cardiology, haematology, neurology, and rheumatology clinics as well as in obstetrics.

Treatment depends on careful anticoagulation, but the value of steroids, immunosuppressive agents, and plasma exchange is still not clear. In obstetrics, although claims of therapeutic success with various anticoagulation or immunosuppressive regimens increase each year, the data remain anecdotal and the overall results poor.

GRAHAM R V HUGHES

Consultant Rheumatologist,
Lupus Arthritis Research Unit,
Rayne Institute,
St Thomas's Hospital,
London SE1 7EH

- 1 Hughes GRV. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. *Br Med J* 1983;287:1088-9.
- 2 Harris EN, Gharavi AE, Boey M, et al. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. *Lancet* 1983;ii:1211-4.
- 3 Hughes GRV, Harris EN, Gharavi AE. The anticardiolipin syndrome. *J Rheumatol* 1986;13:486-9.
- 4 Khamashta MA, Harris EN, Gharavi AE, Morillas L, Hughes GRV. Towards an antibody mediated mechanism for thrombosis. *Arthritis Rheum* 1987;30:553.
- 5 Carreras LO, Vermeylen J, Spitz B, Van Assche A. "Lupus" anticoagulant and inhibition of prostacyclin formation in patients with repeated abortion, intrauterine growth retardation and intrauterine death. *Br J Obstet Gynaecol* 1981;88:890-4.
- 6 Harris EN, Chan JKH, Asherson RA, Aber VR, Gharavi AE, Hughes GRV. Thrombosis, recurrent fetal loss, and thrombocytopenia: predictive value of the anticardiolipin antibody test. *Arch Intern Med* 1986;146:2153-6.
- 7 Gharavi AE, Harris EN, Asherson RA, Hughes GRV. Anticardiolipin antibodies: isotype distribution and phospholipid specificity. *Ann Rheum Dis* 1987;46:1-6.
- 8 Asherson RA, Harris EN, Gharavi AE, Hughes GRV. Systemic lupus erythematosus, antiphospholipid antibodies, chorea, and oral contraceptives. *Arthritis Rheum* 1986;29:1535-6.
- 9 Asherson RA, Chan JKH, Harris EN, Gharavi AE, Hughes GRV. Anticardiolipin antibody, recurrent thrombosis, and warfarin withdrawal. *Ann Rheum Dis* 1985;44:823-5.
- 10 Asherson RA, Lanham J, Hull RG, Boey ML, Gharavi AE, Hughes GRV. Renal vein thrombosis in systemic lupus erythematosus: association with the "lupus anticoagulant." *Clin Exp Rheumatol* 1984;2:75-9.
- 11 Hughes GRV, Mackworth-Young CG, Harris EN, Gharavi AE. Veno-occlusive disease in systemic lupus erythematosus: possible association with anticardiolipin antibodies? *Arthritis Rheum* 1984;27:1071.
- 12 Asherson RA, Mackworth-Young C, Boey ML, et al. Pulmonary hypertension in systemic lupus erythematosus. *Br Med J* 1983;287:1024-5.
- 13 Harris EN, Gharavi AE, Asherson RA, Boey ML, Hughes GRV. Cerebral infarction in systemic lupus: association with anticardiolipin antibodies. *Clin Exp Rheumatol* 1984;2:47-51.
- 14 Asherson RA, Mackay IR, Harris EN. Myocardial infarction in a young male with systemic lupus erythematosus, deep vein thrombosis, and antibodies to phospholipid. *Br Heart J* 1986;56:190-3.
- 15 Hamsten A, Norberg R, Björkholm M. Antibodies to cardiolipin in survivors of myocardial infarction: an association with recurrent cardiovascular events. *Lancet* 1986;ii:113-5.
- 16 Asherson RA, Derksen RH, Harris EN, et al. Large vessel occlusion and gangrene in systemic lupus erythematosus and "lupus-like" disease. A report of 6 cases. *J Rheumatol* 1986;13:740-7.
- 17 Asherson RA, Mercey D, Phillips G, et al. Recurrent stroke and multi-infarct dementia in systemic lupus erythematosus: association with antiphospholipid antibodies. *Ann Rheum Dis* 1987;46:603-11.
- 18 Derue GJ, Englert HJ, Harris EN, et al. Fetal loss in systemic lupus: association with anticardiolipin antibodies. *J Obstet Gynaecol* 1985;5:207-9.
- 19 Lockshin MD, Druzin ML, Goei S, et al. Antibody to cardiolipin as a predictor of fetal distress or death in pregnant patients with systemic lupus erythematosus. *N Engl J Med* 1985;313:152-6.
- 20 Hughes GRV. Connective tissue disease and the skin. *Clin Exp Dermatol* 1984;9:535-44.
- 21 Asherson RA, Derksen RH, Harris EN, et al. Chorea in systemic lupus erythematosus and "lupus-like" disease: association with antiphospholipid antibodies. *Semin Arthritis Rheum* 1987;16:253-9.
- 22 Harris EN, Asherson RA, Gharavi AE, Morgan SH, Derue G, Hughes GRV. Thrombocytopenia in SLE and related autoimmune disorders: association with anticardiolipin antibody. *Br J Haematol* 1985;59:227-30.
- 23 Asherson RA, Lubbe W. Heart valve disease and antiphospholipid antibodies. *J Rheumatol* 1988;15:539-43.
- 24 Harris EN, Englert H, Derue G, Hughes GRV, Gharavi A. Antiphospholipid antibodies in acute Guillain-Barré syndrome. *Lancet* 1983;ii:1361-2.
- 25 Harris EN, Gharavi AE, Patel S, Hughes GRV. Evaluation of the anticardiolipin antibody test: report of a standardisation workshop held April 4, 1986. *Clin Exp Immunol* 1987;68:215-22.

Hyperprolactinaemia

Common and treatable

Hyperprolactinaemia is the underlying cause in almost 15% of women who do not ovulate¹ and usually results from tumours producing prolactin (prolactinomas), the commonest type of pituitary tumour.² Indeed, one necropsy study of unselected patients showed that more than one in 10 had a prolactinoma³; most had presumably been without symptoms. Conversely, mass screening of 10 550 normal adults in Japan found only five who were considered to have a prolactinoma.⁴

The diagnosis of hyperprolactinaemia must be based on more than one measurement. Although the upper limit of the normal range is often quoted as 360 mU/l, it really extends to 700-800 mU/l because of the skewed normal distribution.^{5,6} Even concentrations above this do not necessarily indicate the clinically important hyperprolactinaemia that suppresses pulsatile secretion of gonadotrophin releasing hormone from the hypothalamus leading to secondary gonadal failure.⁷

In women prolactin concentrations up to 1000 mU/l are associated with a low incidence of menstrual irregularity and no response to treatment with bromocriptine.^{8,9} Even higher concentrations are unlikely to be clinically important in a woman who is menstruating normally,¹⁰ and they do not usually require investigation. The discrepancy between clinical and biochemical findings may sometimes be caused by measurement of biologically inactive but immunologically reactive hormone.¹¹

Once pregnancy, the effect of drugs, and hypothyroidism have been excluded the most likely cause of hyperprolactinaemia is a prolactinoma. Other pituitary lesions must, however, be kept in mind. Thus non-functioning pituitary tumours may cause hyperprolactinaemia by interfering with normal hypothalamic inhibition of prolactin secretion. These tumours usually do not respond to medical treatment. The hyperprolactinaemia in patients with such lesions is commonly only mild—up to 3000 mU/l^{12,13}—although it may

occasionally be as high as 8000 mU/l; a plain radiograph of the pituitary fossa usually shows abnormal results. In contrast, prolactinomas may cause any degree of hyperprolactinaemia. Those associated with mild hyperprolactinaemia are usually so small (microadenomas) that they only rarely distort a plain radiograph of the pituitary. Patients with an abnormal pituitary fossa in a plain radiograph should have their visual fields checked and have computed tomography. Computed tomography is not usually necessary in those with normal results in plain films of the pituitary (unless an operation is contemplated) as the examination is unlikely to affect management, is costly, and may be misleading, even with high resolution scans.^{14,15} If, however, there are any clinical features in addition to hyperprolactinaemia that suggest a pituitary lesion computed tomography may be needed.

Clinically important prolactinomas are much more common in women than men, which has been attributed to an effect of oestrogen, although this remains uncertain.¹⁶ The usual presentation of hyperprolactinaemia is amenorrhoea and associated infertility and symptoms of oestrogen deficiency; galactorrhoea occurs in about one third of patients. Many women with galactorrhoea do not, however, have hyperprolactinaemia¹⁷; the condition probably arises from the abnormal sensitivity of breast tissue to normal serum concentrations of prolactin.¹⁸ Such women do not require further investigation of the pituitary, but if the galactorrhoea is sufficiently embarrassing to warrant treatment it usually responds to suppression of prolactin with a dopamine agonist. In men hyperprolactinaemia may cause loss of libido and impotence, although it accounts for these common symptoms only rarely.

Hyperprolactinaemia nearly always responds to treatment with a dopamine agonist, which may reduce the size of an underlying prolactinoma.¹⁹ Bromocriptine is used most often,

although other dopamine agonists are available.^{20 21} Bromocriptine is given in an initial small dose of 1.25 mg with the evening meal, and it is then gradually increased every three to four days to try to avoid side effects. The effectiveness of treatment is assessed by serial measurements of serum prolactin concentration and by return of gonadal function. A dose of 5.0-7.5 mg daily (in two or three divided doses) is usually enough to restore the serum prolactin concentration to normal. Patients with large prolactinomas may require 30 mg or more daily, and even with such doses complete suppression of hyperprolactinaemia may not be achieved.

Dopamine agonists are expensive and may cause severe side effects. It is thus important that they are carefully used. Treatment is usually for infertility, which is often relieved so rapidly that the woman should be warned that she may conceive even before resuming menstruation. Once conception has occurred the drug should be stopped, although there is no evidence that bromocriptine is teratogenic.²² As prolactinomas may enlarge during pregnancy women with tumours large enough to distort the pituitary fossa in a plain radiograph should be considered for ablative treatment beforehand²³; and they should have their visual fields checked every two to three months. Symptomatic enlargement of a tumour may be treated with bromocriptine.²⁴

Women with embarrassing galactorrhoea, women concerned by their amenorrhoea, and men with impotence caused by hyperprolactinaemia also warrant medical treatment. The duration of treatment may be determined by the need to reduce the size of an underlying prolactinoma. Otherwise, it is empirical, and withdrawal should be attempted after six to 12 months, although hyperprolactinaemia commonly²⁵ but not always²⁶ recurs. Symptoms of severe oestrogen deficiency, such as dyspareunia, may also require treatment with a dopamine agonist. A possible alternative is treatment with oestrogen in an oral combined contraceptive preparation. There is an effect related to the dose of oestrogen on prolactin secretion^{27 28} and a theoretical risk that the growth of a prolactinoma might be stimulated, but there is little evidence that this occurs with an oral combined contraceptive,¹⁶ perhaps because the progestogen component may be protective.²⁹ If oestrogens are used serum prolactin concentrations must be measured frequently at first, and oestrogen must be stopped if they rise.

Oestrogen or progestogen, or both may also be considered for contraception as some women, particularly those with mild hyperprolactinaemia, may show spontaneous resolution of their clinical syndrome with return of prolactin concentrations to normal.³⁰ Intrauterine devices may be too large for the atrophic uterus and become ineffective by remaining partly in the cervical canal if ovarian function returns and the uterus enlarges again.

Many women with hyperprolactinaemia do not have any of the above indications for treatment. Women with persistent amenorrhoea caused by hyperprolactinaemia may, however, be at increased risk of osteoporosis in later years because of the associated oestrogen deficiency,³¹⁻³³ and treatment of the hyperprolactinaemia has been shown to increase bone mineral content.³⁴ Treatment for this indication would have to be long term. Treatment with a dopamine agonist would be expensive and incur significant morbidity and a need for contraception.

Prophylactic oestrogen treatment might be possible and would be much cheaper and less likely than bromocriptine to cause side effects.

MARTIN HARTOG

Reader in Medicine,
University of Bristol,
Southmead Hospital,
Bristol BS10 5NB

MICHAEL G R HULL

Reader in Obstetrics and Gynaecology,
Bristol Maternity Hospital,
Bristol BS2 8EG

- Greer ME, Moraczewski T, Rakoff JS. Prevalence of hyperprolactinemia in anovulatory women. *Obstet Gynecol* 1980;56:65-9.
- Horvath E, Kovacs K. Identification and classification of pituitary tumours. In: Cavanagh JB, ed. *Recent advances in neuropathology*. Vol 3. Edinburgh: Churchill Livingstone, 1986;75-95.
- Burrow GN, Wortzman G, Rewcastle NB, Holgate RC, Kovacs K. Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. *N Engl J Med* 1981;304:156-8.
- Miyai K, Ichihara K, Kondo K, Mori S. Asymptomatic hyperprolactinaemia and prolactinoma in the general population—mass screening by paired assays of serum prolactin. *Clin Endocrinol (Oxf)* 1986;25:549-54.
- Lenton EA, Brook LM, Sobowale O, Cooke ID. Prolactin concentrations in normal menstrual cycles and conception cycles. *Clin Endocrinol (Oxf)* 1979;10:383-91.
- Jeffcoate SL, Bacon RRA, Beasall GH, Diver MJ, Franks S, Seth J. Assays for prolactin: guidelines for the provision of a clinical biochemistry service. *Ann Clin Biochem* 1986;23:638-51.
- Polson DW, Sagle M, Mason HD, Adams J, Jacobs HS, Franks S. Ovulation and normal luteal function during LHRH treatment of women with hyperprolactinaemic amenorrhoea. *Clin Endocrinol (Oxf)* 1986;24:531-7.
- Scammell GE, McGarrick G, Chamberlain GVP, Jeffcoate SL. The significance of hyperprolactinaemia: 2 years' experience. *Journal of Obstetrics and Gynaecology* 1982;2:249-51.
- Glazener CMA, Kelly NJ, Hull MGR. Borderline hyperprolactinemia in infertile women: evaluation of the prolactin response to thyrotropin releasing hormone and double-blind placebo-controlled treatment with bromocriptine. *Gynecological Endocrinology* 1987;1:373-8.
- Glazener CMA, Kelly NJ, Hull MGR. Prolactin measurement in the investigation of infertility in women with a normal menstrual cycle. *Br J Obstet Gynaecol* 1987;94:535-8.
- Soong YK, Ferguson K, McGarrick G, Jeffcoate SL. Size heterogeneity of immunoreactive prolactin in hyperprolactinaemic serum. *Clin Endocrinol (Oxf)* 1982;16:259-65.
- Nabarro JDN. Pituitary prolactinomas. *Clin Endocrinol (Oxf)* 1982;17:129-55.
- Bevan JS, Burke CW, Esiri MM, Adams CBT. Misinterpretation of prolactin levels leading to management errors in patients with sellar enlargement. *Am J Med* 1987;82:29-32.
- Teasdale E, Teasdale G, Mohsen F, Macpherson P. High-resolution computed tomography in pituitary microadenoma: Is seeing believing? *Clin Radiol* 1986;37:227-32.
- Davis P, Hoffman J, Tindall G, Brown I. Prolactin-secreting pituitary microadenomas: inaccuracies of high resolution CT imaging. *Am J Neuroradiol* 1984;5:721-6.
- Franks S. Regulation of prolactin secretion by oestrogens: physiological and pathological significance. *Clin Sci* 1983;65:457-62.
- Kleinberg DL, Noel GL, Frantz AG. Galactorrhoea: a study of 235 cases, including 48 with pituitary tumours. *N Engl J Med* 1977;296:589-600.
- Johnston DG, Haigh J, Prescott RWG, et al. Prolactin secretion and biological activity in females with galactorrhoea and normal circulating prolactin concentrations at rest. *Clin Endocrinol (Oxf)* 1985;22:661-78.
- Wass JAH, Williams J, Charlesworth M, et al. Bromocriptine in management of large pituitary tumours. *Br Med J* 1982;284:1908-11.
- Grossman A, Bouloux PMG, Loneragan R, Rees LH, Wass JAH, Besser GM. Comparison of the clinical activity of mesulergine and pergolide in the treatment of hyperprolactinaemia. *Clin Endocrinol (Oxf)* 1985;22:611-6.
- Ferrari C, Crosignani PG. Medical treatment of hyperprolactinaemic disorders. *Hum Reprod* 1986;1:507-14.
- Turkaj I, Braun P, Krupp P. Surveillance of bromocriptine in pregnancy. *JAMA* 1982;247:1589-91.
- Grossman A, Besser GM. Prolactinomas. *Br Med J* 1985;290:182-4.
- Tan SL, Jacobs HS. Management of prolactinomas—1986. *Br J Obstet Gynaecol* 1986;93:1025-9.
- Bergh T, Niluiss SJ, Wide L. Menstrual function and serum prolactin levels after long-term bromocriptine treatment of hyperprolactinaemic amenorrhoea. *Clin Endocrinol (Oxf)* 1982;16:587-93.
- Hancock KW, Scott JS, Lamb JT, Gibson RM, Chapman C. Long term suppression of prolactin concentration after bromocriptine induced regression of pituitary prolactinomas. *Br Med J* 1985;290:117-8.
- Franks S, Jacobs HS, Hull MGR. The oral contraceptive and hyperprolactinemic amenorrhea. In: Cammari F, Muller EE, eds. *Pituitary hyperfunction: physiopathology and clinical aspects*. New York: Raven Press, 1984:175-8.
- Anderson JR, Schroeder E, Lebech PE. The effect in post-menopausal women of natural human and artificial oestrogens on the concentration in serum of prolactin. *Acta Endocrinol (Copenh)* 1980;95:433-7.
- Haug E. Progesterone suppression of estrogen-stimulated prolactin secretion and estrogen receptor levels in rat pituitary cells. *Endocrinology* 1979;104:429-37.
- Martin TL, Kim M, Malarkey WB. The natural history of idiopathic hyperprolactinemia. *J Clin Endocrinol Metab* 1985;60:855-8.
- Klibanski A, Neer R, Beitins IZ, Ridgway EC, Zervas NT, McArthur JW. Decreased bone density in hyperprolactinemic women. *N Engl J Med* 1980;303:1511-4.
- Schlichte JA, Sherman B, Martin R. Bone density in amenorrheic women with and without hyperprolactinemia. *J Clin Endocrinol Metab* 1983;56:1120-3.
- Glazener CMA, Sargood AJ, Jackson PC, et al. Osteoporosis and amenorrhea in young women. *Gynecological Endocrinology* 1987;1:255-61.
- Klibanski A, Greenspan SL. Increase in bone mass after treatment of hyperprolactinemic amenorrhea. *N Engl J Med* 1986;315:542-6.