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CONTENTS OF VOLUME 1

No. 1, January 1978

Effects of salbutamol and metoprolol on plasma renin activity and plasma potassium of normal subjects and of hypertensive patients <i>A. Salvetti, L. Poli, F. Arzilli, L. Sassano, R. Pedrinelli, and M. Motolese</i>	1
Response to TRH, serum thyroid hormone concentration, and serum markers of autoimmunity after antithyroid therapy in Graves' disease <i>B.A. Lamberg, A. Aro, Pirkko Saarinen, T. Tötterman, and Tuulikki Mäkinen</i>	9
Radio-receptor assay of TSH: its use to detect thyroid-stimulating immunoglobulins <i>G. Fenzi, E. Macchia, L. Bartalena, F. Mazzanti, L. Baschieri, and L.J. DeGroot</i>	17
Inhibition of thyrotropin and prolactin secretion by dopamine in man <i>F. Massara, F. Camanni, V. Vergano, L. Belforte, and G.M. Molinatti</i>	25
Differences between temporal patterns of plasma cortisol and corticosteroid-binding globulin binding capacity throughout the twenty-four hour day and the menstrual cycle <i>A. Angeli, R. Frajria, L. Dogliotti, C. Crosazzo, F. Rigoli, and F. Ceresa</i>	31
Hypothalamic-pituitary-ovarian function in hyperprolactinemic women <i>P. Travaglini, B. Ambrosi, P. Beck-Peccoz, R. Elli, M. Rondena, R. Bara, and G. Weber</i>	39
Treatment of patients with prolactinomas <i>K.v. Werder, R. Fahbusch, R. Landgraf, C.R. Pickardt, H.K. Rjosk, and P.C. Scriba</i>	47
Adrenal hyperandrogenism: detection by adrenal scintigraphy <i>John E. Freitas, William H. Beierwaltes, and Ronald H. Nishiyama</i>	59
SHORT COMMUNICATIONS	
Bromocriptine-induced pregnancy in two cases of euprolactinemic hypothalamic amenorrhea <i>T. Nencioni, A. Miragoli, F. Dorato, and F. Polvani</i>	65
Plasma immunoreactive thyrotropin releasing hormone (TRH) values in normal newborns <i>G. Lombardi, G. Lupoli, F. Scopacasa, R. Panza, and M. Minozzi</i>	69
Cord blood reverse T ₃ in normal, premature, euthyroid low T ₄ , and hypothyroid newborns <i>Jody Ginsberg, Paul G. Walfish, and Inder J. Chopra</i>	73
REVIEW ARTICLES	
Nuclear receptors for thyroid hormone <i>L.J. DeGroot, S. Refetoff, J. Bernal, P.A. Rue, and A.H. Coleoni</i>	79
Mechanisms underlying hormone effects on pineal function: a model for the study of integrative neuroendocrine processes <i>Daniel P. Cardinali, and Maria I. Vacas</i>	89
LETTER TO THE EDITOR	
Follow-up during oral contraception <i>P.G. Crosignani</i>	97
ANNOUNCEMENTS	
Seventeenth National Congress of the Italian Society of Endocrinology	99
International Symposium on Pituitary Microadenomas	99

No. 2, April 1978

Effects of estradiol decanoate in ovariectomized women <i>M. Luisi, P.M. Kicovic, E. Alicicco, and F. Franchi</i>	101
Endemic goitre and iodine metabolism in schoolchildren from the Daunia uplands (province of Foggia, Italy) <i>V. De Filippis, G. Cenderelli, U. Cocco, A. Di Cerbo, G. Lo Iudice, and A. Costa</i>	107

Adrenal and gonadal steroids and pituitary response to LHRH in girls. I: Delayed puberty <i>A.R. Genazzani, C. Pintor, F. Facchinetti, A. Faedda, R. Corda, and P. Fioretti</i>	115
The effect of TRH on the release of TSH, PRL and GH in man under basal conditions and following methysergide <i>R. Collu</i>	121
Effect of pinealectomy on arterial blood pressure and food and water intake in the rat <i>A. Zanoboni, A. Forni, W. Zanoboni-Muciaccia, and C. Zanussi</i>	125
Effects of estrogen on ³ H-leucine uptake by the hypothalamus and pituitary: correlation with hypothalamic and serum LHRH and LH <i>S.P. Kalra</i>	131
Etiological factors of endemic goiter in north-eastern Sicily <i>F. Delange, R. Vigneri, F. Trimarchi, S. Filetti, V. Pezzino, S. Squatrito, P. Bourdoux, and A.M. Ermans</i>	137
Adrenal and gonadal steroids and pituitary response to LHRH in girls. II. Precocious puberty <i>C. Pintor, A.R. Genazzani, P. Ibba, L. Pecciarini-Snickars, and R. Corda</i>	143
Klinefelter's syndrome: a study of its hormonal plasma pattern <i>G. Forti, G. Giusti, A. Borghi, M. Pazzagli, G. Fiorelli, E. Cabresi, M. Mannelli, F. Bassi, P. Giannotti, S. Fusi, and M. Serio</i>	149
Determination of thyroid stimulating immunoglobulins (TSI) during the course of Graves' disease. A reliable indicator for remission and persistence of this disease? <i>H. Schleusener, R. Finke, P. Kotulla, K.W. Wenzel, H. Meinhold, and H.D. Roedler</i>	155
A rapid semi-automated method of determining total estrogens in non-pregnancy urine <i>David O.E. Gebhardt, Willem Soederhuizen, and Abraham J. Moolenaar</i>	163
COMMENT	
Unchanged thyrotropin and prolactin responses to thyrotropin releasing hormone after indomethacin treatment <i>P. Masturzo, T. Barreca, A. Gallamini, R. Gianrossi, G. Murialdo, and M.C. Nizzo</i>	167
SHORT COMMUNICATIONS	
The effect of prednisone on serum thyrotropin, thyroxine and triiodothyronine concentrations in hypothyroid patients <i>J. Jensen, G. Nolan, and W. Jubiz</i>	171
Sympathetic innervation and noradrenaline content of normal human thyroid tissue from fetal, young, and elderly subjects <i>A. Melander, J.-G. Ljunggren, K.-A. Norberg, B. Persson, E. Rosengren, F. Sundler, S. Tibblin, and U. Westgren</i>	175
Effect of neurotensin on glucose and insulin portal blood levels in hyperglycemic rats <i>J.M.S. Farina, F. Celotti, M. Motta, and L. Martini</i>	179
REVIEW ARTICLE	
Pathogenesis of neonatal Graves' disease <i>J.M. McKenzie and M. Zakarija</i>	183
LETTER TO THE EDITOR	
Recommendations of the European Thyroid Association for mass screening for neonatal hypothyroidism <i>C. Beckers, F. Delange, R. Hoefler, M.P. König, F. Monaco, and S. Varrone</i>	191
ANNOUNCEMENTS	
17th National Congress of the Italian Society of Endocrinology	193
9th Annual Meeting of the European Thyroid Association	193
54th Annual Meeting of the American Thyroid Association	193
1978 European Symposium on Hormones and Cell Regulation	194
International Symposium on Pituitary Microadenomas	194
Second European Symposium on Hypoglycemia	195
Symposium on Autoimmune Aspects of Endocrine Disorders	195
First International Congress on Hormones and Cancer	196

No.3, July 1978

Kinetics of sodium in rabbit arterial wall: inability of aldosterone to alter extra to intracellular distribution <i>J.G. Llaurado, and G.A. Smith</i>	197
An <i>in vitro</i> study of sex hormone metabolism in the pituitaries and gonads of neonatal and young rats: the effect of prenatal reduction of litter size <i>Z. Kniewald, S. Milković, M. Pernzović, and K. Milković</i>	203
Glucocorticoid receptors in human fetal lung <i>S. Iacobelli, F. Ranelletti, G. Sica, and G. Barile</i>	209
Transmitter mediated arginine vasopressin release from superfused hypothalamus and pituitary gland <i>H. Wagner, H. Häberle, V. Maier, and R.E. Lang</i>	215
Iodine content of human tissues after administration of iodine containing drugs or contrast media <i>A. Costa, O. Brambati Testori, C. Cenderelli, G. Giribone, and M. Migliardi</i>	221
The plasma inorganic iodine and the pituitary-thyroid axis in pregnancy <i>D.A. Koutras, A.D. Pharmakiotis, N. Koliopoulos, J. Tsoukalos, A. Souvatzoglou, and J. Sfontouris</i>	227
Prolactin receptors: a comparison between chloramine-T and lactoperoxidase iodination <i>Kuo-Jang, and V.D. Ramirez</i>	233
Klinefelter's syndrome: effects of short-term testosterone administration on hypothalamic-pituitary axis function <i>G. Forti, A. Borghi, G. Giusti, M. Pazzagli, P. Giannotti, M. Mannelli, S. Fusi, and M. Serio</i>	239
The production of thyroid-stimulating immunoglobulin (TSI) by lymphocytes from patients with Graves' disease cultured with human thyroid subcellular fractions <i>A. Sugenoya, K. Trokoudes, V.V. Row, and R. Volpé</i>	245
Studies of immunoreactivity to human lacrimal gland fractions in patients with ophthalmic Graves' disease <i>J.R. Wall, A. Trewin, S.L. Fang, S.H. Ingbar, and L.E. Braverman</i>	253
Effect of hyperglycemia on the growth hormone response to L-dopa in diabetic subjects <i>A. Barbarino, L. De Marinis, and F. Martino</i>	259
CASE REPORT	
Panhypopituitarism and anemia secondary to traumatic fracture of the sella turcica <i>A. Kanade, A.E. Ruiz, K. Tornoyos, I. Wakabayashi, and A.J. Kastin</i>	263
COMMENTS	
Serum somatomedin and insulin levels in tumor hypoglycemia <i>B. Joffe, M. Kew, G. Beaton, B. Kusman, and H. Seftel</i>	269
The influence of prenatal or neonatal administration of 2-bromo- α -ergocryptine on pituitary prolactin secretion and normal neoplastic mammary growth in adult mice <i>H. Nagasawa, and R. Yanai</i>	273
REVIEW ARTICLE	
The action and control of the calcium-regulating hormones <i>I. MacIntyre</i>	277
LETTERS TO THE EDITOR	
Diagnostic approach to amenorrhea <i>P.G. Crosignani</i>	285
Recommendations for mass screening for congenital hypothyroidism <i>R. Vigneri, and A. Albertini</i>	287
Plasma potassium and adrenergic system <i>F. Massara, F. Camanni, and G.M. Molinatti</i>	289
ANNOUNCEMENTS	
1978 European Symposium on Hormones and Cell Regulation	291
International Symposium on Pituitary Microadenomas	291
International Symposium on Free Thyroid Hormones	292

Second European Symposium on Hypoglycemia	293
Symposium on Autoimmune Aspects of Endocrine Disorders	293
First International Colloquium on Receptors, Neurotransmitters and Peptides Hormones	294
German Society of Endocrinology: Competitions for 1979	295
First International Symposium on Neuroactive Drugs in Endocrinology	295
First International Congress on Hormones and Cancer	296

THE ITALIAN SOCIETY OF ENDOCRINOLOGY	
New Officers	297

No. 4, October 1978

An <i>in vitro</i> procedure for the estimation of thyroid hormone releasing factors in sera of thyrotoxic patients <i>M.L. Maayan, E.M. Volpert, and F.P. Dawry</i>	299
Effect of melatonin on induction of ovulation in the light-induced constant estrous-anovulatory syndrome and possible role of the brain serotonergic system <i>G.P. Trentini, B. Mess, C.F. De Gaetani, and C. Ruzsás</i>	305
Postnatal development of pituitary-thyroid function in male and female rats: comparison of plasma and thyroid T ₃ and T ₄ concentration <i>H. Fukuda, and M.A. Greer</i>	311
The effect of indomethacin on plasma renin activity and urinary aldosterone of patients with essential hypertension <i>R. Pedrinelli, F. Arzilli, L. Cavasini, L. Poli, P. Sassano, and A. Salvetti</i>	315
Thyrotropin receptor-adenylate cyclase system in plasma membranes from normal and diseased human thyroid glands <i>P. Carayon, M. Guibout, and S. Lissitzky</i>	321
Use of direct thyroxine-binding globulin measurement in the evaluation of thyroid function <i>D. Glinoer, M. Fernandez-Deville, and A.M. Ermans</i>	329
The adenylate cyclase-cyclic AMP-phosphodiesterase system in pathological human thyroid <i>V. Macchia, E. Mandato, C. Carella, G. Pisano, and G. Biscaglia</i>	337
Sleep-wake differences in serum prolactin levels in children <i>A. Polleri, P. Masturzo, G. Vignola, T. Barreca, and A. Gallamini</i>	347

COMMENT

Failure of oral bromocriptine to affect hypergastrinemia in two patients with the Zollinger-Ellison syndrome <i>D.F. Child, I. Laing, and P.G. Ganguli</i>	351
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SHORT COMMUNICATIONS

Lack of effect of bromocriptine on ACTH levels in patients with bilateral adrenalectomy for pituitary-dependent Cushing's syndrome <i>N. O'Mullane, B. Walker, J. Jefferson, L. Hipkin, M. Diver, and C. Davis</i>	355
Circulating prolactin and its response to TRH following administration of testosterone undecanoate in normal men <i>P.M. Kicovic, M. Luisi, F. Franchi, and S. Krempf</i>	359
Reciprocal effects of prolactin and thyroxine on the growth rate of rat pups from weaning to puberty <i>J. Shani, and G. Goldhaber</i>	363
The effects of estrogen treatment of carcinoma of the prostate on regional adipocyte size <i>M. Krotkiewski, and P. Björntorp</i>	365

REVIEW ARTICLES

Physical training and diabetes mellitus <i>K. Johansen</i>	367
Hormogenetic errors in thyroid tumor <i>F. Monaco, and M. Andreoli</i>	373

LETTER TO THE EDITOR

Reverse T₃ and screening for congenital hypothyroidism
R. Vigneri, S. Filetti, E. Lisi, S. Squatrito, and P. Polosa
P.G. Walfish, J. Ginsberg, and I.J. Chopra

385

ANNOUNCEMENTS

International Symposium on Free Thyroid Hormones
Second European Symposium on Hypoglycemia
European Workshop on the Biochemistry and Biophysics of the Pancreatic B-cell
Symposium on Autoimmune Aspects of Endocrine Disorders
International Symposium on Human Placenta-Proteins and Hormones
Endocrinology '79
First International Symposium on Neuroactive Drugs in Endocrinology
First International Congress on Hormones and Cancer
Ninth Meeting of the International Study Group for Steroid Hormones
Eighth International Thyroid Congress
International Symposium on Oligozoospermia

389
390
390
391
392
393
393
394
395
396
396

Subject index to volume 1
Authors index to volume 1
Contents of volume 1

397
403
iii

Treatment of patients with prolactinomas¹

K.v. Werder*, R. Fahlbusch**, R. Landgraf*, C.R. Pickardt*, H.K. Rjosk***, and P.C. Scriba*.

*Department of Medicine, Innenstadt, **Department of Neurosurgery, and ***Ist. Department of Gynecology, University of Munich, Fed. Rep. Germany.

ABSTRACT. Fiftyone female patients with prolactin producing tumors (PRL 1100 to 88,000 $\mu\text{U}/\text{ml}$) and 26 male patients with prolactin producing tumors (PRL 6500 to 400,000 $\mu\text{U}/\text{ml}$) 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 (transphenoidal 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 transphenoidal route. Eight patients with microadenoma (PRL < 4000 $\mu\text{U}/\text{ml}$) 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 helpful 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. 20 μU 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

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Correspondence: K. von Werder, Department of Medicine, Innenstadt, University of Munich, Fed. Rep. Germany

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(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 $\mu\text{U}/\text{ml}$.

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 $\mu\text{U}/\text{ml}$ (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 $\mu\text{U}/\text{ml}$ (Fig. 1), though 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

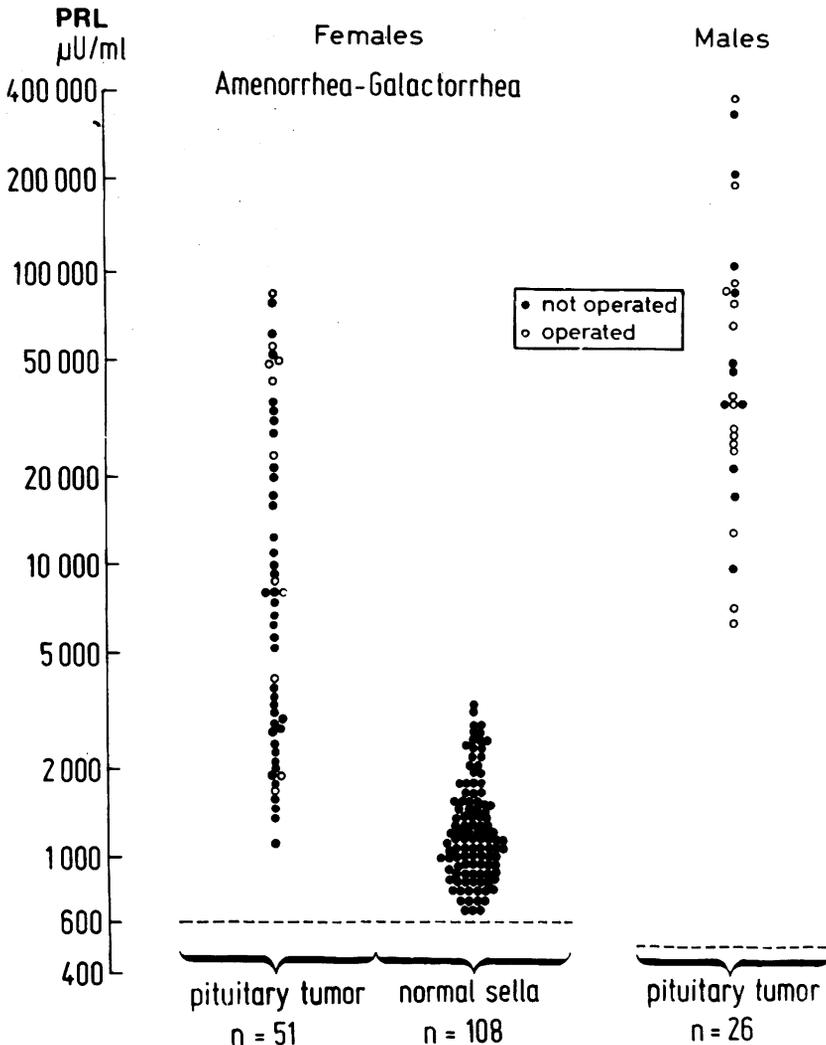


Fig. 1 - Prolactin levels in 51 females and 26 males with prolactinomas compared to 108 hyperprolactinemic patients with no radiological evidence for a pituitary tumor.

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 $\mu\text{U}/\text{ml}$ ranging up to 400,000 $\mu\text{U}/\text{ml}$ 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 trans-sphenoidal hypophysectomy could be observed, though there was a significant fall of the basal prolactin in each of them (Fig. 2).

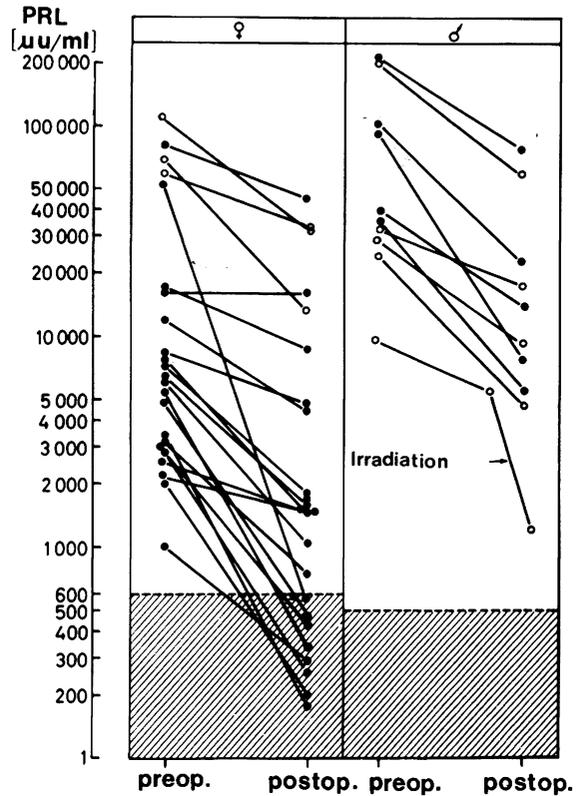


Fig. 2 - Fall of PRL levels in 24 female and 10 male patients after operation.

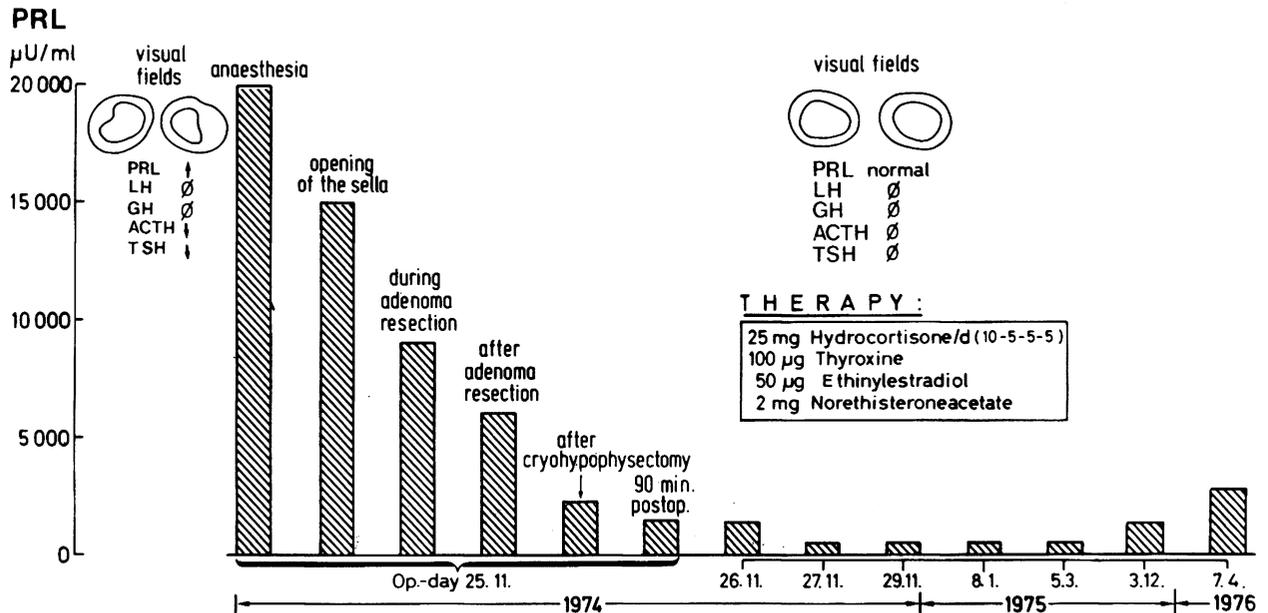


Fig. 3 - Intra and postoperative PRL levels in a 28 yr old patient with a large prolactinoma. The late rise of PRL after initial normalization signals tumor recurrence.

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 transphenoidal 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 post-operative basal prolactin level did not exceed 10,000 $\mu\text{U}/\text{ml}$ (Fig. 4). Four of these patients became preg-

nant after bromocriptine administration and had a completely normal pregnancy with healthy babies. In females with prolactin levels above 10,000 $\mu\text{U}/\text{ml}$ 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 $\mu\text{U}/\text{ml}$, 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 $\mu\text{U}/\text{ml}$. 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-

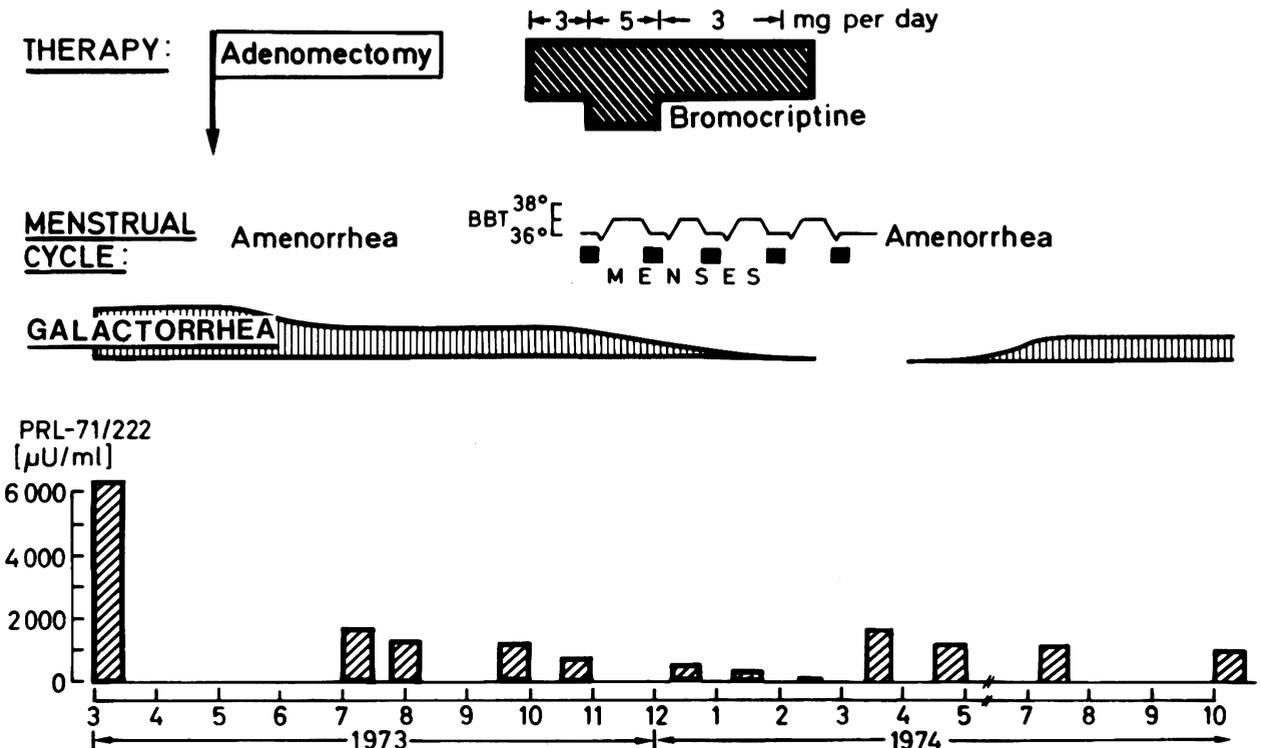


Fig. 6 - Normal ovarian function after partial adenomectomy and subsequent bromocriptine therapy in a 27 yr old patient with galactorrhea, amenorrhea, and pituitary tumor.

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 $\mu\text{U}/\text{ml}$. 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 $\mu\text{U}/\text{ml}$. 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 trans-sphenoidal route. The operation was again not radi-

cally 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

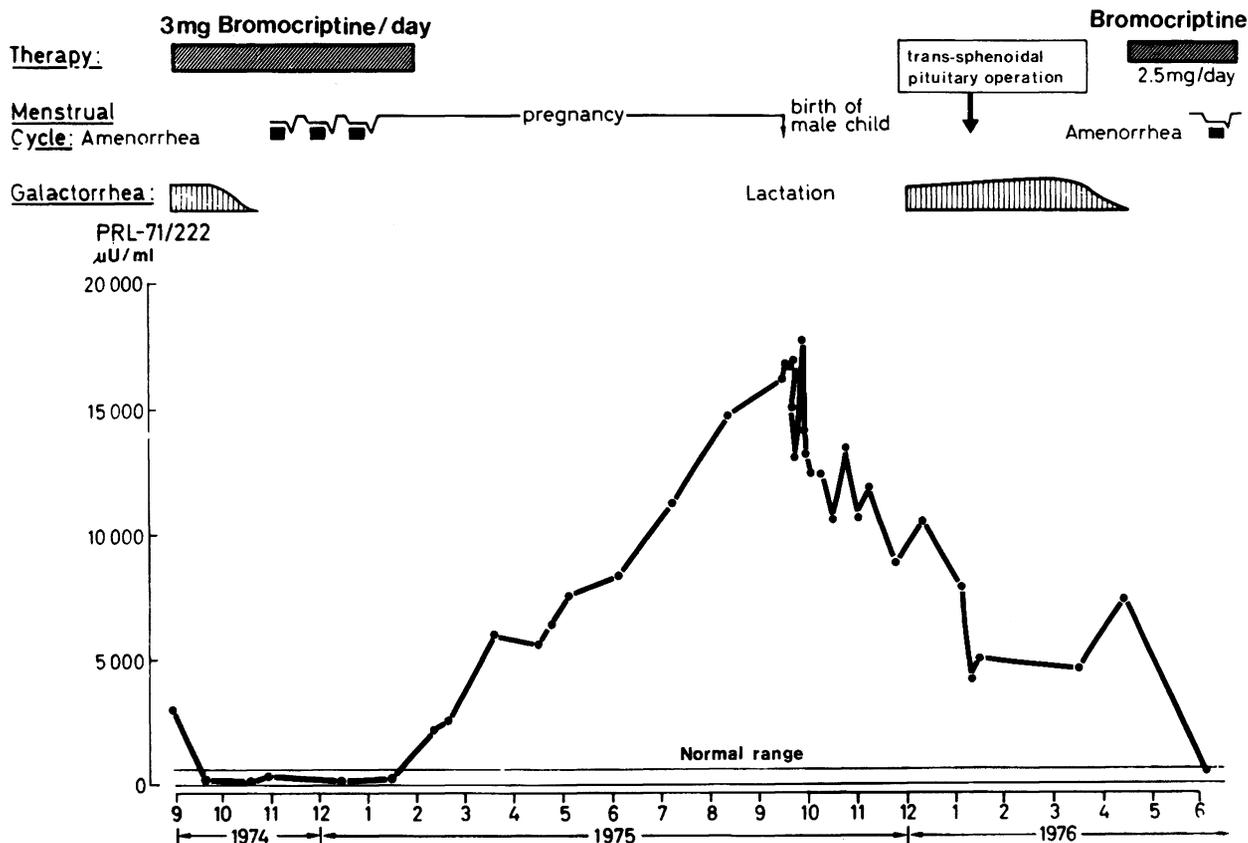


Fig. 7 - Pregnancy after bromocriptine therapy alone in a 24 yr old patient with prolactinoma. Since PRL levels remained elevated compared to pretreatment levels she was operated after delivery before bromocriptine was started again.

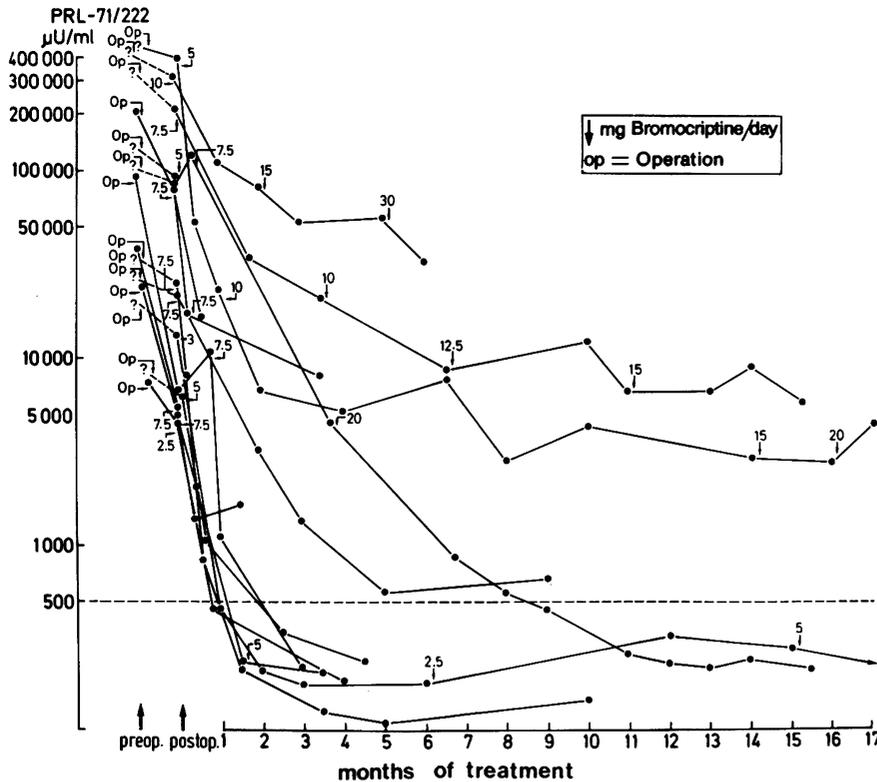


Fig. 8 - Effect of long-term treatment with bromocriptine in 14 male patients after operation of a prolactinoma.

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 $\mu\text{U/ml}$ 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 trans-sphenoidal 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 $\mu\text{U/ml}$. 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 $\mu\text{U/ml}$, 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 $\mu\text{U/ml}$. 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

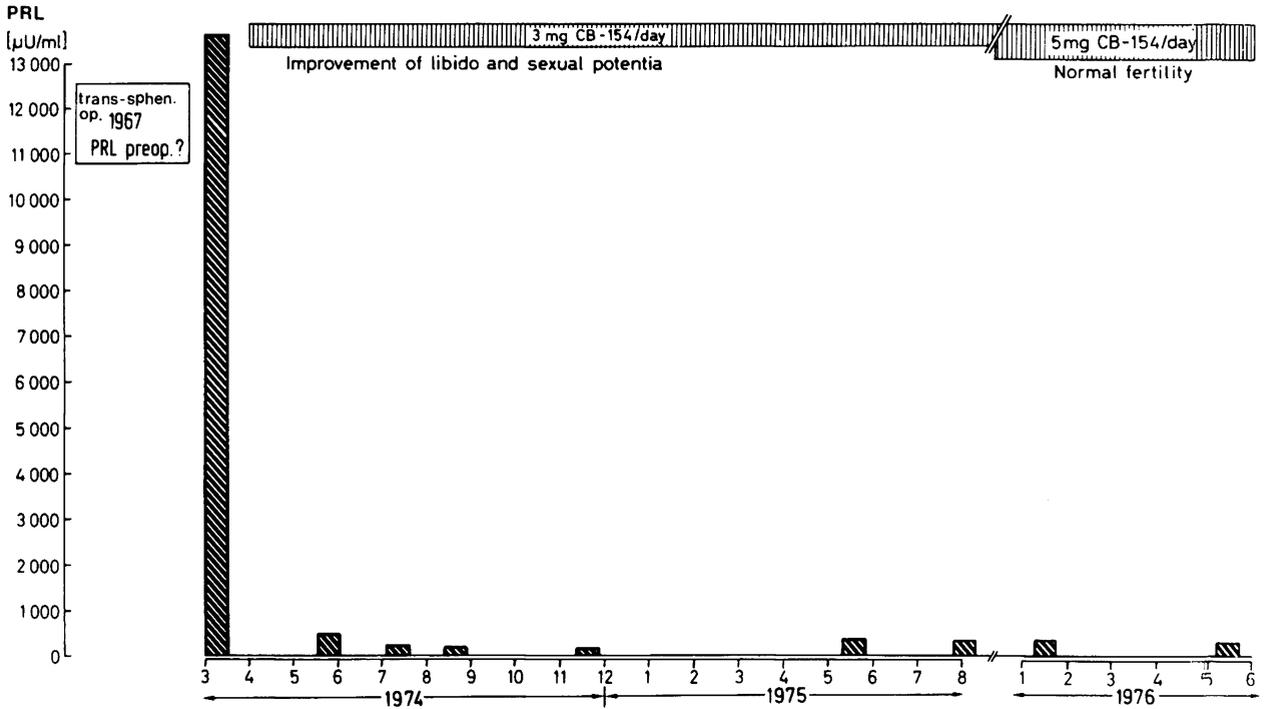


Fig. 9 - Postoperative bromocriptine treatment in a 33 yr old patient with remaining hyperprolactinemia and disturbance of libido and sexual potency.

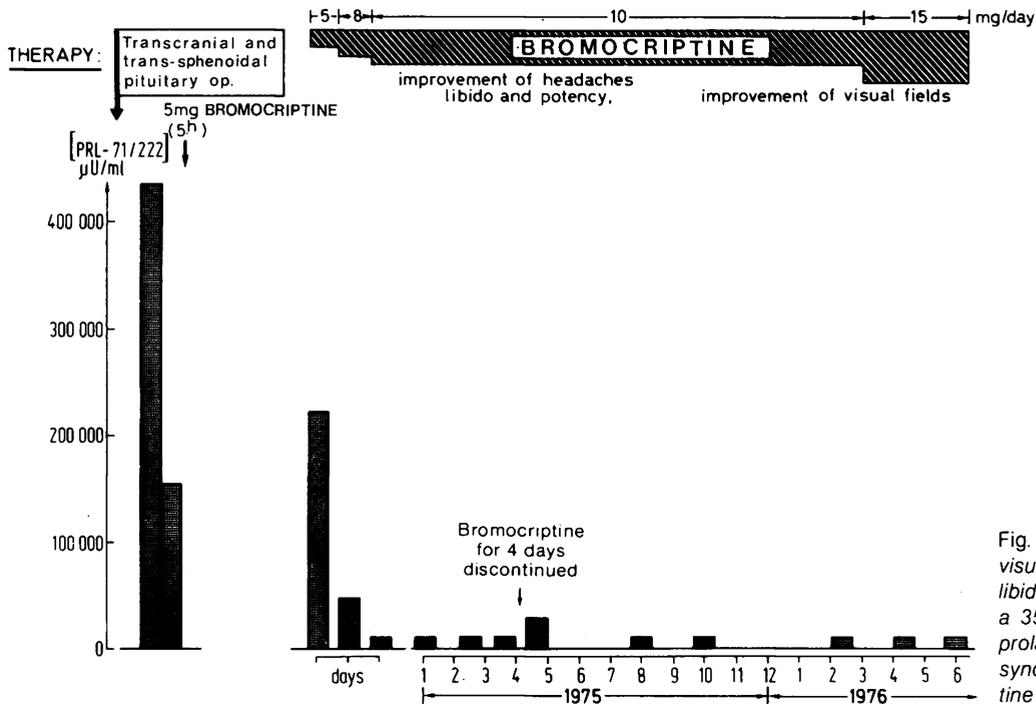


Fig. 10 - Improvement of visual fields, headaches, libido and sexual potency in a 35 yr old patient with a prolactinoma and chiasma syndrome after bromocriptine administration.

Table 1 - PRL levels ($\mu\text{U/ml}$) after withdrawal of long-term bromocriptine treatment in 4 female patients with pituitary tumor.

Patient	PRL 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 pneumoencephalography 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 normalization 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

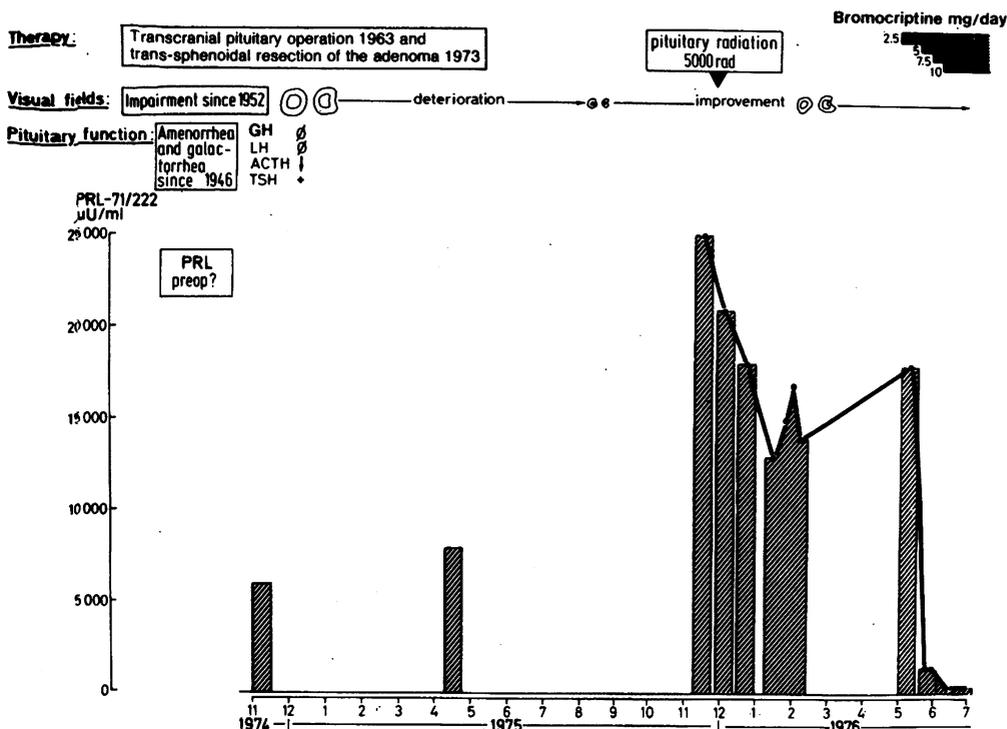


Fig. 11 - Correlation of prolactin levels and pituitary tumor growth as evidenced by increasing visual field defects in a 56 yr old female.

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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