HYPERPROLACTINAEMIA — INVESTIGATION AND RESULTS OF TREATMENT

by

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INTRODUCTION

HUMAN prolactin was isolated in 1971 (Lewis, Singh and Seavey) and this was soon followed by the development of a homologous radioimmunoassay for its measurement in plasma (Friesen, Hwang, Guyda, et al 1973). Many studies have been carried out on patients with pathological conditions where basal plasma prolactin levels are elevated (Edwards, Forsyth and Besser, 1971; Turkington, 1972; Franks, Murray, Jequier, et al, 1975; Ramirez, O'Neill, Bloomer and Jubiz, 1977). The most important clinical application of these studies has been the measurement of plasma prolactin in patients with secondary amenorrhoea. With the advent of prolactin-lowering drugs such as bromocriptine and the development of the transsphenoidal approach to hypophysectomy, it has been possible to treat these patients successfully (Lutterbeck, Pryor, Varga and Wenner, 1971; Hardy, 1971). This paper describes the results of investigation and management of 53 patients with hyperprolactinaemia seen in the Gynaecology/Endocrine Clinic of the Royal Victoria Hospital, Belfast.

PATIENTS AND METHODS

Basal plasma levels of prolactin, luteinizing hormone (LH), follicle stimulating hormone (FSH), 17-β oestradiol, progesterone and testosterone were measured in 220 patients who presented with menstrual abnormalties or infertility and with hirsutism in a few. Thyroid function and a random plasma cortisol were also measured. The blood samples were obtained between 10.00 and 12.00 hours and were taken at least 30 minutes after each patient had been examined. Those who were discovered to have elevated plasma prolactin levels were recalled and had three consecutive blood samples taken at 30 minute intervals. The mean of these samples was then taken at the basal plasma prolactin level. Elevated prolactin levels were found in 42 of the 220 women. Eleven patients who were referred with confirmed hyperprolactinaemia were similarly investigated. Forty of the resulting 53 patients with hyperprolactinaemia also had a combined pituitary function test performed (insulin 0.2 iu/kg bodyweight, gonadotrophin releasing hormone (GnRH) 100 μg and thyrotrophin releasing hormone (TRH) 200 μg intravenously). The plasma prolactin response during a 24 hour period following 2.5 mg bromocriptine orally was also measured in these 40 patients. Visual field assessment was performed in all the patients with hyperprolactinaemia using a Tübinger perimeter. Lateral skull X-rays were taken in all patients and 48 had hypocycloidal polytomography of the pituitary fossa carried out in the lateral

projection. The X-rays were considered independently by three radiologists. They were assessed subjectively as it has been suggested that the estimation of an erperienced radiologist is superior to available methods of quantitative evaluation (Steinbach, Feldman and Goldberg, 1959). The X-rays were considered to be abnormal if there was an increase in sellar size, evidence of sellar asymmetry, a double contour of the sellar outline, thinning of the bony contour of the sella or localised erosion of the sellar floor. In cases where the radiologists did not agree the X-rays were considered jointly, and if no agreement was then reached, they were classified as equivocal. Patients with abnormal X-rays who wished to conceive had air encephalography carried out to exclude suprasellar extension of the pituitary lesion. Twenty-five patients had computerised axial tomography of the pituitary fossa carried out in the transverse plane using an EMI-5005 scanner. This examination was performed before and after intravenous injection of 50 ml (65 per cent) meglumine diatrizoate containing 306 mg iodine per ml.

ASSAY METHODS

Plasma prolactin was measured by radioimmunossay using ^{125} I labelled human prolactin (standard — Medical Research Council Standard A, preparation 71/222, obtained from the National Institute of Biological Standards and Control; prolactin for labelling supplied by the National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, USA; antibody supplied by the Tenovus Institute for Cancer Research, Cardiff (Reagent Code 7110)). This antibody displays minimal cross reactivity with human growth hormone, luteinizing hormone (LH), follicle stimulating hormone (FSH) and thyroid stimulating hormone (TSH). The within-assay coefficient variation was 3.9 per cent at a plasma prolactin concentration of 400 mU/1. The between-assay coefficient variation was 7.9 per cent at this plasma concentration. The plasma samples were assayed in duplicate and the upper limit of the normal range of plasma prolactin in women aged 18-30 years was founnd to be 400 mU/1. Plasma levels of LH, FSH, 17-β oestradiol, progesterone, testosterone, human growth hormone (HGH), TSH, thyroxine and triiodothyronine were all measured by radioimmunoassay (Wilson, 1979). Cortisol was measured by the Mattingly fluorometric technique (1962) and plasma glucose was measured on an auto-analyser by the glucose oxidase technique (Technicon).

A combined pituitary function test was carried out as described by Harsoulis, Marshall, Kuku et al (1973). The responses of LH, FSH and TSH were taken as the mean increase in hormone levels above the basal level 20 and 60 minutes after the beginning of the test. The responses of growth hormone and cortisol were assessed by the peak hormone level achieved during the test and the degree of hypoglycaemia produced by insulin was shown by the lowest plasma glucose level recorded during the test. The plasma prolactin response to the stimulation test was assessed by the maximum increase in plasma prolactin levels expressed as a percentage of the basal level and the plasma prolactin response to the bromocriptine inhibition test was taken as the maximum decrease, expressed as a percentage of basal level. The results of the stimulation test were compared with

those obtained in 11 healthy female volunteers (aged 18-32 years) during the mid-follicular phase of the menstrual cycle and were analysed using the Mann-Whitney U test.

RESULTS

Basal plasma prolactin levels in the 53 patients with hyperprolactinaemia are shown in Figure 1. The highest basal plasma prolactin levels occurred in 36 patients with amenorrhoea (range 1,000-31,500 mU/1) and the lowest levels in the 10 patients with regular menstrual cycles (range 500-2,800 mU/1). However, there was a considerable overlap between the three subgroups. One patient was taking thioridazine. None of the others was on any medication known to influence plasma prolactin levels. All were euthyroid and none had evidence of renal disease.

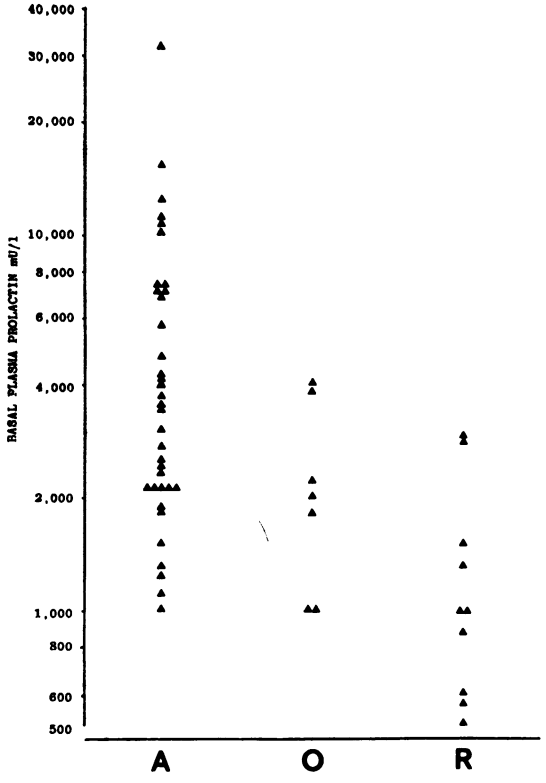

FIG. 1 Basal plasma prolactin levels in 53 hyperprolactinaemic women with amenorrhoea (A), oligomenorrhoea (O) and regular menses (R) (upper limit of normal 400 mU/1).

Two patients had had previous neurosurgery: one had had a transfrontal hypophysectomy for a pituitary chromophobe adenoma and the other had had a craniopharyngioma aspirated. Both were on replacement therapy with thyroxine and cortisone acetate. Eight patients were referred with hyperprolactinaemia fol-

lowing discontinuation of oral contraceptives and in another seven symptoms developed following delivery. In one patient symptoms developed after she sustained a head injury in a road traffic accident. Four patients had been treated with chlomiphene citrate without success but eight others had menstruated while on treatment with this drug. Three of these patients had had successful pregnancies following treatment with chlomiphene citrate and human chorionic gonadotrophin. One patient had had a pregnancy following treatment with follicle stimulating hormone, luteinizing hormone and human chorionic gonadotrophin. Polycystic ovaries had been noted in four patients and bilateral wedge resection of ovaries had been carried out without restoration of ovulation in all four of them.

Patients were considered to have galactorrhoea if they had a history of abnormal lactation or if this could be demonstrated on examination. Twenty of the 36 patients with amenorrhoea, two of the seven patients with oligomenorrhoea and one of the 10 patients with regular menses had galactorrhoea.

Visual fields were assessed clinically in all the patients and were documented using a Tübinger perimeter. None of the patients had any evidence of temporal field loss suggestive of pressure on the optic chiasma.

X-rays of the pituitary fossa were abnormal in 19 of the 48 patients who had hypocycloidal polytomography performed. In 23 patients they were normal and in the remaining six patients the appearances were equivocal. Basal plasma prolactin levels were highest in the patients with abnormal fossae (range 2,100-31, 500mU/1) and the lowest in the patients with normal fossae (range 500-1,500 mU/1) but again there was considerable overlap between the subgroups. Of the 25 patients in whom CT-scans were carried out nine had normal plain X-rays and these nine had all normal CT-scans. The three patients who had equivocal plain X-rays all had normal CT-scans and of the 13 patients with abnormal plain X-rays, 10 had normal and only three had abnormal CT-scans.

Basal levels of TSH, thyroxine and tri-iodothyronine were similar to those in normal females of the same age as were the basal plasma levels of LH, FSH, progesterone and testosterone. The basal plasma levels of 17-β oestradiol in the hyperprolactinaemic patients with amenorrhoea were compared with those in normoprolactinaemic patients of the same age who had amenorrhoea of pituitary or hypothalamic origin. The mean oestradiol level in the hyperprolactinaemic patients (190 $\pm$ 20 pmol/l) was found to be significantly lower ($p<0.05$) than in the normoprolactinaemic patients (260 $\pm$ 20 pmol/l). It was also found that there was a significant correlation between basal plasma prolactin level and 17-β oestradiol level in these patients when the results were analysed by non-parametric tests using Kendall's rank correlation coefficient ($Tau=0.31$; $p>0.01$).

The TSH, LH, FSH, growth hormone, cortisol responses to the stimulation test are shown in Table 1. As none of the patients had adrenal disease the cortisol response was taken to reflect ACTH release by the pituitary to this test. The plasma prolactin response was diminished in all patients compared with control subjects. The response to the bromocriptine inhibition test was a similar in all the patients and showed a fall in plasma prolactin of 80 $\pm$ 5 per cent.

TABLE 1

Results of pituitary tests in 40 hyperprolactinaemic women

	HORMONE RESPONSE		
	EXAGGERATED	NORMAL	IMPAIRED
TSH	5	35	0
LH	6	30	4
FSH	24	15	1
HGH	—	36	4
CORTISOL	—	40	0

Twenty-three of the patients were treated with bromocriptine. Two had transsphenoidal hypophysectomies and 20 remain under observation without any treatment. The remaining eight patients returned to their referring gynaecologists for treatment after initial investigations had been completed. Plasma prolactin levels were restored to normal in 20 of the 23 patients treated with bromocriptine. Two of the remaining three patients defaulted from the clinic before they had been adequately treated. In the third patient plasma prolactin levels remained elevated despite increasing the dose of bromocriptine to 45 mg per day. In the amenorrhoeic patients menses were restored in 18 to 78 (mean 40) days after starting treatment. Ovulatory menstrual cycles as shown by a biphasic temperature record and an elevation of plasma progesterone during the second half of the cycle were established on a dose of bromocriptine of 5 to 10 mg per day. Relief of galactorrhoea was experienced within six weeks in all who had this symptom at the onset of treatment.

Details of eight patients who conceived are shown in Table 2. All patients were required to undertake barrier contraceptive measures until three menstrual cycles had been completed. Contraceptive measures were then discontinued and they were allowed to attempt to conceive. The absence of a predicted menstrual period and the continued elevation of basal body temperature suggested the possibility of pregnancy. When this was confirmed treatment with bromocriptine was discontinued. After delivery all patients who attempted to breast feed succeeded in doing so. Plasma prolactin levels remained elevated post partum in all the patients but despite this one had spontaneous return of menses. All patients with an equivocal or abnormal pituitary fossa before pregnancy were re-Xrayed after delivery. No changes were seen in the radiological appearances of the pituitary fossae of any of them.

Two patients were selected for treatment by transsphenoidal hypophysectomy. Both had evidence of suprasellar extension of the pituitary on air encephalography. Pituitary function tests carried out before and after surgery showed no impair-

TABLE 2

Clinical details of eight hyperprolactinaemic women who conceived on bromocriptine treatment

Patient	Age (years)	Menstrual History	Pituitary Fossa	Plasma Prolactin (mU/l)		Bromocriptine Dose (mg/day)	Total length of Treatment (weeks)	Menstrual Cycles from stopping contraception to conception	Outcome of Pregnancy and Birth Weight (Grammes)
				Before Treatment	During Treatment				
1	30	A + G	Abnormal	15300	120	5	20	2	Female 4000
2	33	A + G	Normal	3000	68	5	20	2	Male 2860
3	29	A + G	Normal	1500	129	5	18	1	Female 2295
4	29	A + G	Normal	2500	140	5	14	1	Male 3500
5	39	A + G	Equivocal	1300	180	5	36	4	Female 3065
6	35	O	Normal	2000	60	5	40	11	Male 3340
7	25	O + G	Equivocal	3700	100	5	18	1	Male 3520
8	28	O + G	Normal	1800	92	10	64	12	30 weeks pregnant

A - amenorrhoea O - oligomenorrhoea G - galactorrhoea

ment following surgery. In the first patient plasma prolactin levels fell to normal 24 hours after surgery (Figure 2) and menses resumed 28 days after a lapse of six years. She conceived seven months after surgery and delivered a full term 3,500g baby girl. In the second patient the plasma prolactin levels did not return to normal after surgery and she continued to have amenorrhoea and galactorrhoea. She was started on bromocriptine and menses were established. Three months later she conceived but aborted after eight weeks. She was restarted on bromocriptine and is now 20 weeks pregnant.

Twenty patients have received no treatment and eleven remain unchanged. One patient resumed normal menses without any treatment although her plasma prolactin levels are still elevated. Two patients with secondary amenorrhoea and elevated plasma prolactin levels became pregnant without treatment and without developing any menses. Both successfully completed uneventful pregnancies.

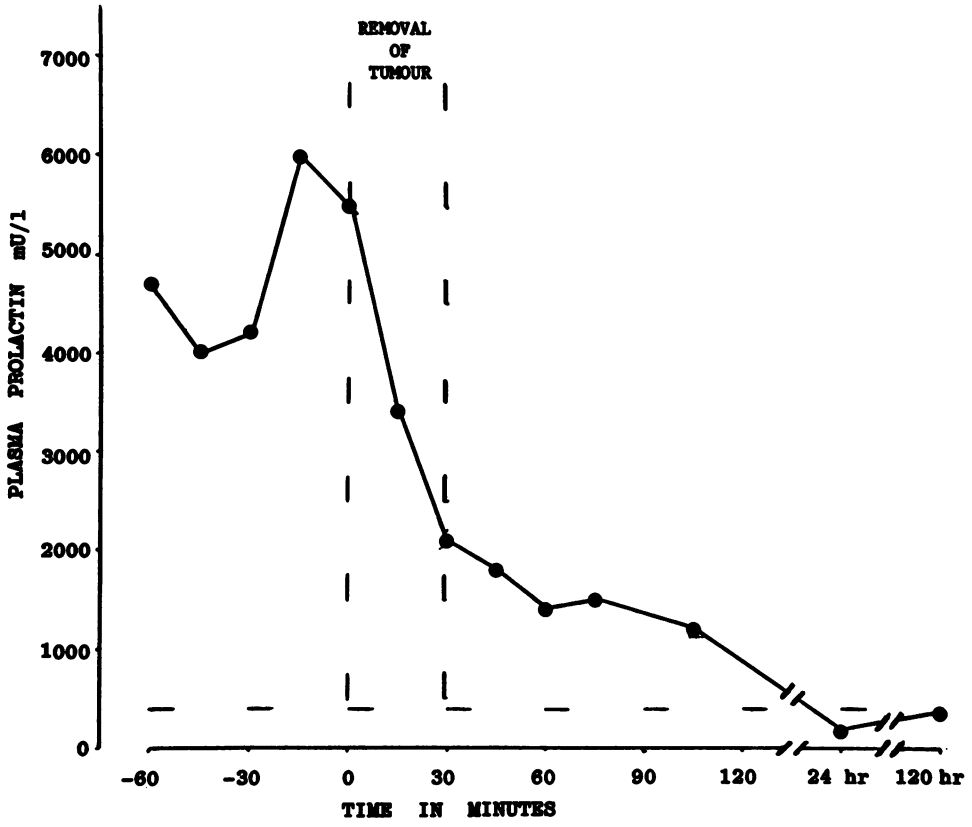

FIG. 2 Plasma prolactin levels following transsphenoidal partial hypophysectomy in one patient.

DISCUSSION

The incidence of hyperprolactinaemia in the patients studied here was 19 per cent and was 28 per cent in the patients with amenorrhoea. This compares with a reported incident of 13.4 to 39 per cent (Bohnet, Dahlen, Wuttke and Schneider, 1975; Franks Murray, Jequier et al, 1975; Glass, Williams, Butt et al, 1976; Bergh, Nillius and Wide, 1977; Pepperell, Bright and Smith, 1977; Seppälä, Lehtovirta and Ranta, 1977; Shearman and Frazer, 1977). The variation in incidence in the reported series is likely to be due to differences in patient groups and to reflect the different pattern of patient referral to each centre. The incidence of galactorrhoea in the patients studied here was 38 per cent and is similar to that reported by others (Bohnet et al, 1975; Franks et al, 1975; Seppälä et al, 1977). It is considerably lower than that reported by Glass et al (1976), Thorner and Besser (1977), Bergh, Nillius and Wide (1977) and Pepperell, Bright and Smith (1977), all of whom reported an incidence of galactorrhoea of approximately 80 per cent cent. Differences are probably due to definitions of what constitutes galactorrhoea and differences in examination technique.

Eight patients were referred with hyperprolactinaemia after discontinuation of oral contraceptives. It is not certain whether the use of these drugs predisposes to the development of hyperprolactinaemia and it should be noted that some of the patients had abnormal menses before starting on oral contraceptives. However, it has been suggested that longterm use of oral contraceptives can result in stimulation of otherwise silent pituitary tumours and lead to hyperprolactinaemia (Sherman and Korenman, 1978). Polycystic ovaries were documented in four patients studied here. This finding has been noted by others (Thorner, McNeilly, Hagan and Besser, 1974, Sepälä and Hirvonen, 1975) and it has been suggested that it may be related to elevated androgen levels in some of these patients. However, only two of the patients studied here had elevated testosterone levels and only one of them had evidence of polycystic ovaries.

The finding that 17-β oestradiol levels in hyperprolactinaemic patients with amenorrhoea were lower than those in similar normoprolactinaemic patients and the finding of a significant negative correlation between basal plasma prolactin and 17-β oestradiol levels would support the hypothesis that there is a direct and dose related action of prolactin on the ovary. These findings are similar to those of Franks and Jacobs (1977) and Reyes, Gomez and Fairman (1977) but are at variance with those of Bergh, Nillius and Wide (1977).

Tests of pituitary function performed in 40 patients showed no consistent pattern. There was an exaggerated TSH response to TRH in five patients. This is similar to the findings of Thorner and Besser (1977) and it has been suggested that it is due to functional dopamine deficiency at the pituitary or hypothalamic level (Besses, Burrow, Spaulding and Donabedian, 1975). The gonadotrophin response to GnRH was very variable being exaggerated in some patients and impaired in a few with very large pituitary tumours. Growth hormone response to hypoglycaemia was also impaired in four with large pituitary tumours. The cortisol response was normal and the prolactin response was impaired in all the patients. Although these tests are useful for assessing pituitary function, the responses are so variable that it is not possible to use them to distinguish patients with pituitary tumours from patients with hyperprolactinaemia due to other causes. Muller, Genazzani, Camanni et al (1978) described a test using nomiphensine which is the only test that is claimed to be able to distinguish between hyperprolactinaemic patients with and without pituitary tumours.

None of the patients studied here had visual field defects due to pressure effects on the visual pathways. This finding is similar to that of Kase, Andriole and Sobrinho (1973) and Jones and Kemmann (1976). It is not surprising as most patients with hyperprolactinaemia do not have large pituitary tumours. In this series 19 of the 48 patients who were fully investigated radiologically were considered to have abnormal pituitary fossae but only six had gross changes compatible with the presence of a large pituitary adenoma. The remainder had changes compatible with the presence of a pituitary microadenoma. The importance of carrying out polytomography in these patients was stressed by Vezina and Sutton (1974). They found a sella of normal size in 14 out of 20 patients who subsequently were shown to have abnormalities on tomography

compatible with the presence of a small pituitary adenoma. Transsphenoidal surgery later confirmed the presence of a tumour in each case.

Computerised transverse axial tomography was performed in 25 patients in this series. It was found to be of no value in confirming the presence of an intrasellar tumour or in excluding suprasellar extension of the pituitary. Part of the difficulty was due to the fact that the X-ray beam width in the scanner used was 13 mm but it is hoped that narrowing this beam width and introducing special computer procedures to obtain coronal and sagittal views of the skull will help to improve the diagnostic value of this procedure. At present air encephalography and metrizamide cisternography are the only reliable methods of excluding suprasellar extension of the pituitary. This is of primary importance for selection of appropriate treatment for the patient with hyperprolactinaemia.

Twenty-three of the patients in this series were treated with the dopamine-agonist bromocriptine. Those who wished to become pregnant were only treated after suprasellar extension of the pituitary had been ruled out (see below). Patients who did not wish to conceive but who were known to have enlargement of the pituitary fossa were only treated after they had been fully informed of possible complications of an unplanned pregnancy and had agreed to undertake barrier contraception if appropriate. Treatment proved to be highly successful in all but one patient in whom plasma prolactin levels were not restored to normal even on 45 mg bromocriptine per day. This woman had normal growth hormone and cortisol responses to hypogycaemia, a normal TSH response to TRH and exaggerated LH and FSH responses to GnRH. At follow up she was reassessed and as the radiological appearance of the pituitary fossa was then considered to be abnormal, she was offered a transsphenoidal hypophysectomy which she declined.

All the eight patients who wished to conceive succeeded in doing so. There are two major concerns about treating these patients with bromocriptine. The first is the possibility of teratogenic effects of this drug and in order to reduce this the drug was stopped as soon as the pregnancy was confirmed. However, the patients had all conceived at least four weeks earlier and the fetus had been exposed to bromocriptine during that time. Despite this none of the children born to the mothers was found to have any congenital abnormality. Griffith, Turkalj and Braun (1978) reported the outcome of 448 completed pregnancies in mothers treated with bromocriptine in the early weeks of pregnancy and found no increase in the frequency of spontaneous abortion, twin pregnancy or congenital malformation compared with the general population. The second concern about the use of bromocriptine in these patients is the possibility that an underlying pituitary tumour may expand during pregnancy. The exact risk of this occuring is unknown but there are a number of reports of patients in whom it has occurred and who have been successfully treated (Kajtar and Tomkin, 1971; Child, Gordon, Mashiter and Joplin, 1975; Gemzell, 1975; Thorner, Besser, Jones, et al 1975; Jewelewicz, Zimmerman and Carmel, 1977; Linquette, Buvat, Gauthier et al 1977; Bergh, Nillius and Wide, 1978).

In order to avoid this complication it has been proposed that some destructive procedure should be carried out to the pituitary before conception occurs. Thorner et al (1975) advised external radiation but this does not always prevent the development of visual field defects during pregnancy (Thorner et al, 1975; Lambert, Seldenrath, Kwa and Birkenhäger, 1976). Also, the possible benefits of radiation need to be balanced against the unwanted side effects (Atkinson, Allen, Hadden, et al 1979). Other alternative methods of preventing expansion of a pituitary tumour during pregnancy include internal radiation with yttrium 90 as proposed by Child et al (1975) and surgical removal of the tumour (Hardy, 1971).

The problem which remains is how likely is the patient with hyperprolactinaemia to develop visual symptoms during pregnancy. Bergh, Nillius and Wide (1978) reported 17 term pregnancies in 14 amenorrhoeic women with hyperprolactinaemia and radiological evidence of pituitary tumour. Only two patients developed visual symptoms during pregnancy and these resolved after delivery. Mornex, Orgiazzi, Hugues et al (1978) reported no complications during pregnancy in eight patients with slight or clear enlargment of the pituitary fossa. Of the three patients studied here with equivocal or definite abnormality of the pituitary fossa who conceived while on bromocriptine treatment, none developed visual complications during pregnancy and none had radiological evidence of further pituitary enlargement after pregnancy. It is our current practice to assess the pituitary fossa in hyperprolactinaemic patients by means of a lateral skull X-ray and hypocycloidal polytomography in the lateral projection. If an abnormality is detected and the patient wishes to conceive, suprasellar extension of the pituitary is excluded by means of air encephalography in consultation with the neurosurgical unit. The patient is then treated with bromocriptine. This treatment is stopped when she conceives. She is reviewed at two weekly intervals in a joint ante-natal/endocrine clinic where visual fields, visual acuity and fundal appearance are checked at each visit. If suprasellar extension of the pituitary is confirmed, transsphenoidal partial hypophysectomy is carried out. After conception such a patient is similarly reviewed.

Twenty patients studied here have been followed up without treatment. One has resumed normal menses although her prolactin levels are still elevated and two conceived without treatment and completed successful pregnancies. This shows that ovulation and pregnancy may occur in the presence of elevated prolactin levels. It has been proposed that plasma prolactin levels interfere with the action of the gonadotrophins on the ovary (Thorner and Besser, 1977) and interfere with the release of gonadotrophin releasing hormone by the hypothalamus (Fuxe, Löfström, Hökfelt et al 1978). Clearly this does not occur in all hyperprolactinaemic patients. Some of these patients who have received no treatment have radiological evidence of pituitary tumour. There have been several reports of regression of pituitary tumour size in patients with longterm treatment with bromocriptine (Vaidya, Aloorkar and Seth, 1977; Corenblum, 1978; Nillius, Bergh, Lundberg et al 1978; Sobrinho, Nunes, Santos and Mauricio, 1978; McGregor, Scanlon, Hall et al 1979). However, there is insufficient evidence so far to suggest that all patients with hyperprolactinaemia and evidence of pituitary tumour should be treated for a long period with bromocriptine when there is no other indication for doing so.

SUMMARY

Forty-two (19 per cent) of 220 patients with menstrual abnormalities or infertility were found to have hyperprolactinaemia, including 32 (28 per cent) of 115 patients with amenorrhoea. Galactorrhoea occurred in 20 (38 per cent) of a group of 53 hyperprolactinaemic patients and radiological evidence of a pituitary tumour was found in 19 (39 per cent) of a group of 48 of them.

Studies of pituitary function showed that basal levels and reserves of the other anterior pituitary hormones were usually normal or increased. Bromocriptine lowered plasma prolactin levels in all patients. Examination of the pituitary fossa by computerised axial tomography using an EMI-5005 was of no help in the differential diagnosis of the underlying cause of the hyperprolactinaemia. The most useful investigations in this respect were the lateral skull X-ray and polytomography of the pituitary fossa.

Twenty patients were kept under review without treatment and two of them conceived and completed successful pregnancies. Twenty-one patients were treated with bromocriptine. Plasma prolactin levels were restored to normal in 20 and eight who wished to conceive succeeded in doing so. Two patients with suprasellar extension of the pituitary had transsphenoidal partial hypophysectomies and both subsequently conceived. This form of treatment should be reserved for patients with suprasellar extension of the pituitary who wish to conceive.

ACKNOWLEDGEMENTS

We are grateful to the consultants at the Royal Victoria Hospital, Belfast who referred patients for investigation, to Drs. J. O. Y. Cole, F. S. Grebbell, E. M. McIlrath and W. H. T. Shepherd for advice about the pituitary X-rays and CT-scans, to Mr. C. J. F. Maguire for documenting the visual fields, and to Mr. D. S. Gordon and Mr. I. C. Bailey for carrying out the transsphenoidal hypophysectomies. We are also indebted to Mr. D. S. Gordon for his advice about the management of many of the patients, to the staff of the biochemistry department, Royal Victoria Hospital, Belfast for the hormone assays, to the nursing staff of the Gynaecology/Endocrine clinic and the Metabolic Unit where the investigations were performed and to Mrs. B. Briggs for typing this manuscript.

J. D. Wilson was in receipt of a Royal Victoria Hospital research fellowship.

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CELLULAR DYNAMICS OF HAEMOPOIESIS. Clinics in Haematology, Vol. 8, No. 2, June 1979. Edited by L. G. Lajtha. (VIII + 310. Illustrated. £8.25). London, Philadelphia, Toronto; W.B. Saunders Company Ltd. 1979.

SINCE 1969 several techniques have been developed which have given the opportunity for analysis of various populations of haemopoietic cells and the factors which control their multiplication and differentiation. These methods define cells and populations of cells in functional rather than morphological terms. The contributors to this book give a very lucid account of these methods, the physiological information which they have provided and, in some chapters, a brief account of some of their clinical applications.

The book is *not* just another of these topical but ill-constructed collections of reviews written in a jargon incomprehensible to all but a chosen few. A deliberate and largely successful attempt has been made to present the subject in a form suitable for non-super-specialists. Inevitably there is some overlap between different contributions but this seems to maintain continuity rather than to irritate with tedious repetition.

The overall emphasis is on the physiological rather than the pathological. This is not a criticism but it probably means that the book will not be immediately attractive to the general clinician. For haematologists and immunologists it is a "must".

T.A.McN.