CLINICAL RESEARCH

Treatment of prolactinomas with megavoltage radiotherapy

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Abstract

The outcome of treatment of 36 women with prolactinomas using megavoltage radiotherapy combined with interim dopamine agonists (bromocriptine, lysuride, pergolide) was reviewed; 16 of the women showed radiological evidence of a macroadenoma. The most common presenting symptom was secondary amenorrhoea; 26 of the patients had galactorrhoea. In 29 patients who wished to conceive the ovulation rate (as indicated by circulating progesterone concentrations) was 97% and the successful fertility rate 86%. No patient had enlargement of the tumour during pregnancy and there were no complications of radiotherapy. No further tumour enlargement was detected in serial skull radiographs, and an improvement in size of the fossa was noted in 45% of those assessed.

When medical treatment was withdrawn a mean of 4.2 years (range 1-11) after radiotherapy in the 27 patients who had completed their families the serum prolactin concentration had fallen appreciably in 26 of them and later became normal in eight. The incidence of growth hormone deficiency rose from 24% of the whole group before radiotherapy to 79% afterwards. Only one patient required thyroxine, and one was receiving gonadotrophin. No patient became deficient in adrenocorticotrophic hormone.

A regimen of megavoltage radiotherapy and interim bromocriptine allows women with prolactinomas safely

to undergo pregnancy and results in the long term prospect of tumour shrinkage and control of hyperprolactinaemia.

Introduction

Prolactinomas—pituitary tumours secreting prolactin—are the most common type of pituitary adenoma; at least 40% of the previously described “functionless” tumours are now thought to secrete prolactin.¹ Although some degree of hyperprolactinaemia may be seen with any mass lesion affecting the hypothalamo-pituitary axis, we find that most patients with pituitary tumours and serum prolactin concentrations above 1500 mU/l show immunocytochemical and electronmicroscopical evidence for the tumour origin of the prolactin. Patients with small prolactinomas are usually women, who most frequently present with symptoms attributable to the high serum prolactin concentration, such as galactorrhoea, oligomenorrhoea or amenorrhoea, and infertility.^{1,2} In large prolactinomas mass effects of the tumour such as headache, visual field impairment, or oculomotor nerve palsies often predominate.

The optimal definitive treatment of prolactinomas remains controversial. While medical treatment is highly effective, transsphenoidal or transethmoidal hypophysectomy is the preferred treatment in some centres; but even in highly skilled hands surgical cure of the hyperprolactinaemia is reported in only 40-80% of cases^{2,3} and recurrence of hyperprolactinaemia occurs in half of these.³ Furthermore, there is a significant risk of hypopituitarism, particularly of gonadotrophin deficiency. Since patients are often young and present with disorders of menstruation or fertility, such an outcome would be particularly discouraging and should be avoided if possible.

The alternative medical approach is to attempt to control the pituitary tumour with radiotherapy. As this is not immediately effective dopamine agonists may be used in the interim to reduce circulating prolactin concentrations to normal, reverse the hypogonadism, and achieve fertility if desired. Dopamine agonists—for example, bromocriptine—however, only rarely produce long term control of prolactinomas in the absence of radiotherapy, the serum prolactin concentration usually rising again once treatment is stopped.¹ There is also the risk of

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tumour enlargement during any subsequent pregnancy as a result of the increased oestrogen drive to the tumour.⁴ There are only sporadic reports of a few patients with prolactinomas treated by radiotherapy, and no large scale studies with long term follow up have been published.⁵ We have therefore surveyed our long term results of radiotherapy in 36 women with documented prolactinomas and report the effects of treatment on circulating prolactin concentrations and residual pituitary function.

Patients and methods

We studied 36 women with prolactinomas (table I). Their ages ranged from 18 to 48 years (mean 27.7) and they represented an unselected series of women presenting with amenorrhoea or menstrual irregularity (34 patients), regular menses with infertility (one), or

(bromocriptine, lysuride, or pergolide) was started. Once the desired number of successful pregnancies had been completed dopamine agonist treatment was withheld at one to two yearly intervals and not reinstituted if the serum prolactin concentration (measured after at least two months without treatment) was within the normal range. For each patient the latest full reassessment is presented here. This was one to 11 years (mean 4.2 years) after radiotherapy (table II). Eighteen patients were retested for pituitary reserve while they were taking bromocriptine and 18 after the bromocriptine had been stopped.

TABLE II—Distribution of time to follow up investigations after megavoltage radiotherapy in 36 women with prolactinomas

Time in years	1	2	3	4	5	6	7	8	9	10	11
No of patients	1	6	7	9	6	2	1	1		1	1

TABLE I—Details of 36 patients with prolactinomas treated with radiotherapy and bromocriptine

Case No	Age at presentation (years)	Presenting symptoms	Initial serum prolactin (mU/l)	Radiological appearance of fossa		Years after treatment
				Before treatment†	After treatment	
1	18	Primary amenorrhoea	10 500	B4	No change	2
2	36	Secondary amenorrhoea	8 000	B1	No change	5
3	25	Secondary amenorrhoea*	> 2 000	B0	No change	2
4	34	Secondary amenorrhoea*	2 200	B3	No change	4
5	36	Secondary amenorrhoea*	4 000	B4	No change	9
6	22	Secondary amenorrhoea*	2 100	B1	No change	3
7	33	Secondary amenorrhoea*	> 4 000	B4	No change	3
8	35	Oligomenorrhoea*	1 900	B3	Improved	4
9	25	Secondary amenorrhoea*	3 400	B4	Improved (B3)	2
10	37	Secondary amenorrhoea	> 5 000	B4	No change	4
11	27	Secondary amenorrhoea†	4 600	B3	—	—
12	21	Secondary amenorrhoea	> 5 000	B3e	Improved (B3)	5
13	26	Secondary amenorrhoea	7 600	B4	—	—
14	26	Secondary amenorrhoea†	1 800	B3	Improved	6
15	34	Oligomenorrhoea*	> 2 500	B4	Improved	7
16	28	Secondary amenorrhoea*	34 000	B4	Improved	5
17	31	Secondary amenorrhoea*	4 200	B3e	Improved	5
18	33	Secondary amenorrhoea*	> 2 500	B3	No change	2
19	27	Oligomenorrhoea*	> 4 000	B5	Improved (B3)	2
20	24	Secondary amenorrhoea*	2 400	B3	—	—
21	23	Secondary amenorrhoea*	> 1 300	B3	—	—
22	22	Secondary amenorrhoea*	4 500	B3	Improved (B1)	5
23	21	Secondary amenorrhoea	3 200	B1	No change	5
24	25	Secondary amenorrhoea*	100 000	B4	Improved	10
25	48	Headache (posthysterectomy)	30 000	B4	—	—
26	30	Secondary amenorrhoea†	2 400	B3	No change	3
27	27	Oligomenorrhoea	2 200	B4	Improved	3
28	26	Secondary amenorrhoea	—	B5	—	—
29	20	Secondary amenorrhoea*	4 000	B4	—	—
30	25	Oligomenorrhoea*	1 400	B3	No change	2
31	32	Secondary amenorrhoea*	> 2 500	B4	No change	7
32	26	Secondary amenorrhoea*	3 400	B0	No change	3
33	25	Secondary amenorrhoea†	> 4 000	B4	Improved	2
34	25	Secondary amenorrhoea*	2 500	B3	Improved	5
35	27	Secondary amenorrhoea†	> 4 000	B3	No change	3
36	28	Regular cycles and infertility (deficient luteal phase syndrome)	1 300	B3	No change	3

*Spontaneous galactorrhoea.

†Galactorrhoea found on examination.

‡See table III for classification. (B3e indicates blister over 3 mm plus erosion.)

headache (one) associated with a mean basal serum prolactin concentration (at least three measurements) greater than 1300 mU/l (normal less than 360 mU/l) and abnormal radiological appearances of the pituitary fossa and treated by megavoltage radiotherapy during 1972-80. Other causes of hyperprolactinaemia (drug treatment, renal failure, hypothyroidism) were excluded. No patient in the series had a visual field defect on presentation or developing during follow up.

Endocrine testing consisted in measuring basal hormone values (serum prolactin, thyroxine, and free thyroxine index) and responses of serum growth hormone (GH) and plasma cortisol to insulin induced hypoglycaemia and of gonadotrophin and thyrotrophin (TSH) to gonadotrophin and thyrotrophin releasing hormones (GnRH and TRH). Tests were performed in a standard manner using 0.15 U soluble insulin per kg, 200 µg TRH, and 100 µg GnRH given together.⁶ The normal minimum responses to symptomatic hypoglycaemia with lowest blood sugar concentrations less than 2.2 mmol/l (40.0 mg/100 ml) are a serum GH concentration of 20 mU/l and plasma cortisol concentration of 580 nmol/l (21 µg/100 ml). Full testing was carried out in every subject before treatment and at yearly intervals after radiotherapy. Shortly before or during radiotherapy treatment with dopamine agonists

In patients who desired fertility mechanical contraception was stopped once three regular cycles had occurred after the end of radiotherapy. Dopamine agonists were stopped on confirmation of conception, usually less than one week after the first missed period. The patients were then monitored at monthly intervals throughout their pregnancies clinically and by plotting the visual fields by Goldmann perimetry.

Radiological appearances of the pituitary fossa were assessed from standardised posteroanterior and right lateral films. Comparison of initial and last available films was made independently by a consultant neuroradiologist. The pituitary fossa was graded according to standardised criteria⁷ (tables I and III).

Radiotherapy—Pituitary irradiation was carried out using a 4 MeV or 15 MeV linear accelerator to deliver a lesion dose of 4500 cGy (rads) in 25 fractions over 35 days. Treatment was planned individually, using the smallest target volume compatible with uniform irradiation of the lesion as detected radiologically. With immobilisation in a plastic shell, x ray simulation and full isodosimetry, a three field technique was employed to localise irradiation to the pituitary and minimise dose to the optic pathways, brain stem, and temporal lobes.

TABLE III—Classification of pituitary fossa from skull radiographs

Grade	Lateral view	Posteroanterior view
B0	Single contour	Flat floor; no blistering
B1	Less than 1 mm difference between contours	Minimal slope; less than 1 mm dip
B2	1-3 mm difference between contours; less than 3 mm blister	1-3 mm dip
B3	Over 3 mm blister	Asymmetry over 3 mm
B4	Double contour throughout	Asymmetry over 3 mm
B5	Both sides of fossa expanded in all directions (ballooned fossa)	

Assays—Serum concentrations of prolactin, GH, TSH, luteinising hormone (LH), follicle stimulating hormone (FSH), and thyroxine were determined by standard double antibody radioimmunoassays. MRC standards were used in the peptide assays. Plasma cortisol concentration was measured by fluorometry and blood sugar concentration by the neocuproine technique.

Statistics—Where appropriate comparisons were made by Student's unpaired *t* test. Figures are given as means and standard error of the mean, unless otherwise stated.

Results

During radiotherapy there was usually depilation over the temporal portal areas, but this recovered over several months. No other short term or long term clinical side effects of radiotherapy were noted.

SERUM PROLACTIN

Before treatment the serum prolactin concentration was 3000 mU/l or greater in 20 patients (56%) and above 2000 mU/l in 30 (89%) (table I). The five patients with concentrations between 1300 mU/l and 2000 mU/l had clear radiological abnormalities but none had a generally ballooned fossa. In 35 of the 36 patients the serum prolactin concentration fell to normal after treatment with dopamine agonists. In one patient a dose of only 15 mg bromocriptine daily lowered the serum prolactin concentration from 34 000 mU/l to 1200 mU/l.

Twenty seven patients who had completed their families stopped taking dopamine agonists after radiotherapy. In 26 of them the serum prolactin concentration was lower than the pretreatment value, often considerably so, and in eight patients (30% of those assessed; 22% of the total series) the concentration had become normal two to 10 years after radiotherapy (figure). No patient with a normal serum prolactin concentration after radiotherapy showed any evidence of recurrence of hyperprolactinaemia during subsequent study after up to two years without bromocriptine. One patient (case 7) showed no change in serum prolactin concentration five years after radiotherapy; in nine this could not be assessed, as the patients were still trying to conceive or were pregnant at the time of reassessment. The rate of normalisation of the concentration appeared to be inversely related to the pretreatment value, but detailed analysis was not possible as in many cases the basal sera were not fully diluted out—that is, concentrations were reported as “greater than 4000 mU/l”—owing to lack of parallelism of diluted samples with standards in the assay. In none of the five patients with pretreatment serum prolactin concentrations below 2000 mU/l had the value become normal three to five years after radiotherapy.

PITUITARY RESERVE

GH—Eight of the 36 patients were deficient in GH before radiotherapy and were included among the 34 patients subjected to insulin hypoglycaemia tests at reassessment (the remaining two patients were pregnant and thus could not be retested). The original eight patients remained GH deficient but a further 19 had also developed GH deficiency, which had occurred by three years after treatment. Thus, of the 34 patients reassessed, 24% were GH deficient before treatment and 79% at follow up. There was no difference in the proportion of patients who were GH deficient when tested during or after treatment with bromocriptine.

Adrenocorticotrophic hormone (ACTH)—One patient was ACTH deficient before treatment and remained so at follow up. Of the 34 patients reassessed by insulin induced hypoglycaemia, all had normal

serum cortisol responses indicating normal ACTH reserve. The peak cortisol responses before and after treatment were not significantly different (before treatment 888 (SEM 20.3) nmol/l (32 (0.7) µg/100 ml); after treatment 843 (SEM 26.1) nmol/l (31 (0.9) µg/100 ml)).

TSH—Three patients had additional primary hypothyroidism, but treatment of this had no effect on circulating prolactin concentrations; they were not subjected to statistical analysis. One patient (case 28) developed secondary hypothyroidism. She had a normal free thyroxine index 10 years after radiotherapy, but this fell to 55 (normal range 58-174) at 11 years, with a subnormal serum free thyroxine concentration of 8 pmol/l (0.6 ng/100 ml) (normal range 11-30 pmol/l; 0.8-2.3 ng/100 ml). In the remaining 32 patients there was no significant difference in free thyroxine index before and after treatment (91 (SEM 3.4) v 90 (SEM 3.0) respectively). Despite normal serum TSH concentrations after TRH and normal thyroxine values, one patient (case 5) developed an abnormal “delayed” pattern of response, the serum TSH 60 minutes after TRH being higher than at 20 minutes.

Serial serum prolactin concentrations after at least two months without dopamine agonist treatment in patients presenting with prolactinomas treated with megavoltage radiotherapy. O = serum prolactin concentration reported as “greater than” value shown.

This occurred eight years after radiotherapy. A similar pattern was seen in another patient (case 28) one year before she became biochemically hypothyroid.

LH and FSH—Three patients had deficient gonadotrophin responses to GnRH before treatment, and these remained abnormal after radiotherapy. All other patients developed regular menstrual cycles while taking dopamine agonists, and LH and FSH responses to GnRH remained normal in all. Four patients, however, developed late menstrual irregularity. One (case 28) became transiently amenorrhoeic five years after radiotherapy and then suffered irregular and heavy menstruation necessitating hysterectomy. Two further patients (cases 5 and 24) developed oligomenorrhoea nine and 10 years after radiotherapy, when they were aged 45 and 35 years respectively; in one of these the plasma oestradiol concentration was low (70 pmol/l; 19 pg/ml), while the second was found to have low gonadotrophin concentrations during testing with clomiphene (150 mg/day for 10 days). Both patients had completed their families (one and two children respectively). Hence these patients had a hypothalamopituitary axis in which gonadotrophin release was insensitive to the negative feedback of oestrogens at a time when fertility was no longer important. A fourth patient (case 19; age 29) became amenorrhoeic two years after radiotherapy. She had normal gonadotrophin responses to GnRH but absent responses to clomiphene and thus also showed a hypothalamic disturbance in endogenous GnRH release.

FERTILITY

Of the total series of patients, 29 wished to conceive. This was achieved by 25 patients after radiotherapy and while taking bromocriptine with progress to full term, normal delivery in all. This represents a successful fertility rate of 86%. In 21 of the patients conception occurred while taking bromocriptine alone; two patients, who before treatment had failed to respond to clomiphene, conceived readily with the addition of clomiphene for five days each cycle after radiotherapy and while taking bromocriptine. Two patients required exogenous gonadotrophin (menotrophin; Pergonal); one of these was deficient in gonadotrophin before and after radiotherapy, while the other was intolerant of bromocriptine at the dose necessary to ensure ovulation. One patient was amenorrhoeic two years after radiotherapy and began gonadotrophin treatment. Eight patients completed two successful pregnancies, while a further patient completed three. All babies were normal. One patient had a twin pregnancy. Only four patients who wished to conceive had remained unsuccessful. In three of these there was clear evidence of ovulation in terms of sustained rises in serum progesterone concentrations to normal during the luteal phases of their cycles. Thus in patients desiring fertility the ovulation rate as witnessed either by conception or by clear biochemical evidence was 97%. In patients in whom conception was achieved during treatment with bromocriptine after radiotherapy, this occurred within two months of attempts at conception in 64% and within four months in 91% (table IV). No patient developed pregnancy symptoms or signs of tumour expansion at any time during pregnancy.

TABLE IV—Interval to conception from time of stopping mechanical contraception in 22 women treated with bromocriptine and megavoltage radiotherapy

Time in months	1	2	3	4	5	6
No of patients	8	6	1	5	1	1

RADIOLOGICAL FINDINGS

In 16 patients the fossa was graded radiologically as B4 or B5 at presentation, suggesting a macroadenoma (diameter greater than 1 cm). In the remaining 20 patients (56%) there were only minor radiological changes in the fossa, usually a small blister. Review of pituitary fossa radiographs after radiotherapy in 29 patients showed definite evidence of return to normal or remineralisation in 13, representing 45% of the group assessed. The mean follow up period in the group showing radiological improvement (4.7 (SEM 0.6) years) was not significantly different from that in patients showing no change (3.8 (SEM 0.5) years), and changes were seen in patients with both microadenomas and macroadenomas.

Discussion

The effects of megavoltage x irradiation for prolactinomas have been reported in very few patients.⁶ Inevitably, follow up periods have been short, as assays for the concentration of prolactin in blood have been available for clinical purposes only since 1970. In a recent review Sheline noted that most studies have included only small groups of patients, usually totalling six to eight, with brief periods of follow up.⁵

Samaan *et al* reported on two patients treated originally by radiotherapy alone, in one of whom the treatment resulted in a normal serum prolactin concentration at three years.⁸ In eight patients reported by Kleinberg *et al* the concentration fell by a mean of 74% but remained above normal in all,⁹ while in a second series of eight patients the concentration became normal in one.¹⁰ Antunes *et al* also noted in six patients that the serum prolactin value, although it fell by 93%, failed to return to normal in any patient; the mean pretreatment concentration, however, had been 52 000 mU/l.¹¹ On these limited data in patients with large tumours it was suggested that radiotherapy tends to lower the serum prolactin concentration but that it seemed rarely possible to return it to normal.⁸ Nabarro studied 15 patients treated by radiotherapy and reported that it had little effect in lowering the serum prolactin concentration when the

basal value was above 5000 mU/l.¹ These results, however, may have been due to limited follow up. In our patients megavoltage radiotherapy resulted in normal serum prolactin concentrations in eight out of 27 patients whose initial concentrations were as high as 7600 mU/l. In addition, serum prolactin fell in all but one other patient and showed no evidence of return to high values; this is in contrast with the rebound that regularly occurs in patients when sole treatment with bromocriptine is stopped. There was an associated definite decrease in tumour mass, as assessed by gross changes in pituitary fossa radiographs, in 13 of 29 patients (45%), and there was no evidence of enlargement of the fossa in any. Probably more refined investigations, such as high resolution CT scanning, would have detected smaller degrees of shrinkage.^{12 13} It has been suggested that some 25% of macroprolactinomas³ and 3-5% of microprolactinomas undergo expansion during pregnancy. No evidence of this was seen in any of our patients given radiotherapy, as assessed clinically or by comparison of preconception and postpartum skull radiographs. This further supports the view that radiotherapy prevents this complication and limits tumour growth potential.

Of the 29 patients who desired fertility, 25 (86%) successfully conceived and continued to term and delivery, nine of them proceeding to second or third pregnancies after radiotherapy. Conception occurred rapidly, usually within two to four months. In only a single patient was radiotherapy and dopamine agonist treatment not followed by adequate ovulation despite normal prolactin and normal gonadotrophin responses to GnRH.

Hypopituitarism was not a problem, and only one patient required hormone replacement therapy (thyroxine). Most patients became GH deficient on dynamic testing, however, usually three years after radiotherapy, but this was of no clinical relevance since the patients were adult. Shalet also noted an early loss of GH reserve in children given various doses of hypothalamic radiation both for cerebral tumours and for leukaemia prophylaxis.¹⁴ We found no evidence of impaired adrenocortical function or reserve; two patients developed a delayed pattern of TSH responses to TRH at least eight years after radiotherapy, one becoming hypothyroid one year later. The delayed TSH response to TRH may be associated with hypothalamic dysfunction. Similarly, three patients developed menstrual irregularities more than five years after radiotherapy, the pattern suggesting a defect of hypothalamic GnRH synthesis or release. This may also be true for the GH deficiency. Similar conclusions have been reached after analysis of the hypopituitarism induced by high dose equivalent radiotherapy for head and neck tumours.^{15 16} Nevertheless, in our study this necessitated only one patient being treated with hormone replacement therapy. If hypopituitarism were to develop, with longer follow up, it would occur after passage of sufficient time to allow successful completion of planned families and towards the end of the period of normal fertility.

There was no instance of late complication affecting the optic pathways or brain in this series (nor in our total series of 332 patients with pituitary tumours irradiated by these methods since 1961). A lesion dose of 4500 cGy (rads) given in 25 fractions over 35 days by an isodose planned three field technique ensured that the dose to vulnerable neural tissue did not exceed 180 cGy (rads) daily; we agree with Sheline that this is an important factor in avoiding such potentially serious complications.⁵

Young women with small prolactinomas have a life expectancy of over 50 years and all possible detriments from treatment must be considered, however remote in time. Whenever tissues receive therapeutic doses of radiation there is clearly a possibility of late carcinogenesis. No tumours were encountered in our series, but the overall time of observation was short. Nevertheless, the possibility of this complication requires theoretical consideration when recommending optimal management. Radiation induced tumours have been described but rarely after pituitary irradiation and almost always as individual case reports, so that true incidence estimates are not available; most have been fibrosarcomas arising in the "high dose zone" around

the sella after latent periods of five to 20 years.¹⁷ The situation is further complicated by a possible but smaller risk of carcinogenesis over decades in the "lightly irradiated surrounding tissues" that cannot be scaled with the same dose dependency.¹⁸ On present evidence radiation induced tumours are a rare complication—possibly very rare—of the treatment of pituitary tumours by modern megavoltage methods. In macroadenomas this remote possibility never affects treatment policy, but in microadenomas of young women this factor will continue to require consideration.

Alternative treatments for prolactinomas include the use of bromocriptine alone and transsphenoidal or transethmoidal hypophysectomy. In a recent series of 84 women with prolactinomas treated by transsphenoidal hypophysectomy the mean age, presenting symptoms, and distribution of microadenomas and macroadenomas were similar to those in our series.² Return of serum prolactin concentrations to normal from values of 2000 mU/l or above, however, occurred in only half of the patients, and in one of the largest series (366 patients) serum prolactin concentrations fell to normal in only 31%.¹⁹ Although only a quarter of our patients had a normal serum prolactin concentration when bromocriptine was stopped at a mean follow up of four years, this rate may be expected to increase with time and bromocriptine may readily be reinstituted until then. It is therefore possible to treat these patients with bromocriptine knowing that their requirements will be gradually reduced and that eventually the drug may be stopped altogether. This may be compared with a recent report of 44 patients in which it was shown that of the 80% of patients with microprolactinomas and normal serum prolactin concentrations after transsphenoidal hypophysectomy, half showed subsequent recurrence with a rise in prolactin concentration.³ Transsphenoidal surgery may also be associated with a significant incidence of hypopituitarism.²⁰

Treating small prolactinomas with bromocriptine alone does not lead to continuing normal serum prolactin concentrations when bromocriptine is stopped,¹⁹ and the risk of pregnancy induced tumour expansion remains. Although there is one report that bromocriptine may lead to a permanent lowering of the serum prolactin concentration in occasional patients with large prolactinomas,²¹ it is these patients who are most at risk during pregnancy.⁴ Our data agree with the findings of others in suggesting that definitive radiotherapy of prolactinomas obviates the risk of field defects and headache arising during pregnancy.^{7, 22} Radiotherapy in patients who do not require fertility in the immediate future should be delayed until plans for conception are definite. Our experience suggests that this regimen of megavoltage radiotherapy and bromocriptine is safe, effective, and protective and is of clear benefit in hyperprolactinaemic hypogonadism due to prolactinomas.

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ONE HUNDRED YEARS AGO The British public has been much disappointed with the animal which, during the past week, has been the talk of London. There can be no doubt that the average Englishman has long been under the impression that the sacred animal of Siam is a variety of elephant as brilliantly white as a white mouse, or, at least, of a "deadwhite" hue, or very pale drab, like some seabirds. The truth is, that a perfect "white" elephant is a real albino: the natural colouring matter of the epidermis being absent, the colour of the blood in the cutaneous vessels gives a pale pink tint to the hide. Precisely the same condition causes the blood-red colour of a white rabbit's iris. This pale pink coloration resembles that seen in a well fed Berkshire boar, and the black mottling in the ears of the elephant now deposited at the Zoological Gardens by Mr. Barnum further reminds us of a pattern very common in domesticated pigs. In a leading daily paper, Professor Flower has already described the peculiarities of the new arrival with scientific accuracy; Sir Joseph Fayrer informs us, and several Anglo-Indians concur in his opinion, that the peculiar local deficiency of pigment in this elephant is very frequently seen in British India, and this animal has been chosen in his own country, long before he was sold to Mr. Barnum, to represent the rarer purely "white" elephant, because an example of that purer type could not be obtained. Possibly the arrangement of the very little "white" on Mr. Barnum's elephant's hide was sufficient, according with some local superstition. This elephant is not a fine specimen of his kind, being hog-backed and small for his age, but his tail is perfect, and his tusks are very well formed. He may be instructively compared with the male Indian elephant presented by His Royal Highness the Prince of Wales, a far nobler animal, bigger for his age, and well formed. He is, however, a "muktar," that is to say, an elephant whose tusks are never developed. The Hindus speak of a specimen of this variety as though it were a different animal from the "hottar," or long-tusked elephant. (*British Medical Journal* 1884;ii:179.)