokinet.* **41,** 261–309.
28. Di Sarno, A., Landi, M. L., Cappabianca, P., et al. (2001). *J. Clin. Endocrinol. Metab.* **86,** 5256–5261.
29. Ezzat, S., Asa, S. L., Couldwell, W. T., et al. (2004). *Cancer* **101,** 613–619.
30. Fahy, U. M., Foster, P. A., Torode, H. W., Hartog, M., and Hull, M. G. (1992). *Gynecol. Endocrinol.* **6,** 183–188.
31. Freda, P. U., Andreadis, C. I., Khandji, A. G., et al. (2000). *J. Clin. Endocrinol. Metab.* **85,** 8–13.
32. Freda, P. U. and Wardlaw, S. L. (1999). *J. Clin. Endocrinol. Metab.* **84,** 3859–3866.
33. Freeman, M. E., Kanyicska, B., Lerant, A., and Nagy, G. M. (2000). *Physiol. Rev.* **80,** 1523–1631.
34. Frieze, T. W., Mong, D. P., and Koops, M. K. (2002). *Endocr. Pract.* **8,** 296–303.

35. Gillam, M. P., Middler, S., Freed, D. J., and Molitch, M. E. (2002). *J. Clin. Endocrinol. Metab.* **87,** 4447–4451.
36. Giros, B., Sokoloff, P., Martres, M. P., Riou, J. F., Emorine, L. J., and Schwartz, J. C. (1989). *Nature* **342,** 923–926.
37. Glaz, E. (2001). In: *Textbook of clinical endocrinology and metabolism*. Leovey, A. (ed.). Medicina: Budapest.
38. Hall, W. A., Luciano, M. G., Doppman, J. L., Patronas, N. J., and Olsdfield, E. H. (1994). *Ann. Intern. Med.* **120,** 817–820.
39. Jackson, D. M. and Westlind-Danielsson, A. (1994). *Pharmacol. Ther.* **64,** 291–370.
40. Jaffe, C. A. and Barkan, A. L. (1992). *Endocrinol. Metab. Clin. North Am.* **21,** 713–735.
41. Kelly, M. A., Rubinstein, M., Asa, S. L., et al. (1997). *Neuron* **19,** 103–113.
42. Kletzky, O. A. and Vermesh, M. (1989). *Fertil. Steril.* **51,** 269–272.
43. Korbonits, M., Morris, D. G., Nanzer, A., Kola, B., and Grossman, A. B. (2004). *Front. Horm. Res.* **32,** 63–95.
44. Kovacs, K., Stefaneanu, L., Horvath, E., et al. (1991). *Virchows Arch. A. Pathol. Anat. Histopathol*. **418,** 439–446.
45. Krieger, D. T. (1983*). Endocr. Rev.* **4,** 22–43.
46. Lamberts, S. W., de Lange, S. A., and Stefanko, S. Z. (1982). *J. Clin. Endocrinol. Metab.* **54,** 286–291.
47. Leslie, W. D., Abrams, D. N., Greenberg, C. R., and Hobson, D. (1996). *J. Nucl. Med.* **37,** 1589–1591.
48. MacLeod, R. (1976). In: *Frontiers in neuroendocrinology*. Martini, L. and Ganong, W. F. (eds.). Raven Press: New York.
49. Melmed, S., Dowling, H., and Frohman, L. (1994). *Am. J. Med.* **97,** 468–473.
50. Miller, J. W. and Crapo, L. (1993). *Endocr. Rev.* **14,** 443–458.
51. Missale, C., Nash, S. R., Robinson, S. W., Jaber, M., and Caron, M. G. (1998). *Physiol. Rev*. **78,** 189–225.
52. Monsma, F. J. Jr., McVittie, L. D., Gerfen, C. R., Mahan, L. C., and Sibley, D. R. (1989). *Nature* **342,** 926–929.
53. Murata, Y., Ando, H., Nagasaka, T., et al. (2003). *J. Clin. Endocrinol. Metab.* **88,** 1988–1993.
54. Oppizzi, G., Liuzzi, A., Chiodini, P., et al. (1984). *J. Clin. Endocrinol. Metab.* **58,** 988–992.
55. Passos, V. Q., Souza, J. J., Musolino, N. R., and Bronstein, M. D. (2002). *J. Clin. Endocrinol. Metab.* **87,** 3578–3582.
56. Pinzone, J. J., Katznelson, L., Danila, D. C., Pauler, D. K., Miller, C. S., and Klibanski, A. (2000). *J. Clin. Endocrinol. Metab.* **85,** 3053–3057.
57. Pivonello, R., Ferone, D., de Herder, W. W., et al. (2004). *J. Clin. Endocrinol. Metab.* **89,** 2452–2462.
58. Pivonello, R., Matrone, C., Filippella, M., et al. (2004). *J. Clin. Endocrinol. Metab.* **89,** 1674–1683.
59. Saiardi, A., Bozzi, Y., Baik, J. H., and Borrelli, E. (1997). *Neuron* **19,** 115–126.
60. Saveanu, A., Lavaque, E., Gunz, G., et al. (2002). *J. Clin. Endocrinol. Metab.* **87,** 5545–5552.
61. Schlechte, J. A. (2003). *N. Engl. J. Med.* **349,** 2035–2041.
62. Selbie, L. A., Hayes, G., and Shine, J. (1989). *DNA* **8,** 683–689.
63. Serri, O., Chik, C. L., Ur, E., and Ezzat, S. (2003). *Can. Med. Assoc. J.* **169,** 575–581.
64. Shimon, I. and Melmed, S. (1998). *Ann. Intern. Med.* **129,** 472–483.
65. Snyder, L. A., Roberts, J. L., and Sealfon, S. C. (1991). *Neurosci. Lett.* **122,** 37–40.
66. Thapar, K., Kovacs, K., Scheithauer, B. W., and Lloyd, R. V. (eds.) (2001). *Diagnosis and management of pituitary tumors.* Humana Press: New Jersey.
67. Toldy, E., Locsei, Z., Szabolcs, I., et al. (2003). *Endocrine* **22,** 267–273.
68. Verhelst, J. and Abs, R. (2003). *Treat. Endocrinol.* **2,** 23–32.
69. Verhelst, J., Abs, R., Maiter, D., et al. (1999). *J. Clin. Endocrinol. Metab.* **84,** 2518–2522.
70. Webster, J., Piscitelli, G., Polli, A., Ferrari, C. I., Ismail, I., and Scanlon, M. F. (1994). *N. Engl. J. Med.* **331,** 904–909.
71. Yamakita, N., Komaki, T., Murai, T., and Kawamura, S. (1999). *Intern. Med.* **38,** 266–271.