JOURNAL OF ENDOCRINOLOGICAL INVESTIGATION

Official Journal of the Italian Society of Endocrinology

Volume 1, 1978
Pages 1-404

Editrice Kurtis s.r.l.

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LETTER TO THE EDITOR

ANNOUNCEMENTS

Treatment of patients with prolactinomas[1]

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ABSTRACT. Fiftyone female patients with prolactin producing tumors (PRL 1100 to 88,000 μU/ml) and 26 male patients with prolactin producing tumors (PRL 6500 to 400,000 μU/ml) were studied. Only 25% of the females had visual field defects which were present in 70% of the males. All females had amenorrhea but only 35 had galactorrhea. Hypopituitarism was rarely seen in the females but in most of the male patients. Twentyfour females and all male patients were operated (transsphenoidal or transfrontal operation). PRL normalized in only eight females and in none of the males. Two patients became pregnant postoperatively, four after postoperative treatment with bromocriptine. Bromocriptine induced regular menses in 4 other patients operated by transsphenoidal route. Eight patients with microadenoma (PRL < 4000 μU/ml) were treated with bromocriptine alone of whom two became pregnant. The males were also treated with bromocriptine leading to a significant fall of the PRL level accompanied by improvement of libido, sexual potency and headache. Two patients received radiation postoperatively, which led to a fall of PRL and improvement of visual fields. Since PRL levels remained low after withdrawal of bromocriptine for several months an antiproliferative effect of this drug is suggested. Thus differential therapy of PRL producing tumors is possible: In females selective neurosurgery can alone or combined with medical therapy normalize PRL secretion and ovarian function. In patients with microadenoma bromocriptine alone can be successful. In patients with inoperable large tumors radiation should be advocated. Additional bromocriptine therapy may be helfpful to stop tumor growth and alleviate the effects of hyperprolactinemia.

INTRODUCTION

Since the radioimmunoassay for human prolactin (PRL) has become available (1, 2), a large number of patients with elevated prolactin levels has been discovered. Particularly in females hyperprolactinemia associated with or without pituitary tumors has been shown to be frequently the cause of galactorrhea, amenorrhea or anovulatory menstrual cycles (3, 4). But also in the male, where galactorrhea is usually absent, it could be shown that many pituitary tumors formerly thought to be hormonally inactive were in fact producing prolactin (3,5). As it has turned out the pituitary prolactinoma is the most frequent of all endocrinologically active pituitary tumors (6, 7). In the last five years we have been following more than 180 patients with hyperprolactinemia in our endocrine clinic, who were treated either by surgical procedures (6), by conventional radiation, with bromocriptine or a combination of these therapeutic regimens (8).

MATERIALS AND METHODS

The patients investigated were referred to us because of amenorrhea and galactorrhea, because of clinical evidence for pituitary insufficiency or because of visual field problems. All patients (51 females - age 21 to 63 years - and 26 males - age 16 to 42 years) were admitted to the hospital before the initiation of surgical or medical therapy in order to perform the endocrine evaluation. If patients were operated pituitary function tests were repeated 6 weeks postoperatively.

Human prolactin was measured by radioimmunoassay using the VLS-hPRL for labelling, kindly donated by the National Institute of Health. As standard served pooled pregnancy serum, which was calibrated with the MRC-Research-Standard A-71/222 (9), kindly supplied by the National Institute for Medical Research, Holly Hill, London. 20μU of the MRC-Standard A-71/222 are equivalent to 1 ng VLS-hPRL from the NIH. As hPRL-antibody served a rabbit-antiserum raised against the « little » fragment of serum-hPRL, as described previously

[1]Presented in part at the V International Congress of Endocrinology, Hamburg 1976, Abstr. 101. Supported by Deutsche Forschungsgemeinschaft, SFB 51.

Key-words: Prolactin, prolactinomas, bromocriptine

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Received July 18, 1977; accepted November 2, 1977.

(10). The bound/free separation was performed by double-antibody procedure. No cross reactivity with other pituitary hormones or lactogenic hormones was observed in our radioimmunoassay, the lower limit of detection was 5 μU/ml.

Other hormone determinations: human growth hormone (GH), luteinizing hormone (LH), follicle stimulating hormone (FSH), and thyrotropin (TSH) were measured by standard double-antibody radioimmunoassay (3). Serum cortisol was also measured by radioimmunoassay, thyroxine by competitive protein binding analysis.

Pituitary function was evaluated with the following stimulation tests: thyrotropin releasing hormone (200 μg TRH) for the stimulation of TSH and PRL; gonadotropin releasing hormone (25 μg GnRH) for the stimulation of LH and FSH; insulin hypoglycemia (0.15 U/kg body weight) for the stimulation of cortisol and GH.

Anatomical evaluation in order to demonstrate a pituitary tumor: All patients had lateral skull X-ray as well as sella tomography. Most of the patients had computer-tomography (CT) of the skull. In all patients visual fields were examined.

RESULTS AND DISCUSSION

Prolactin levels in 51 female patients with amenorrhea and/or galactorrhea and pituitary tumors ranged from 1100 to 88,000 μU/ml (Fig.1). As it has been shown (6), there was a good correlation between tumor size and the amount of circulating prolactin. Thus the prolactin levels in 108 females with amenorrhea, galactorrhea and normal sella did not exceed 4000 μU/ml (Fig. 1), thougn it cannot be excluded that these patients also harbor a pituitary microadenoma which has not led to changes of the osseous structure of the sella turcica (11). None of

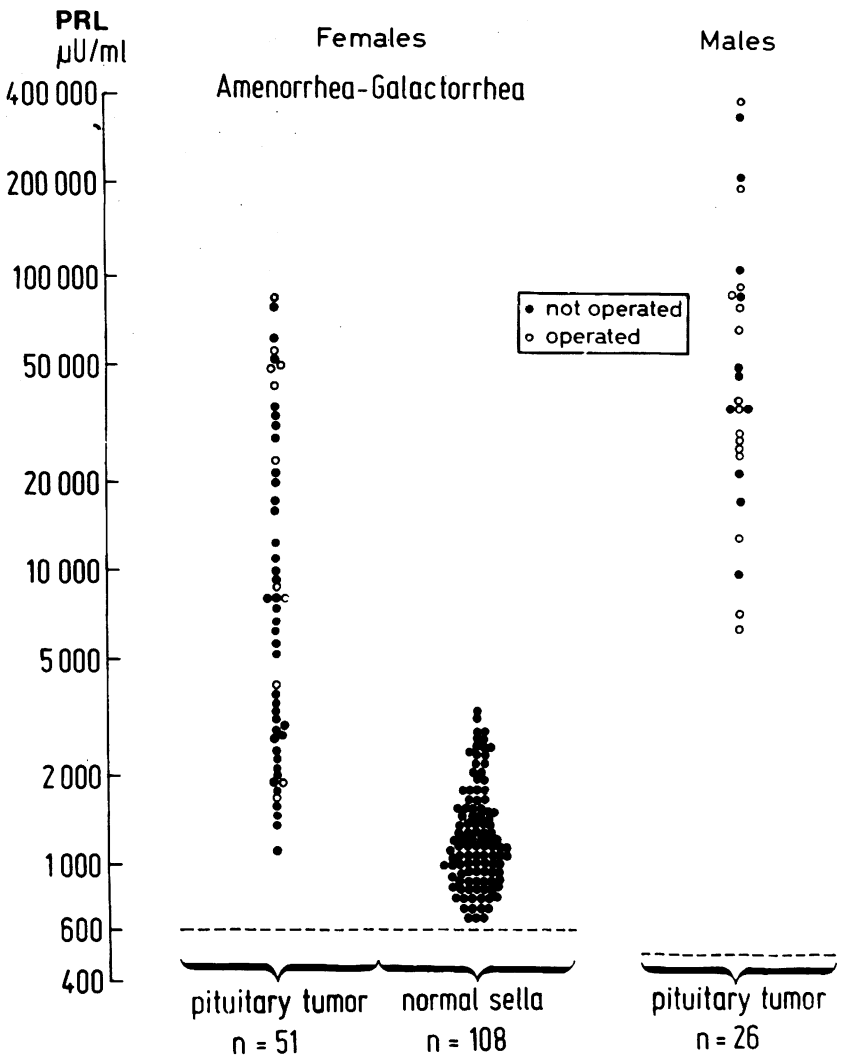

Fig. 1 - *Prolactin levels in 51 females and 26 males with prolactinomas compared to 108 hyperprolactinemic patients with no radiological evidence for a pituitary tumor.*

these patients had any evidence of pituitary insufficiency documented by pituitary function tests. Only 25% of the females with pituitary tumors had visual field defects whereas 70% of the male patients had suprasellar extension of the tumor documented by CT and visual field defects. Only 11 male patients of 26 were investigated before the first operation (Fig. 1), though all had prolactin levels above 6000 μU/ml ranging up to 400,000 μU/ml in one patient after several transfrontal and transsphenoidal pituitary operations, again giving evidence for the good correlation between tumor size and prolactin concentration. Hypopituitarism demonstrated by insufficient responses of pituitary hormones secretion after appropriate stimulation was rarely seen in the females (9%) whereas most of the male patients had lack of growth hormone (82%) and gonadotropin (75%) secretion.

All patients with pituitary tumors and signs of pituitary insufficiency and/or evidence for suprasellar extension were operated by trans-sphenoidal and sometimes trans-cranial route (6). As it has been shown (6), it is extremely difficult to eradicate the prolactin excess by surgical means if prolactin levels are very high (Fig. 2). Thus prolactin levels in 24 females were normalised only in 8, of whom 2 became pregnant, whereas they remained elevated in the other 16 patients (Fig. 2). In the male patients with the higher prolactin levels no normalization after transsphenoidal hypophysectomy could be observed, though there was a significant fall of the basal prolactin in each of them (Fig. 2).

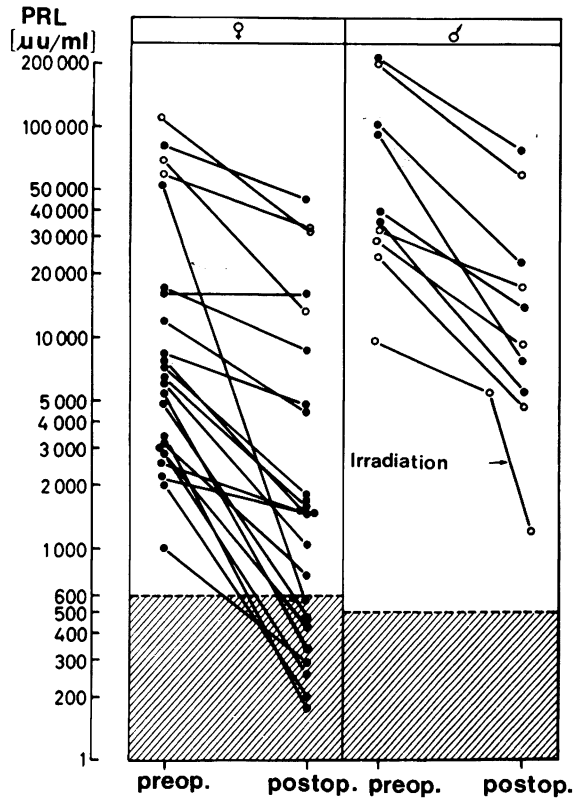

Fig. 2 - *Fall of PRL levels in 24 female and 10 male patients after operation.*

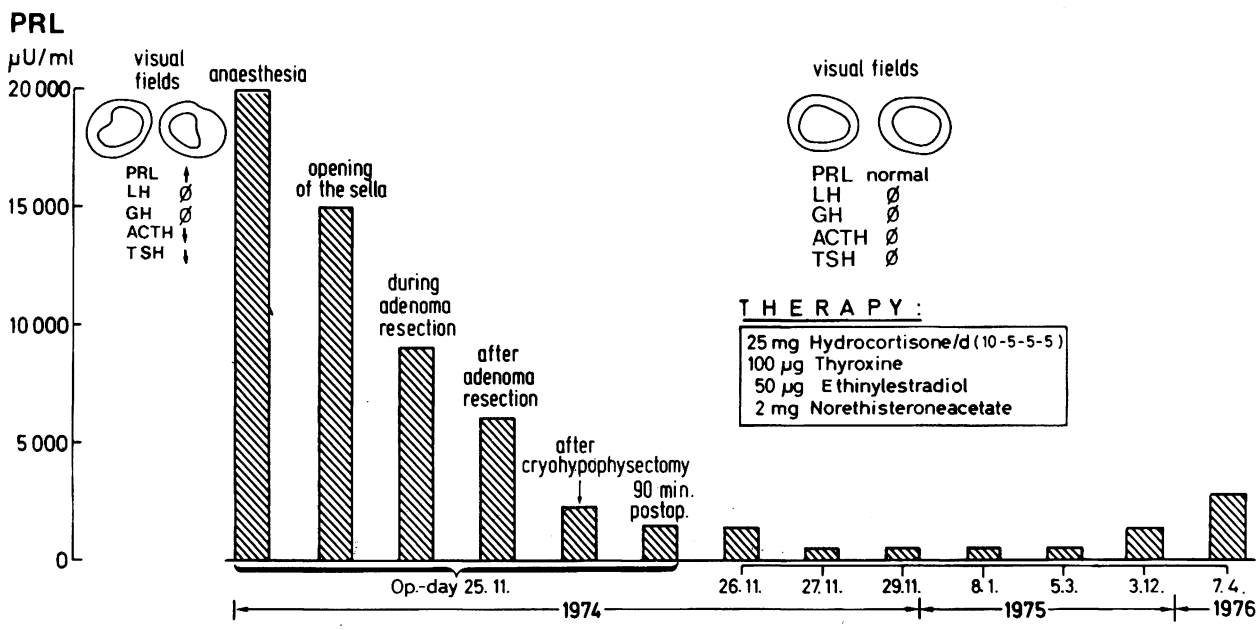

Fig. 3 - *Intra and postoperative PRL levels in a 28 yr old patient with a large prolactinoma. The late rise of PRL after initial normalization signals tumor recurrence.*

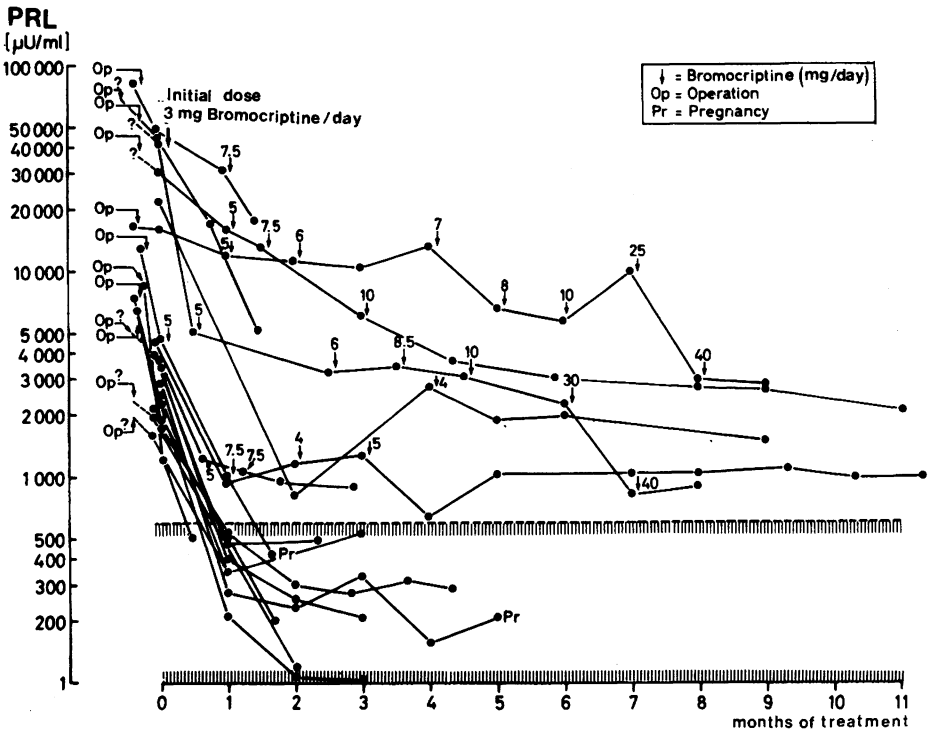

Fig. 4 - *Effect of long-term treatment with bromocriptine in 19 female patients with prolactinoma.*

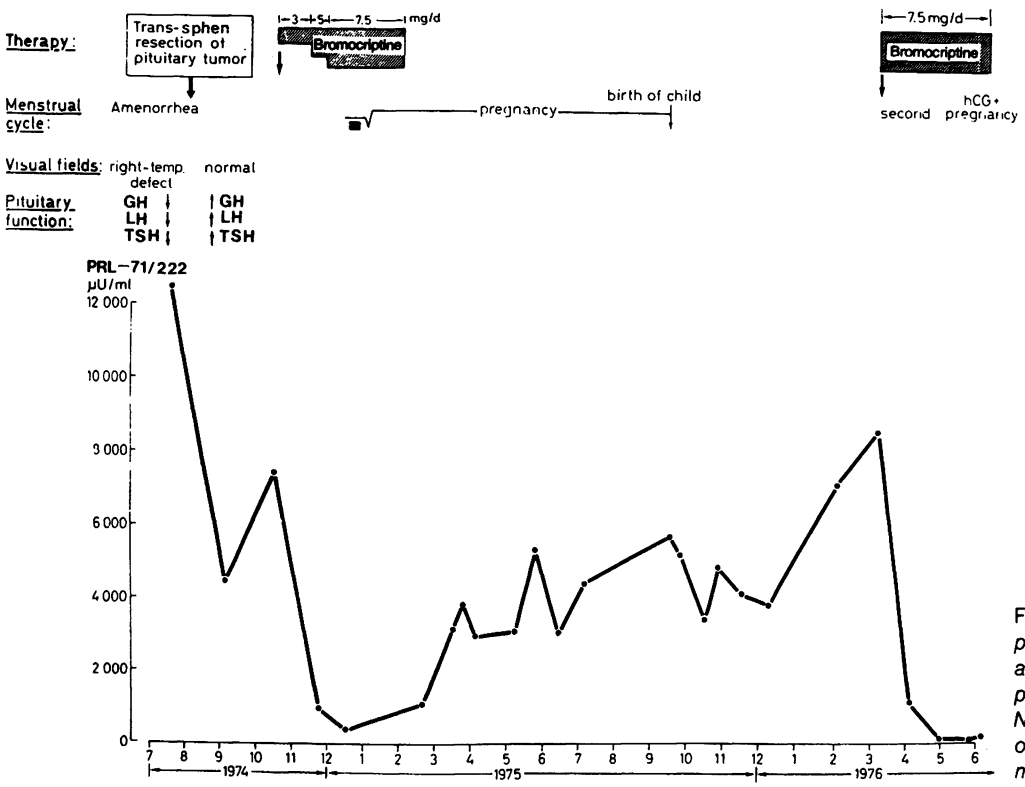

Fig. 5 - *Pregnancy after partial adenomectomy in a 32 yr old patient with prolactinoma. Normal PRL-levels were obtained only after bromocriptine therapy.*

A typical example for a female patient with galactorrhea, amenorrhea, a pituitary tumor and chiasma syndrome is shown in Figure 3. This patient who had already impaired anterior pituitary function preoperatively together with suprasellar extension of a large prolactin producing adenoma was operated by transsphenoidal route in addition with cryotherapy. Right after the operation the prolactin levels were normalized and visual field came back to normal whereas the patient had now complete anterior pituitary failure and required substitutional therapy including estrogens because of severe symptoms due to estrogen deficiency. Though in this case a radical ablation of the pituitary was intended and performed, during recent follow up a gradual increase of the prolactin levels was observed suggesting recurrence of pituitary tumor growth (12). While revising this manuscript no further increase of her serum PRL level has been observed (September 14, 1977).

Since it has been shown that prolactin levels can be effectively lowered by dopamine agonists (13, 14, 15, 16), we have treated 19 female patients with pituitary tumors with bromocriptine, which was well tolerated by all of the patients. Bromocriptine in daily dosages varying from 3 to 7.5 mg normalized prolactin levels in female patients with pituitary tumors, if the postoperative basal prolactin level did not exceed 10,000 μU/ml (Fig. 4). Four of these patients became pregnant after bromocriptine administration and had a completely normal pregnancy with healty babies. In females with prolactin levels above 10,000 μU/ml even larger doses up to 30 and 40 mg did not lead to normalization of prolactin secretion and therefore possible cyclic ovarian function.

A typical example of a patient with a prolactinoma with prolactin levels above 12,000 μU/ml, visual field defects and partial pituitary insufficiency documented by inadequate responses of GH, LH and TSH is shown in Figure 5. Since this patient wanted to become pregnant, in contrast to the patient shown in Figure 3, a selective adenomectomy was intended, so that after the operation pituitary function could recover or remain intact. Due to remaining adenoma tissue, the basal prolactin levels after operation fluctuated between 4000 and 7000 μU/ml. She was therefore treated with 7.5 mg bromocriptine per day. After the first menstrual period she became pregnant and delivered a normal child. After normal breastfeeding period she was again treated with bromocriptine and became pregnant again, giving birth to a second child in February 1977.

A similar case is shown in Figure 6. After surgical resection of the pituitary adenoma without destroying residual pituitary function, the still elevated prolactin levels could be completely normalized by bromocriptine administration leading to disappearance of gal-

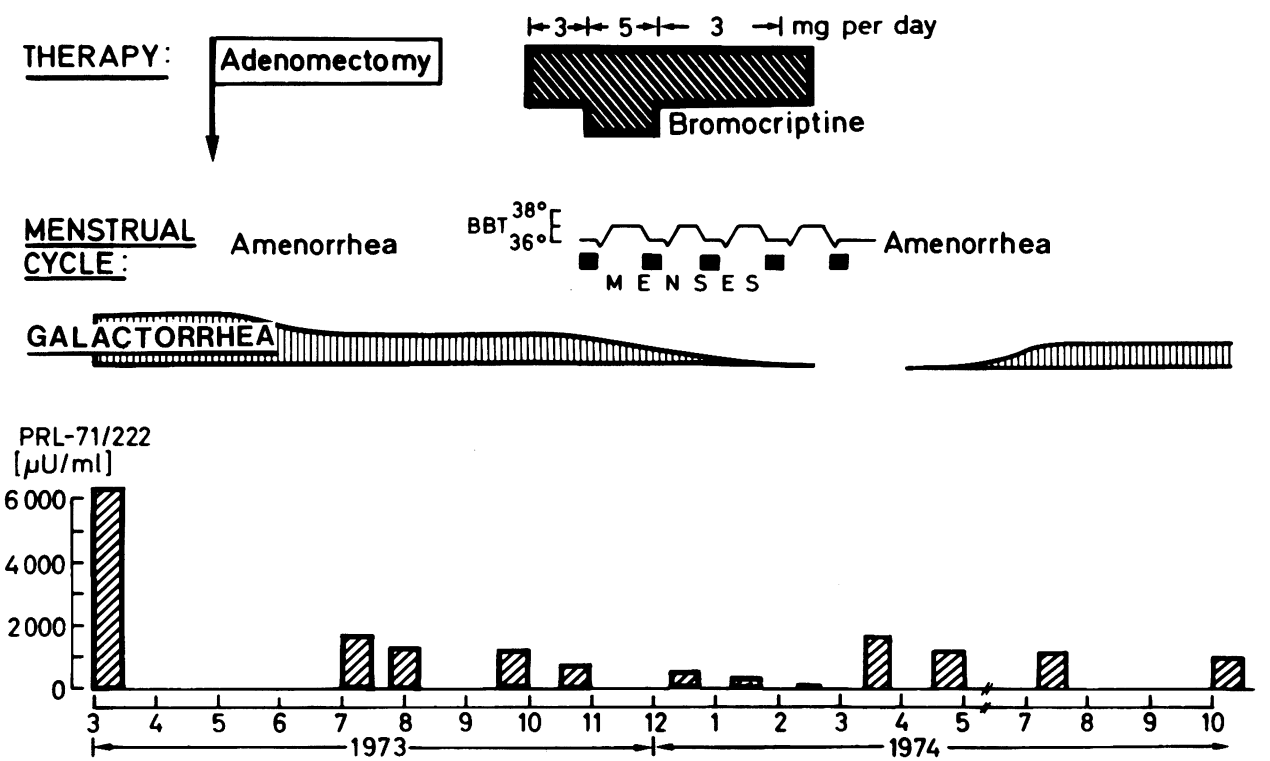

Fig. 6 - *Normal ovarian function after partial adenomectomy and subsequent bromocriptine therapy in a 27 yr old patient with galactorrhea, amenorrhea, and pituitary tumor.*

actorrhea and normal menstrual cycles. After bromocriptine withdrawal, which was given only for a short period, prolactin levels increased again to the initial value and galactorrhea and amenorrhea reoccurred.

When prolactin levels were only moderately elevated and patients wanted to become pregnant and when the pituitary tumor was small without any evidence of pituitary dysfunction or suprasellar extension of the tumor we have treated these patients with bromocriptine alone. Figure 7 shows the course of treatment in a patient with an asymmetrically growing pituitary tumor without visual field defects and no evidence for anterior pituitary dysfunction. Prolactin levels were 3000 μU/ml. After therapy with 3 mg bromocriptine per day the prolactin levels had normalized and she ovulated regularly. She became pregnant and bromocriptine was withdrawn after which the prolactin levels rose again during pregnancy up to 18,000 μU/ml. She delivered a normal child and since her prolactin levels did not fall to pretreatment levels and she suffered from heavy galactorrhea she was then operated by transsphenoidal route. The operation was again not radically performed, because a second pregnancy was desired. Therefore her prolactin levels did not drop to normal which made bromocriptine therapy necessary again leading to regular menses.

There is a twofold reason why the indication for bromocriptine therapy is not confined to females. The first reason for trying to normalize prolactin levels in male patients is that also in the male, in contrast to former beliefs, hyperprolactinemia exerts biological effects (3, 5, 13, 17). It is a frequent clinical observation that male patients with high prolactin levels suffer from lack of libido in the presence of normal testosterone secretion or adequate substitutional testosterone therapy (3, 5). Since prolactin has also a diabetogenic, i.e. insulin antagonistic effect, the glucose tolerance can deteriorate and diabetes mellitus can become evident.

We have treated 14 male patients who all had postoperatively elevated prolactin levels and complained of headaches, depression, particularly loss of libido and impotence in the presence of adequate testosterone substitution with bromocriptine (Fig. 8). In 7 of the patients prolactin levels were normalized by bromocriptine whereas prolactin levels remained

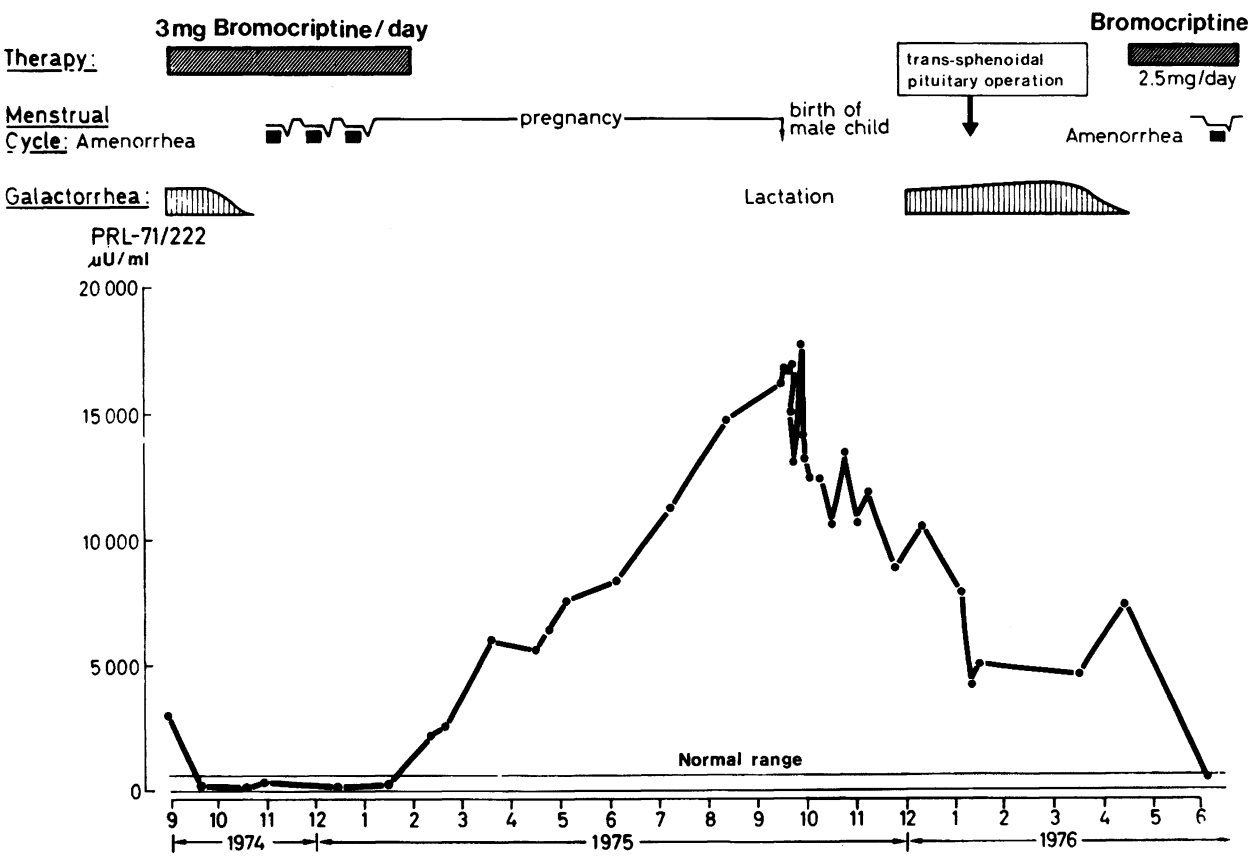

Fig. 7 - *Pregnancy after bromocriptine therapy alone in a 24 yr old patient with prolactinoma. Since PRL levels remained elevated compared to pretreatment levels she was operated after delivery before bromocriptine was started again.*

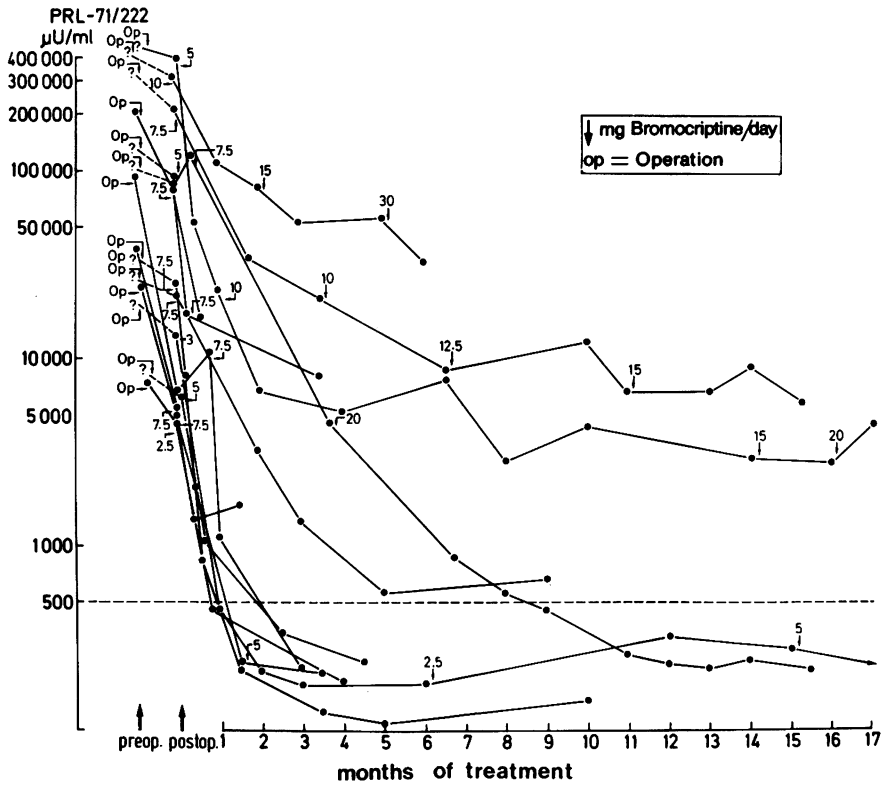

Fig. 8 - *Effect of long-term treatment with bromocriptine in 14 male patients after operation of a prolactinoma.*

elevated though considerably lowered in the other 7 patients. The fall of prolactin was in general accompanied by clinical improvement and feeling of well being. In contrast to the female prolactin levels above 10,000 µU/ml could be normalized by bromocriptine which may be due to the lack of estrogens in the males with their permissive action on prolactin secretion (18). This is also demonstrated by a male patient who had been operated by transsphenoidal route because of a pituitary prolactinoma which was previously thought to be hormonally inactive (Fig. 9). Postoperatively he was still having prolactin levels above 12,000 µU/ml. He suffered from lack of libido and sexual impotence though there was no evidence for pituitary dysfunction and peripheral testosterone levels were in the normal range. He was put on bromocriptine and after the relatively small dose of 3 mg per day prolactin secretion normalized and sexual potency as well as libido and fertility reverted to normal (Fig. 9).

The other reason for treating males and females with prolactinomas and postoperatively persisting hyperprolactinemia with bromocriptine is the now accumulating evidence, that this drug may have an antiproliferative effect on lactotropic pituitary tumor growth (19, 20).

Four patients with pituitary tumors and elevated prolactin levels were treated for 5 to 20 months with bromocriptine in dosages ranging from 5 to 40 mg per day (Table 1). Bromocriptine therapy was withdrawn for a period of 1 - 11 months, after which the prolactin levels were still found to be significantly lower during at least three different measurements on three different days compared to the pretreatment levels. This may also suggest an antiproliferative effect, though we know little about the spontaneous secretory activity of these tumors. Further evidence for such an effect may be a male patient with excessive hyperprolactinemia after two trans-frontal and two trans-sphenoidal operations (Fig. 10). His prolactin levels were extremely elevated - 400,000 µU/ml, which is equivalent to 20 µg of hormone protein per ml. This patient who suffers now from complete panhypopituitarism due to his invasively growing and inoperable prolactin producing tumor, complained mainly about headaches, lack of libido and sexual potency, and suffered from depression. He also had impaired visual fields. Under chronic bromocriptine therapy he feels subjectively better and the prolactin levels have fallen from 400,000 to less than 5000 µU/ml. There was no evidence for progression of tumor growth but in contrast the perimetry demonstrated improvement of his visual field which may be interpreted as actual shrinking of the pituitary tumor (Fig. 10). Alternatively the improvement could be due to relief from pressure of the

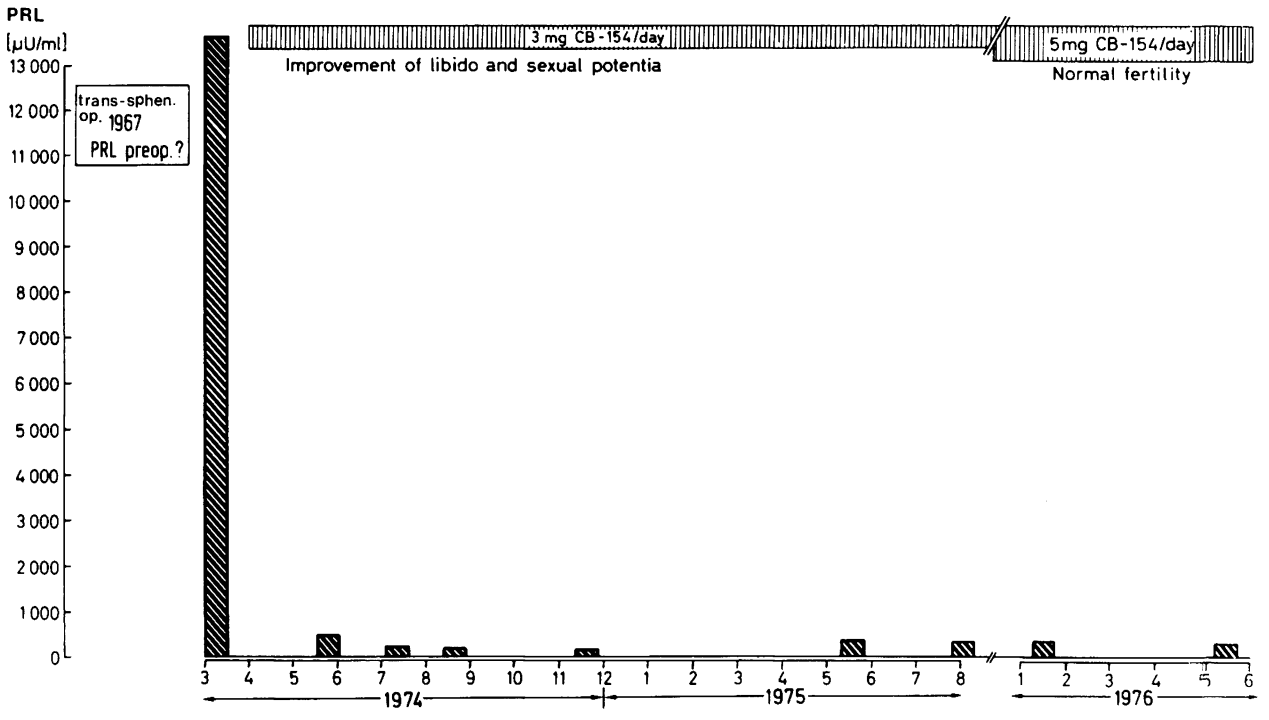

Fig. 9 - *Postoperative bromocriptine treatment in a 33 yr old patient with remaining hyperprolactinemia and disturbance of libido and sexual potency.*

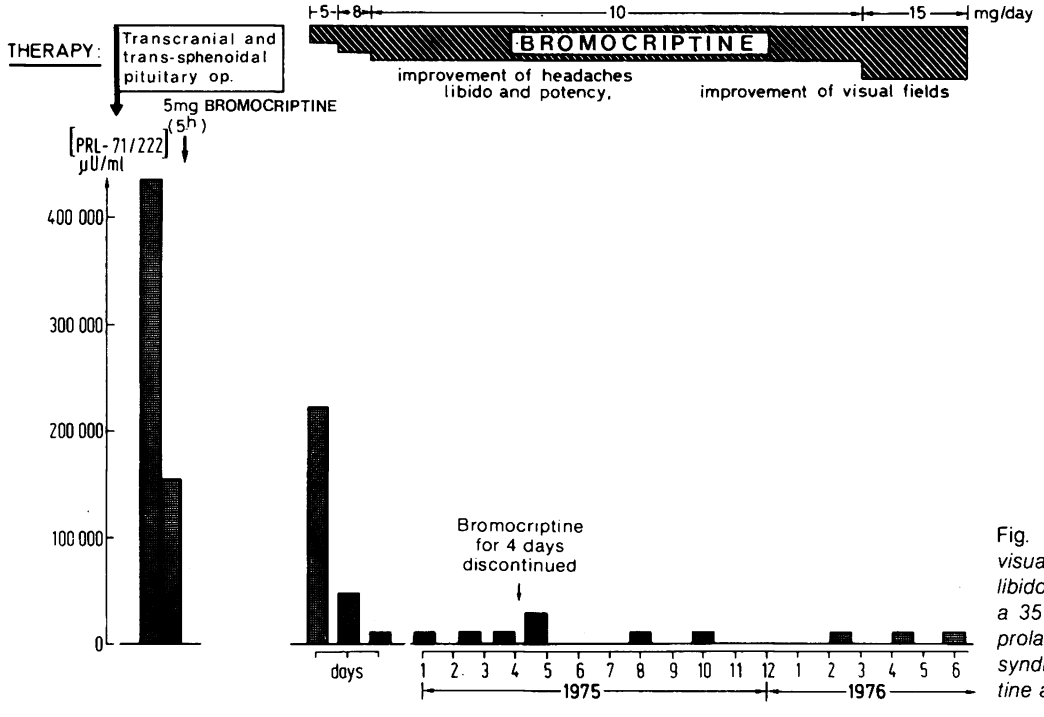

Fig. 10 - *Improvement of visual fields, headaches, libido and sexual potency in a 35 yr old patient with a prolactinoma and chiasma syndrome after bromocriptine administration.*

Table 1 - *PRL levels (μU/ml) after withdrawal of long-term bromocriptine treatment in 4 female patients with pituitary tumor.*

Patient	before therapy	PRL after withdrawal of therapy	Duration of treatment (months)	Bromocriptine (mg/day)	Time without bromocriptine (months)
A.L.	49,340	12,982	12	12.5	1
J.H.	41,910	15,655	5	40	8
S.L.	16,680	10,678	13	40	11
G.G.	5,237	3,100	20	5	2

anterior pathway by tumor and/or edematous changes. It could only be proven by pneumencephalography which was not done or computer tomography which is not possible in this patient because of the many metal clips from previous operations.
That prolactin levels correlate to tumor size has been mentioned before (6). That prolactin levels correlate in individual patients also with tumor growth is documented by a patient with galactorrhea, amenorrhea and a pituitary tumor who was operated by trans-frontal and trans-sphenoidal route because of impairment of visual fields (Fig. 11). When this patient was first admitted to our hospital after two operations the prolactin levels were still elevated. During follow up deterioration of visual fields occurred due to tumor growth accompanied by a sharp rise of basal prolactin. She was inoperable because of severe congestive heart failure and was therefore irradiated after which prolactin levels fell and a slight improvement of her visual field occurred. She was afterwards put on bromocriptine which led to a prompt normalisation of her prolactin secretion.
Bromocriptine has been shown to inhibit growth hormone secretion in patients with acromegaly (21, 22, 23, 24). That bromocriptine can be helpful in patients with hypersecretion of GH and PRL is demonstrated in the patient shown in Figure 12. This acromegalic patient demonstrates quite clearly the problems we sometimes face in managing patients with endocrine active pituitary tumors. She was first operated in 1969 by trans-frontal operation in an outside institution. Preoperative growth hormone and prolactin levels were not known. The indication for operation was the clinical picture of acromegaly. Because of suprasellar extension of the pituitary tumor leading to visual field disturbances she was operated again by trans-frontal approach which did not lower her growth hormone levels at all, though in 1974 when she appeared at a follow up her growth hormone levels were 20 ng/ml and her prolactin

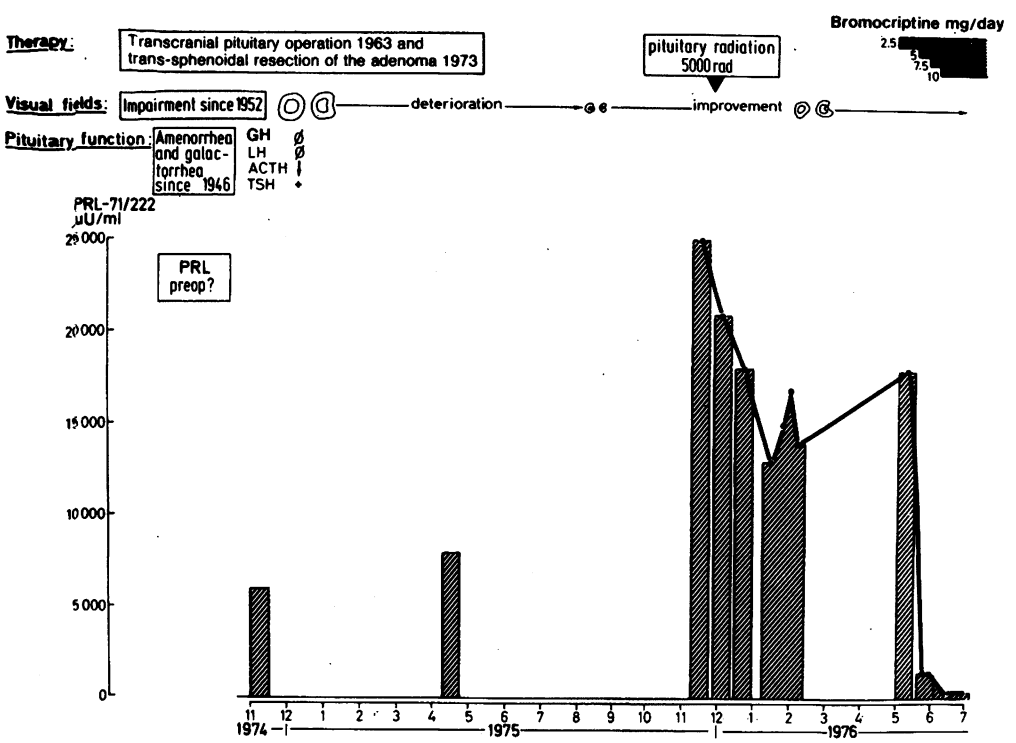

Fig. 11 - *Correlation of prolactin levels and pituitary tumor growth as evidenced by increasing visual field defects in a 56 yr old female.*

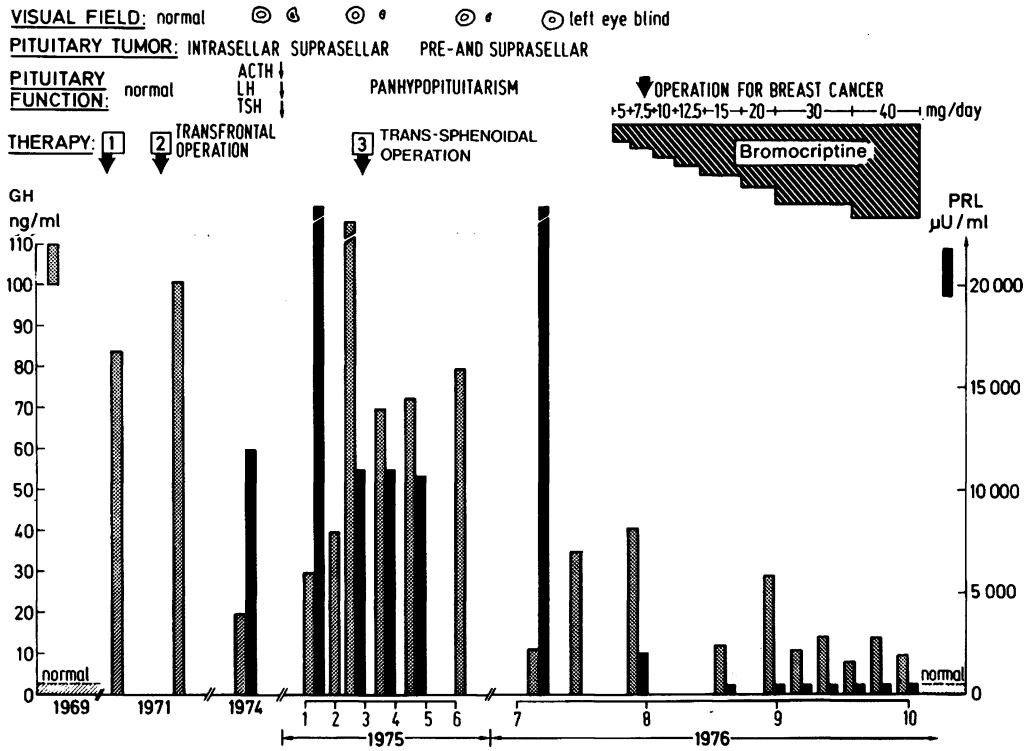

Fig. 12 - *Effect of multiple surgery and bromocriptine on PRL an GH levels in a 40 yr old patient with acromegaly and hyperprolactinemia.*

levels were 10,000 µU/ml, demonstrating that she had hypersecretion of both GH and PRL. Because of rapid deterioration of the visual function of her left eye, she came again to our hospital and she was operated a third time, this time by trans-sphenoidal route. Again there was no significant effect on growth hormone and prolactin levels which were still very high. By computer tomography it could be demonstrated that she had para and suprasellar tumor growth leading to complete blindness of her left eye. We put her therefore on bromocriptine therapy which effectively lowered growth hormone and even more effectively prolactin levels. We thought this to be particularly important since she had in the meantime developed breast cancer which had to be operated.

The connection between the occurrence of breast cancer and hypersecretion of two lactotropic hormones is still object of speculation (25). In this case we think that in addition to bromocriptine therapy radiation of her tumor will be necessary after recovering from mastectomy.

That bromocriptine can inhibit two hormones secreted by pituitary tumor has also been shown in a case recently reported by Horn et al. (26), where bromocriptine led to lowering of TSH and prolactin in a TSH and prolactin producing pituitary tumor.

CONCLUSIONS

From the observations of the 51 female and 26 male patients with pituitary tumors we can make the following conclusions:

1) Hyperprolactinemia associated with pituitary tumors can be treated surgically, medically and with radiotherapy.

2) All patients having visual field defects or signs of impairment of pituitary function should be operated. If operation is impossible pituitary radiation can be an alternative. If prolactin does not normalize after operation or radiation, particularly when these patients suffer from depression, lack of libido or impotence despite adequate testosterone levels, bromocriptine therapy is indicated.

3) In females with prolactin levels above 5000 µU/ml who want to become pregnant, a gentle neurosurgical procedure should induce normalization or lowering of prolactin secretion without disturbing gonadotropic function that postoperative bromocriptine therapy can lead to normal ovulatory cycles.

4) In patients with small pituitary tumors and hyperprolactinemia without any evidence of pituitary insufficiency or visual field defects bromocriptine alone is indicated. If pregnancy occurs these patients have to be monitored during pregnancy by measuring prolactin levels and visual fields in monthly intervals since the enhanced estrogen production may activate pituitary tumor growth. Radiographic control of the sella turcica with appropriate precautions is advisable one month before term.

5) Patients with endocrine active pituitary adenomas

secreting two different hormones seem to be responsive to bromocriptine therapy leading to the abolition of both hormone excesses.
6) There is some evidence that bromocriptine exerts an antiproliferative effect on pituitary tumor growth, which justifies postoperative bromocriptine administration. If consequent postoperative therapy can prevent recurrence of pituitary tumor growth in every patient has to be established in the future.

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