

# BROMOCRIPTINE FOR VISUAL FIELD DEFECTS IN PROLACTINOMAS

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## INTRODUCTION

The introduction of bromocriptine (2-bromocryptine mesylate), a semi-synthetic ergot alkaloid, has revolutionised the treatment of the amenorrhoeagalactorrhoea syndrome due to excessive prolactin secretion (Thorner *et al.*, 1975). In a significant number of cases, this hyperprolactinaemia is caused by a radiologically obvious pituitary tumour (L'Hermite *et al.*, 1977; Bergh *et al.*, 1978 a) which may expand causing pressure effects on adjacent structures notably the optic chiasma. Optic chiasmal compression resulting in visual field impairments may occur in nonpregnant patients with radiologically normal fossae (Vaidya *et al.*, 1978) but is more common during pregnancy especially when a large tumour is present (Corenblum *et al.*, 1975; Bergh *et al.*, 1978 b; Burzaco *et al.*, 1978). Many authors would therefore recommend that hyperprolactinaemic patients with even the slightest suggestion of fossa enlargement should not be allowed to become pregnant until definitive treatment is instituted to the adenoma either by irradiation or a surgical removal (Hardy, 1973; Child *et al.*, 1975; Besser, 1978). Prolactin secretion is under an inhibitory control by the hypothalamus through the prolactin

inhibiting factor (PIF) (Clark *et al.*, 1978). This factor, released through dopaminergic stimulation, reaches the prolactin-producing cells via the hypothalamohypophyseal portal system and inhibits prolactin release (Enjalbert *et al.*, 1978). Recently it was shown that dopamine itself could behave as a PIF and could interact directly with dopamine receptors on the pituitary cells (Besser, 1978). Bromocriptine, a dopamine agonist (Clark *et al.*, 1978), could therefore inhibit prolactin secretion by dopaminergic influence on the hypothalamus, stimulating PIF release (Fluckiger, 1978). More likely, bromocriptine decreases prolactin secretion by acting as a functional analogue of PIF and directly activating dopamine receptors on the pituitary lactotrophs (Clark *et al.*, 1978).

There is some evidence to suggest that bromocriptine not only inhibits prolactin release but also prevents the hormone synthesis (Davies *et al.*, 1974). Animals studies have also shown that bromocriptine could reduce mitotic rate, cell proliferation and even size of pituitary tumours (Quadri *et al.*, Lloyd *et al.*, 1975).

It is conceivable therefore that bromocriptine could be used in man to reduce tumour mass which has expanded either independently or through a stimulatory effect of pregnancy. This reduction should relieve chiasmal compression and normalise visual fields, obviating the need for other active emergency intervention such as an operation.

This paper describes two hyperprolactinaemic patients with visual field defects which improved on bromocriptine therapy.

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## Case I

Miss L. Y., a 23 year old Chinese, was first seen in March 1979 with a history of menstrual problems of 3 years duration. She attained menarche at the age of 14 and the menses were regular with a cycle of  $30 \pm 2$  days and duration of 8-9 days. For the last three years, her periods had become progressively delayed, initially for 1-2 weeks, later for 2-3 months. The flow too became more scanty and lasted for only 1-2 days until she was completely amenorrhoeic in December 1977. She was otherwise healthy and had no other complaint except for an occasional left-sided headache associated with giddiness and blurring of vision. These symptoms would resolve spontaneously and had not been worse since first noted in 1971. There was no previous drug history and she had not been on contraceptive pills. She was seen by a gynaecologist who noted the galactorrhoea and started her on bromocriptine 2.5 mg tds a month prior to attending the Endocrine Clinic.

On examination, she was healthy-looking with a pulse of 80/min. and BP 110/80. There was no feature to suggest acromegaly or hypothyroidism. Examination of the heart, lungs, abdomen and fundi showed no abnormality but milky discharge could be expressed from both breasts.

Investigations showed a haemoglobin of 10.0 g/dl., white blood cells of 4200/cu. cm with a normal differential and an ESR of 4 mm/hr. Blood urea was 28 mg/dl., potassium 3.4 mmol/l, sodium 140 mmol/l and chloride 105 mmol/l.

Random blood sugar was 108 mg/dl. and the morning cortisol 12 ug/dl., Serum  $T_4$  was 6.2 ug/dl., FT<sub>4</sub>I 1.84 and TSH 1.5 mU/l. Serum FSH

was 3.4 IU/l, LH 3.6 IU/l and plasma oestradiol 67 pg/ml. These values were all within the normal range. Serum prolactin was in the upper limit of normal initially (650 mU/l) while the patient was on bromocriptine but this became elevated when the medication was withheld (fig. 1).

Visual field assessment showed a small defect on the upper temporal quadrant in both eyes. The fields were reassessed after one month and these defects were found to be persistent (fig. 2a-b).

Plain x-rays showed a normal-size fossa with thinning of the sella turcica posteriorly (fig. 4), confirmed on the tomograms. CAT-Scan was done,

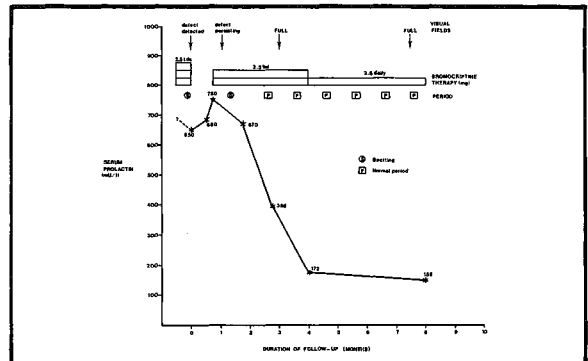


Fig. 1 Serum prolactin of patient L. Y. Prolactin was normal during the first visit as the patient was prescribed bromocriptine earlier. The level increased after stopping treatment, but this came down with the reinstitution of bromocriptine. Bromocriptine treatment resulted in spotting (S) followed by normal regular periods (P) and restoration of full visual fields.

followed by air-encephalographic studies.

After the second visual field assessment, the patient was started on bromocriptine 2.5 mg bd. Her period returned after two months and had been regular with a cycle of  $30 \pm 3$  days and a

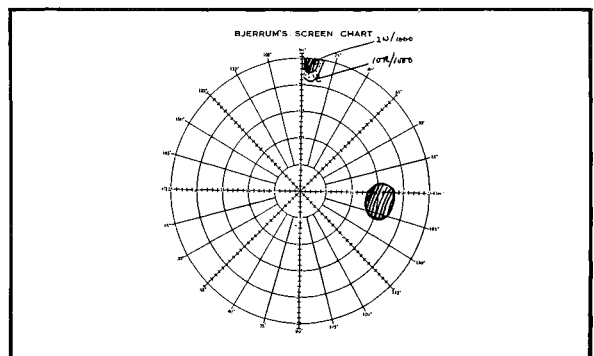
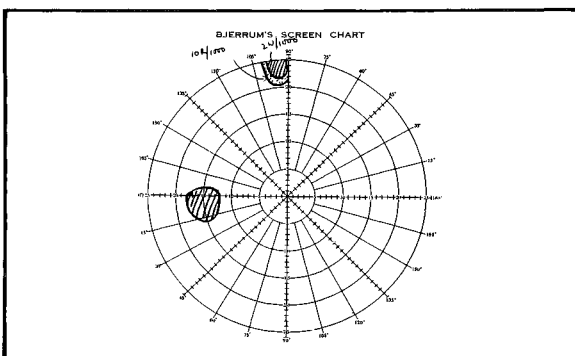


Figure 2a-b Visual fields of patients L. Y. before bromocriptine therapy showing a localized defect to both white targets in the left eye. (Fig. 2a) and the right eye (Fig. 2b).

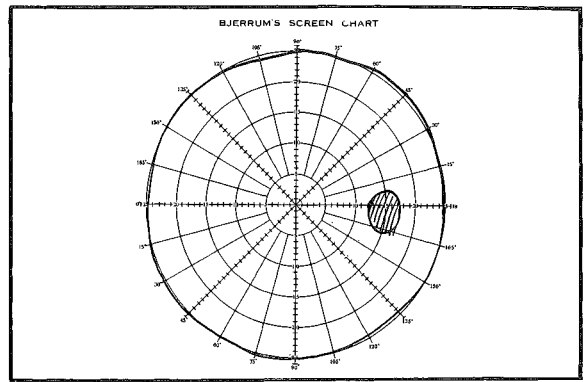
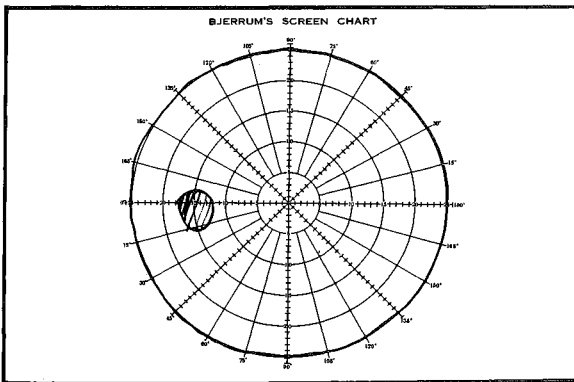


Figure 3 a-b Restoration of full visual fields in patient L.Y. for both the left (Fig. 3a) and the right eye (Fig. 3b).

duration of 5-7 days. She had no further complaint of blurring vision but still suffered from giddiness and left-sided headache especially on rapid standing.

There was no breast discomfort but a clear serous discharge could still be expressed bilaterally.

A repeat Bjerrum's screening was done after two months on bromocriptine and the visual fields were found to be full (fig. 3a-b). Bromocriptine was reduced to a maintenance dose of 1.25 mg daily and the latest serum prolactin showed a normal value. A visual field done at the last visit in January 1980 was normal and the patient was otherwise well.

## Case 2

Mrs. O.S.Y., a Chinese aged 27 years, was referred to the Endocrine Clinic in June 1978 for management of visual field defects in pregnancy. Her history dates back to February 1975 when she first presented to Kluang District Hospital for secondary amenorrhoea of 10 months' duration and a 4-year history of expressed galactorrhoea.

Her period was regular and normal previously. She had been married for 6 years but had never conceived. She was subsequently referred to the Neurology Institute, Kuala Lumpur for further investigations and management. The visual fields were found to be normal and full with a visual acuity of 6/6 in both eyes. Serum  $T_4$  and the brain scan were normal but skull x-rays showed an enlarged and eroded fossa.

She was first treated with L-Dopa and later with ergotamine tartarate and 'Largactil' but showed no

improvement. Bromocriptine was started in May 1977 and her period returned and galactorrhoea ceased.

She again presented to the clinic in June 1978 complaining of headache and blurring of vision especially on the left eye for one week. Her periods had been regular since August but had stopped again since November, 1977 even though she was still taking bromocriptine. Examination showed

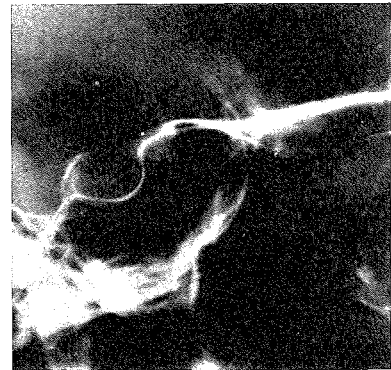


Fig. 4: Cone-view of the pituitary fossa of patient L.Y. with thinning of the inferior and posterior walls.

that she was pregnant with a fundal height of 28-30 weeks. Perimetry showed marked visual field constrictions in both eyes, more so on the left (fig. 5a-b) and visual acuity reduced to 1/60. Fundoscopy showed slight pallor of the medial margins of both discs. Her serum prolactin was markedly elevated (greater than 13,200 mU/l), FSH was 5.2 IU/l, LH > 25 IU/l and plasma oestradiol > 800 pg/ml. Plasma cortisol (9 ug/dl) and serum  $T_4$  (5.5 ug/dl) were normal.

The patient was started on bromocriptine 2.5 mg tds and this was increased to 2.5 mg qid a week

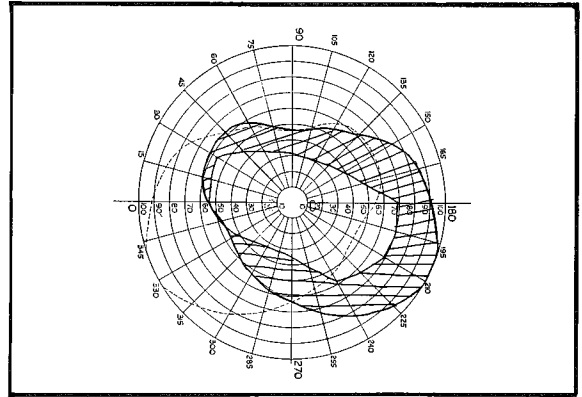
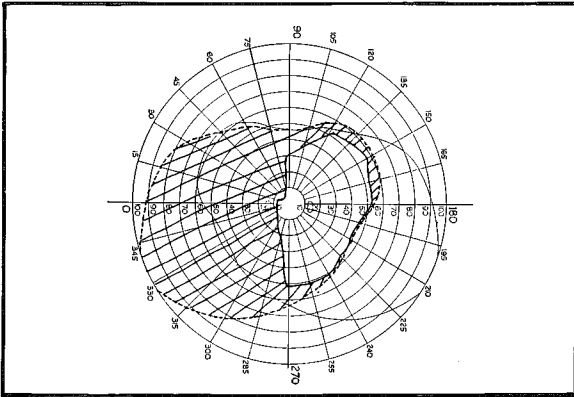


Figure 5 a-b Visual fields of patient O.S.Y. before bromocriptine therapy showing constriction of the visual fields in the left eye (Fig. 5a) and the right eye (Fig. 5b).

later. Perimetry was repeated after two weeks of bromocriptine therapy. The visual fields were found to be normal with no residual defect (fig. 6a-b) and the acuity improved to 6/5 in both eyes.

The patient went into spontaneous labour and delivered a normal, healthy baby boy on 9th August 1978. She was discharged prematurely on the third postpartum day and was lost to medical follow-up.

During this period she was on bromocriptine 2.5 mg daily; her menses were regular but the galactorrhoea persisted even though she was not breastfeeding.

She was referred again to the Endocrine Clinic in June 1979. Serum FSH was 1.1 IU/l, LH 1.5 IU/l, plasma oestradiol 25 pg/ml and the prolactin was just at the upper limit of normal (690 mU/l). The skull X-rays showed no significant fossa changes and the visual fields were full. After the assessment, bromocriptine was stopped but the patient was kept under close supervision. She had no treatment for five months during which time her visual fields were regularly assessed and found to be normal. Her menses, however, stopped after two months and serum prolactin rose to 25,000 mU/l. With the re-institution of bromocriptine the periods returned and galactorrhoea ceased. Air studies showed an enlarged and eroded fossa with marked suprasellar extension (fig. 7a-b) and she was referred to a neurosurgeon for an operation.

## DISCUSSION

The amenorrhoea-galactorrhoea syndrome - previously referred to as Argonz del Castillo', Forbes-Albright or Chiari-Frommel Syndrome - is the result of hyperprolactinaemia caused by

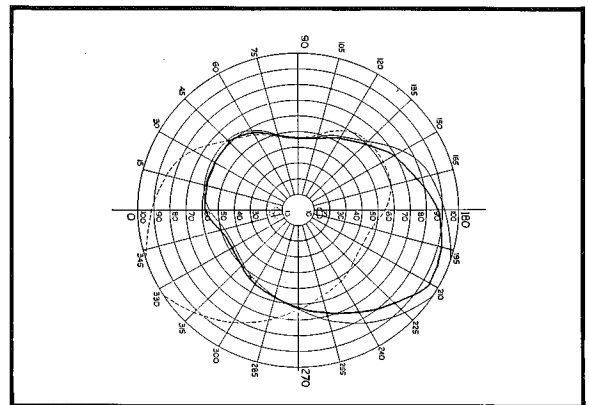
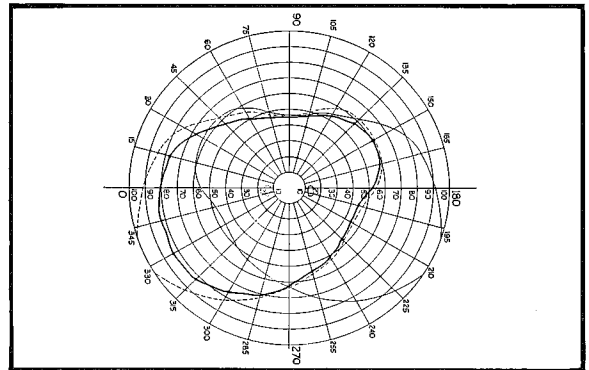


Fig. 6a-b: Visual fields of patient O.S.Y. after institution of bromocriptine therapy: normal, full visual fields for the left eye (Fig. 6a) and the right eye (Fig. 6b).

prolactin-producing pituitary adenomas (Hardy *et al*, 1978). These prolactinomas may be large so as to cause obvious sella changes, but the fossa may be completely normal or show only a localised blistering or erosion when the tumour is small (Bergh *et al*, 1978 c; Hardy *et al*, 1978).

Case 1, with just a localised thinning of the sella turcica on tomographic studies probably has a prolactin-producing microadenoma. Her serum prolactin was in the normal range when first seen at the Endocrine Clinic but this was most likely related to the bromocriptine she had for a month prior to referral. The level gradually rose when treatment was withheld but came down again after reinstatement of bromocriptine (fig. 1). The initiation of bromocriptine resulted in spotting after a week, followed by normal, regular periods.

It was somewhat surprising to find the localised defects in the visual fields when the fossa was of normal size with only a minimal thinning of its posterior wall. Though visual field impairments with apparently normal fossae have recently been described (Friesen and Tolis, 1977; Vaidya *et al*, 1978) it was felt that the localised defects should be confirmed. No treatment was given or started and these disappeared after two months - full vision was restored, concomitant with normalisation of the menstrual cycles.

CAT-Scan with contrast enhancement was done to try to delineate possible suprasellar extension but this failed to confirm. The scan was initially reported as 'a slightly enlarged but empty sella' (fig. 8) but a review suggested that this was a misclassification due to computer summation of the sphenoid sinus underlying the fossa. Air-encephalographic studies confirmed that the sella was not empty but again failed to show significant suprasellar extension to account for the visual field impairments (fig. 9). The suprasellar lesion causing the chiasmatal compression was probably too small to be confidently resolved with present radiological techniques. This case perhaps illustrates the need for tomographic studies and visual-field assessments for any hyperprolactinaemic patient suspected of harbouring a pituitary tumour, even when the fossa is of normal size on the plain x-rays.

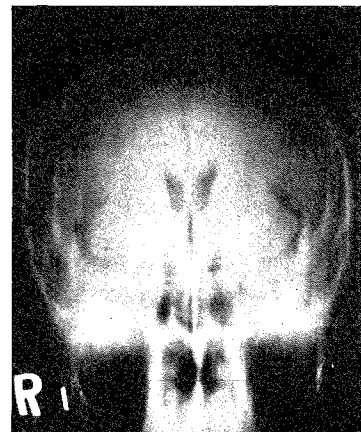
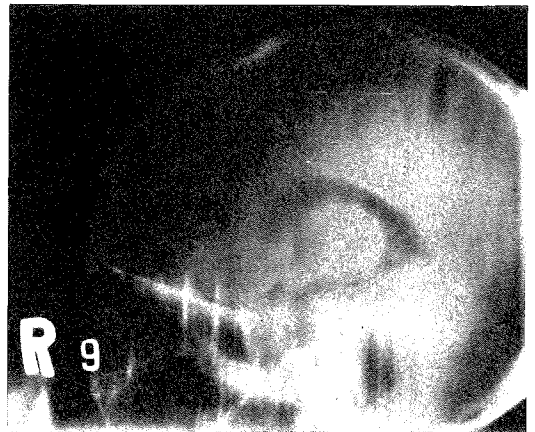


Fig. 7a-b: Airencephalographic studies of patient O.S.Y. showing an enlarged pituitary tumour which had extended both inferiorly and suprasellarly in the lateral (Fig. 7a) and the anteroposterior views (Fig. 7b).

The second case illustrates the fact that bromocriptine not only normalises menses and stops galactorrhoea but also restores fertility.

More importantly, it highlights the danger in allowing pregnancy in a patient with a large and untreated prolactinoma and having no close supervision during the pregnancy. The patient was seven months pregnant when she presented to the clinic with bilateral visual field impairments and markedly raised serum prolactin. Bromocriptine was immediately instituted and it was gratifying to note the rapid fall in the serum prolactin level to the normal range (fig. 10) with restoration of normal and full vision by the second week (fig. 11). She was able to continue with the pregnancy and had a full term normal delivery.

It was interesting to note that after delivery she was on only a small dose of bromocriptine and this was able to suppress prolactin to within the normal range, maintaining normal menstrual cycles and vision. It was thought possible that the tumour had necrosed during the postpartum period (Bachdev *et al*, 1976) though she was well and had no feature to suggest hypopituitarism. To further test this hypothesis, bromocriptine was withheld while patient was kept under close supervision. With the cessation of bromocriptine therapy, serum prolactin rose from 690 mU/l to 7900 mU/l within a month and to 25000 mU/l after five months (fig. 10). Even though her visual fields remained full, her periods ceased after two cycles and the galactorrhoea returned. It was likely that the previously normal prolactin level was due to a suppression by the bromocriptine and not the result of tumour necrosis. Reinstitution of bromocriptine at a dose of 2.5 mg bd again rapidly suppressed prolactin with a resumption of normal menstrual cycles.

The rapid reduction in the prolactin level with bromocriptine therapy and a subsequent prompt

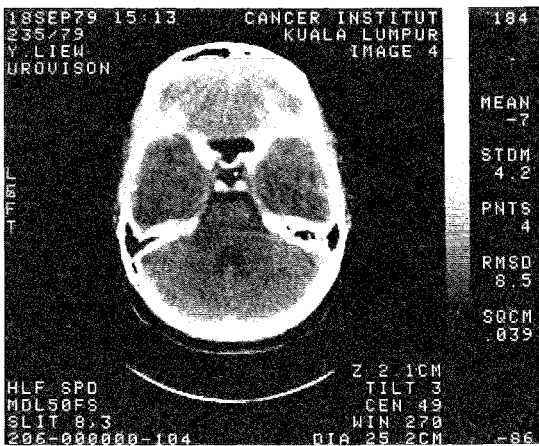


Fig. 8 CAT scan of patient Y.L. at the Pituitary level. Note the hypodense fossa due to computer summation of the underlying sphenoid sinus.

rise when therapy was withheld underlies the concept that bromocriptine, as a dopamine agonist, only inhibits prolactin secretion without affecting the underlying pathology (Besser, 1978, George *et al*, 1979). Recent evidence however suggests that bromocriptine not only inhibits secretion but also blocks prolactin synthesis (Davies *et al*, 1974). An increase in hormone production

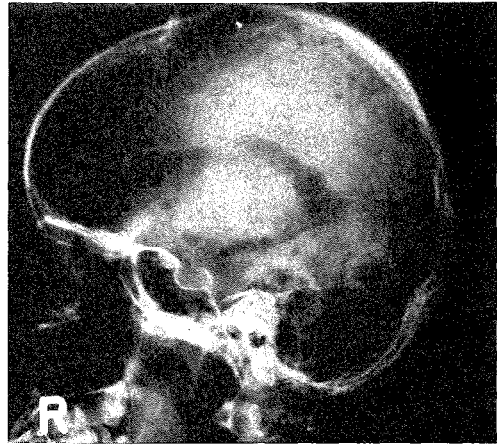


Fig. 9 Airencephalographic studies of patient L.Y. indicating a full sella but without an obvious suprasellar extension.

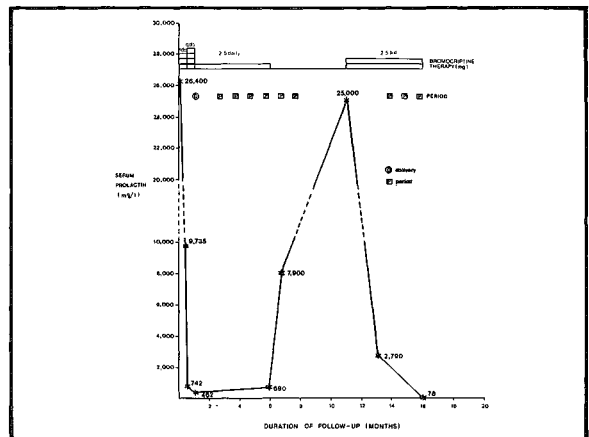


Fig. 10 Serum prolactin of patient O.S.Y. The initial value was greater than 26,400 mU/l and this dropped rapidly to less than 500 mU/l with bromocriptine therapy. This low value was maintained after delivery (⊙) on 2.5 mg daily and periods were regular. The serum prolactin rose rapidly to over 25,000 mU/l when bromocriptine was withheld and amenorrhoea recurred.

The level fell rapidly to about 100 mU/l and the periods returned with the reinstatement of bromocriptine.

must relate to an increase in the number and/or size of the hormone-producing cells. Hence, a reduction in hormone production should be associated with reduction in the size and/or number of the active cells. Studies in rats have indicated that bromocriptine can reduce mitosis and even cause tumour necrosis and shrinkage (Quadri *et al*, 1972; Lloyd *et al*, 1975) but these have not been conclusively proven in man (George *et al*, 1979). Indirect evidence of tumour shrinkage with bromocriptine therapy is now forthcoming. This

relates to the restoration of normal visual fields (Bergh *et al*, 1978 a-b; Corenblum *et al*, 1975; Burzaco *et al*, 1978) as is described in this paper. Lately, however, direct evidence of tumour

entail a life-long replacement therapy with a number of drugs including steroids. This may not be acceptable in our country because of poor patient compliance and backup service.

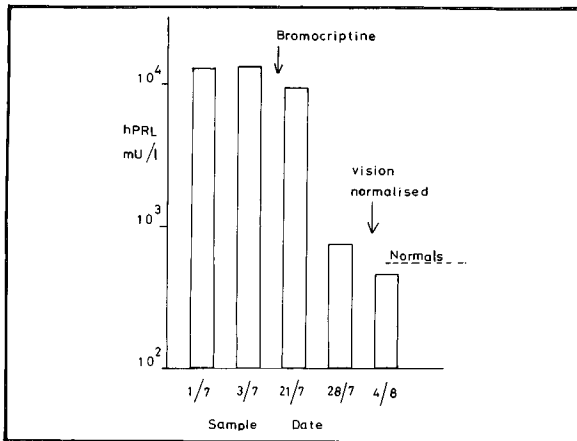


Fig. 11: Serum prolactin of patient O.S.Y. before and immediately after the initiation of bromocriptine therapy. Normal and full visual fields were restored after two weeks. (Serum prolactin plotted on logarithmic scale; hPRL - Serum prolactin; normals - upper limit of serum prolactin in normal controls.)

Furthermore, fertility may have to be compromised and this can be a problem with childless couples. In this respect, it is worth noting the recent reports that with a reduction in tumour size using bromocriptine, there is also improvements in the other pituitary hormones (Corenblum *et al*, 1975; Asfour *et al*, 1977; McGregor *et al*, 1979).

regression became available by airencephalographic studies (George *et al*, 1978) and a serial CAT-scanning (McGregor *et al*, 1979b).

A few authors are now questioning the wisdom of pretreatment with surgery or irradiation before allowing patients to become pregnant (Hancock *et al*, 1978) as experience has shown that the risk of tumour enlargement - even during pregnancy - is minimal (Bergh *et al*, 1978). Many would now allow hyperprolactinaemic patients to become pregnant but would keep them under close supervision during the pregnancy (Bergh *et al*, 1978) and if tumour complication arises, then bromocriptine should be reinstated (Bergh *et al*, 1978; Hancock *et al*, 1979). Recently, encouraging report is available on the use of bromocriptine on pituitary tumours other than the prolactin-producing (Wass *et al*, 1977, McGregor *et al*, 1979 a).

While bromocriptine may not cure the underlying disease, it offers a unique opportunity to treat hyperprolactinaemic patients with the amenorrhoea-galactorrhoea syndrome, even those with obvious pituitary lesion. Bromocriptine therapy would not only normalise menses, stop galactorrhoea but would also restore fertility. External irradiation may not be effective or may take a long time to have an effect (Gomez *et al*, 1977) while a radioactive implant may induce pituitary hypofunction (Child *et al*, 1975; Bergh *et al*, 1978). Surgery offers a good chance of a cure in experienced centres employing the transsphenoidal approach, especially when the tumour is small (Hardy *et al*, 1978). However, the result is usually unsatisfactory with a large tumour especially one with suprasellar extension, because of incomplete removal or an induction of hypopituitarism (Hardy *et al*, 1978).

It would seem that bromocriptine, for the present at least, is well-suited for the treatment of prolactinomas in this country where neurosurgical operation is a taboo and the service is almost non-existent. Bromocriptine therapy should also be the first choice in the treatment of hyperprolactinaemic patients who develop visual field defects either spontaneously or as a result of a pregnancy.

The development of panhypopituitarism would

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