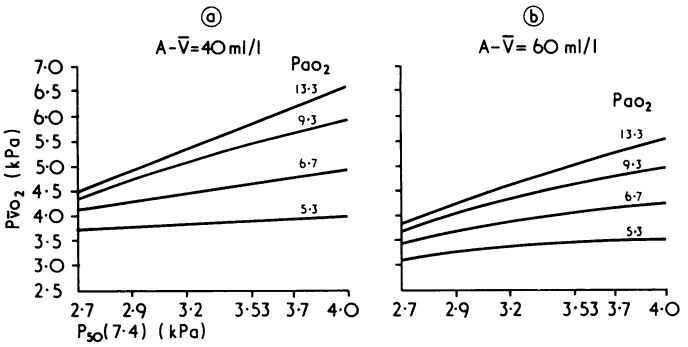

FIG. 2—Calculated relationships between P_{50} (7·4) and $P\bar{v}O_2$ for Pao_2 of 13·3, 9·3, 6·7, and 5·3 kPa. Oxygen capacity of 200 ml/l blood and arterial pH of 7·40 are assumed. In (a) arteriovenous content difference ($a-\bar{v}$) is 60 ml/l and in (b) 40 ml/l.

Conversion: SI to Traditional Units—1kPa ≈ 7·5 mm Hg.

(McKenzie *et al.*, 1964). If high-concentration oxygen therapy could provide a Pao_2 of around 13·3 kPa (100 mm Hg) in such shocked patients the transport of oxygen to the cells of the body could be facilitated by an increase in P_{50}, which would then allow oxygen to be delivered with a higher $P\bar{v}O_2$ (fig. 2 b). This would cause an improvement in the Po_2 gradient driving diffusion of oxygen from capillaries to the site of oxygen usage in the cellular mitochondria (Flenley, 1967). This suggestion now awaits direct trial when a therapeutic agent to raise P_{50} becomes available.

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Prolactin Studies in "Functionless" Pituitary Tumours

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Summary

Hyperprolactinaemia was found in all 17 women and in one out of six men who presented with hypogonadism and a radiologically enlarged sella turcica but no other clinical endocrine dysfunction. Some of the women also had galactorrhoea. The greater the level of hyperprolactinaemia in these 18 patients the larger their sellae turcica except in two patients with unusual features. The sella turcica was usually asymmetrically enlarged and there was rarely an upward extension of tumour, though the sella floor often showed some erosion on tomography. An oral dose of bromocriptine suppressed the hyperprolactinaemia in most patients at the same rate as in normal post-partum women.

Nine of the 18 patients with hyperprolactinaemia had low basal luteinizing hormone (LH) levels. The LH responsiveness to 100 μg of LH-releasing hormone (LHRH) was tested in 12, and eight showed subnormal values. Of eight biopsy specimens obtained four showed acidophil granules on light microscopy, and in five granules of various sizes were seen on electron microscopy.

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Introduction

Amenorrhoea with or without galactorrhoea has long been known to be common in women with radiologically evident pituitary tumours (Forbes *et al.*, 1954), and when there is no associated acromegaly or Cushing's disease it has been customary to refer to these as "functionless" pituitary tumours. Lewis and van Noorden (1974) have commented that not all these tumours are chromophobes histologically, and on both light and electron microscopy the tumours may vary from being inactive to showing intense secretory activity. Thus, histological evidence or serum hormone levels can show that these tumours may not be "functionless".

The frequency of hyperprolactinaemia with these tumours is not precisely known though Jacobs and Daughaday (1973) put it at 30%. Hyperprolactinaemia occurs in some men with functionless pituitary tumours (Thorner *et al.*, 1974), but again its frequency has not been determined. Vezina and Sutton (1974) found that all 20 of their patients with hyperprolactinaemia and associated amenorrhoea and galactorrhoea had radiological evidence of a pituitary tumour after careful tomography, even though a plain *x*-ray examination of the pituitary fossa showed it to be of normal size in 14 patients. All their patients subsequently had transphenoidal surgery, and pituitary tumours were found in each case.

We report here an analysis of 18 patients with hypogonadism or visual field defects or both who also had hyperprolactinaemia.

Patients and Methods

Six men and 17 women all presented with hypogonadism or visual field defects or both, and all also had radiologically enlarged sellae. None had received any treatment directed to the pituitary gland. Their clinical features are summarized in the table. All 17 women and one man had hyperprolactinaemia. Eight of these patients were later treated by pituitary implantation of yttrium-90.

RADIOLOGY

The sella turcica was examined first by plain *x*-ray examination and then by lateral tomography using polytome hypocycloidal tomography at 3-mm cuts. Air encephalography was also performed in 14 patients and was limited to tomographic studies in anteroposterior and lateral projections of the region of the sella turcica and basal cisterns.

The lateral area of the sella turcica was measured by projecting the largest area on lateral tomography on to white cardboard (linear magnification ×5). The sella outline was traced and cut out. The weight of the cut-out piece was noted and converted to mm^2 by comparison with a standard of known area after allowing for magnification.

TESTS OF PITUITARY FUNCTION

Luteinizing Hormone Releasing Hormone (LH-RH) Test.—To assess the pituitary gonadotrophic reserve 100 μg of LH-RH was given intravenously and serum LH assayed at 0, 20, and 60 minutes. The mean and normal range for LH in both sexes at 0 minutes is 5 (3–8) U/l, at 20 minutes 16 (8–34) U/l, and at 60 minutes 13 (6–34) U/l.

Acute Prolactin Suppression Test.—Bromocriptine 2·5 mg (2 brom-α-ergocriptine, Sandoz) was given by mouth at breakfast to nine patients, and blood samples were collected at hourly intervals for four hours. Our normal response in post-partum women was a mean percentage fall in prolactin levels after two hours of 65% (range 37–93%). We also calculated a "mean" percentage fall at two hours for those patients who had available three- and four-hour prolactin values from which we could derive "two-hour equivalent" falls. For this purpose the three-hour and four-hour values were converted to a "two-hour equivalent" using semi-log paper assuming a simple exponential fall; this enabled the percentage suppression to be based on two or three prolactin measurements.

ASSAYS

Both serum LH and follicle-stimulating hormone (FSH) were measured by double antibody radioimmunoassay as previously described (Marshall *et al.*, 1973) using M.R.C. 69/104 standards. The normal mean and range for the follicular phase for FSH is 3·5 (2–8) U/l.

Serum prolactin was measured by double antibody radioimmunoassay using antiserum 65/5 supplied by Professor H. Friesen. The human prolactin for labelling was that supplied by the National Institutes of Health, Bethesda, Maryland (batch VLS No. 1). Our laboratory normal range is 2–25 μg/l for women and <2–13 μg/l for men. In one of the men serum prolactin was 16 μg/l, but we regarded this as normal.

Serum oestradiol was measured by a highly specific radioimmunoassay using an antiserum raised in rabbits against oestradiol-6-oxine coupled to bovine serum albumin supplied by Dr. E. Youssefnejadan. Tritiated oestradiol was used as label in the assay itself and also as an internal standard for assessing recovery in the ether-extraction step. Dextran-coated charcoal was used to separate bound and unbound oestradiol. The normal follicular-phase range is 27–138 ng/l. Plasma testosterone was measured by radioimmunoassay by the method of Collins *et al.* (1972). The normal male range is 2–10 μg/l.

HISTOLOGY

The pituitary needle biopsy specimens were obtained during transethmoidal implantation of radioactive yttrium seeds. Tissue from the pituitary fossa was withdrawn by suction into a hypodermic syringe and decanted into a petri dish. Solid fragments were divided and fixed separately for light and electron microscopy. For light microscopy neutral formaldehyde solution (10% formalin) was used and paraffin-embedded sections were stained by the Pearse trichrome periodic-acid Schiff method. For electron microscopy glutaraldehyde fixation and osium tetroxide after fixation was used, and sections embedded in epoxy resin were stained with uranyl acetate and lead citrate.

Results

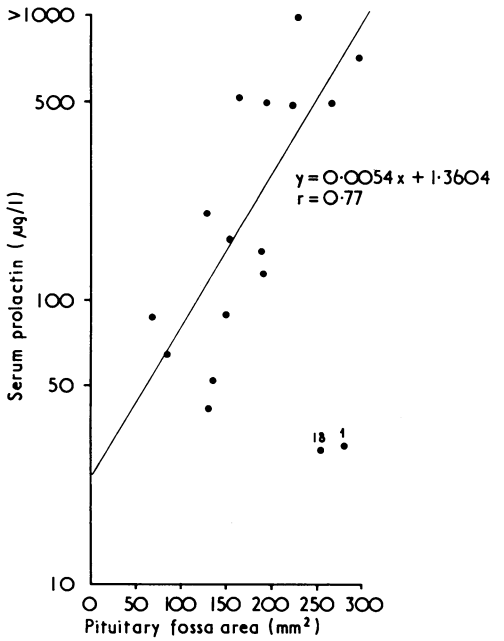
Radiology.—The lateral area of the sella turcica was measured in 17 of the 18 patients with hyperprolactinaemia in whom lateral tomography had been performed. If we exclude two patients a correlation between basal prolactin and the size of the fossa is evident ($r=0·77$; see fig.). The two exceptions are the only man (case 18) and the woman (case 1) with the largest upward extension. Of these 18 enlarged sellae 14 were asymmetrical (nine right and five left) and in 10 patients the sella, floor was eroded. This erosion bore some relation to fossa size, the floor tending to be intact in the smaller fossae. Air encephalography showed upward extension of tumour in two cases

Clinical Features and Results of Pituitary Function Tests in 23 Patients with Hypogonadism or Visual Field Defects or Both and Radiologically Enlarged Sellae

Case No.	Age (Years)	Presenting Syndrome: Duration (Years)	Presenting Features	Headache	Visual Field Defect	Gonad Function: Basal Oestradiol (ng/l)	Basal Testosterone (μg/l)	Pituitary Function: Basal Prolactin (μg/l)	Basal FSH (U/l)	LH Response to 100 μg LH-RH I.V. (U/l) at: 0 min	20 min	60 min	TSH* Response to 200 mg TRH I.V. (mU/l) at: 0 min	20min	60 min	Insulin-induced Hypoglycaemia†: Peak Serum GH Response (mIU/l)	Peak Plasma Cortisol Response (μg/l)
								Women									
1	33	6	2° A.+G.	–	–	17		31	3	<2	3	3					
2	34	10	2° A.	+	–	<2		500		<1			4	9	5	38	200
3	26	5	2° A.+G.	–	–	<2		720		3			2	5	6		
4	38	10	2° A.+G.	+	–	13		1450	<1	2	5	5	3	19	16	26	
5	26	8	2° A.+G.	–	–	10		490	2	4							
6	32	7	2° A.+G.	+	–	17		500	5	5	5	4				>50	
7	31	8	2° A.+G.	–	–			126	2	2	8	6	2	26	19	11	225
8	24	3	2° A.+G.	–	–	12		150	4	3	17	19	<1	19	2	>50	255
9	22	4	2° A.+G.	–	–	12		530	2	<1	3	2	1	11	10	140	290
10	26	8	2° A.+G.	–	–			170		4						>50	290
11	37	2	2° A.+G.	–	–	21		90	4	5	9	9	3	5	8	27·5	120
12	21	6	1° A.	–	–	<2		53	<1	<1	2	2	2	10	17		
13	36	7	2° A.+G.	–	–	57		42		8						30	225
14	29	6	2° A.+G.	+	–	10		205	2	3	4	3	<1	16	11	25	225
15	40	1	2° A.+G.	–	+			65		5			1	12	10		170
16	26	11	2° A.	–	–			88	6	<1	6	5				>50	
17	30	3	2° A.+G.	–	–	8		38		2	25	28	2	12	8		280
								Men									
18	55	10	I.	–	–		0·6	30	1	<1	<1	<1	<1	3	4	<1	165
19	61	10	I.	+	+			16	<1				2	2	2		
20	63	5	I.	–	–			5								<1	
21	48	½	Visual Loss	–	+			7		3							
22	35	4	I.	–	–		0·7	2	<1	<1	2	2	<1	6	3	>50	260
23	59	½	I.	–	–			10	<1	1	4	5				<1	230
			Normal ranges			27–138 (follicular phase)	2–10 (men)	2–25 (women)	2–8	3–8	8–34	6–34	<1–4	4·5–25	4–20	>20	>200

†TSH = Thyrotrophin-stimulating hormone.
*Hypoglycaemia was considered to have been induced if there was a blood sugar of <2·2 mmol/l (<400 mg/l) on at least two occasions.
2° = Secondary. 1° = Primary. A. = Amenorrhoea. G. = Galactorrhoea. I. = Impotence.

only (case 1 20 mm, case 4 6 mm) while the man had a partially empty sella.



Correlation between serum prolactin and pituitary fossa size (lateral area of sella turcica) in 17 patients. 1 = Woman with 2-cm upward extension of tumour. 18 = Only man. Regression line excludes both these patients.

Serum Prolactin and Bromocriptine.—Among the 18 patients with a raised basal prolactin value the range was 30–1450 μg/l (see table). The suppressibility of this hyperprolactinaemia by an oral dose of bromocriptine was tested in nine patients and compared with the results in normal post-partum women. The mean percentage fall in our patients at two hours was 30% (range 5–77%) while the calculated mean (see Methods) percentage fall at two hours was 42% (range 7–71%), as compared with a mean percentage fall of 65% in post-partum women (range 37–93%). Thus seven out of nine of our patients showed normal suppressibility as defined by the range of normal post-partum women.

Gonadotrophins and Gonad Function.—The basal LH levels were subnormal in nine of the 18 subjects with hyperprolactinaemia. The basal FSH levels were measured in 12 patients and were subnormal in only three. The LH response to LH-RH was tested in 12 patients, and eight, six of whom had low basal values, showed diminished responses.

In all but one of the 13 women who had their basal oestradiol levels measured were these values below the normal follicular phase range. The basal oestradiol in the two patients with amenorrhoea but without galactorrhoea who had their levels estimated was subnormal and indeed below assay sensitivity. The basal testosterone level in the man with hyperprolactinaemia was also very low.

Biopsy.—Light microscopical evidence of activity was assessed by the method described by Lewis and van Noorden (1974), cellular and nuclear pleomorphism being taken as indices of activity. Four acidophil and four chromophobe tumours were examined. Three of the acidophil tumours showed signs of activity while all four chromophobe tumours were inactive. Electron microscopy in five cases showed grannules of various sizes (Joplin *et al.*, 1975). No correlation was seen between prolactin levels and histological features of activity or granule size.

Discussion

Our data suggest that serum prolactin levels should be measured in patients with amenorrhoea or hypogonadism the basis of which is not evident, especially if the sella turcica appears to be enlarged on *x*-ray examination. We did not always find galactorrhoea in patients with hyperprolactinaemia because a prepared breast, probably including adequate oestrogenization, is necessary for this to occur.

We have shown a positive correlation in patients between basal serum prolactin and the size of the pituitary fossa. Such a relationship has already been shown in acromegaly with growth hormone (Wright *et al.*, 1969) and in Nelson's syndrome with ACTH (Besser *et al.*, 1972).

In our series 78% (14/18) of pituitary tumours were radiologically asymmetrical, while in acromegaly this was so in 63% (81/129—unpublished observations). This is in keeping with the histological character of the normal pituitary gland; while growth hormone (GH) cells occur in two lateral masses in the anterior pituitary prolactin cells develop for the most part lateral to the GH-producing cells (Russfield, 1968).

Our findings of low serum LH in half of our patients and impaired LH-RH responsiveness in two-thirds disagree with those of Thorner *et al.* (1974) who found raised basal LH levels and exaggerated LH-RH responsiveness in some of their patients with hyperprolactinaemia. None of our patients showed an exaggerated response.

The suppressibility of hyperprolactinaemia by bromocriptine was normal in most of our patients. Thus we did not find this acute test useful diagnostically, but the drug's usefulness as a therapeutic agent in such cases has already been documented (Thorner *et al.*, 1974) and confirmed by ourselves (to be published).

The lack of correlation between histological activity or granule size and basal prolactin may have several explanations. Firstly, prolactin levels may be determined by tumour size as well as by activity. Secondly, the evidence of activity or the granules seen may represent activity by hormones other than prolactin or may represent altered prolactin that is not assayed by our present method. Further clarification of these points will emerge when immunofluorescent studies for specific hormones are more generally available.

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