amenorrhea should also include measurement of serum prolactin and assessment of oestrogen production.

In summary, pelvic ultrasonography and measurements of LH, FSH and testosterone may be of some diagnostic value when set in the appropriate clinical context (Table 1). By contrast, routine measurements of adrenal androgens are not indicated, and measurement of sex hormone-binding globulin (primarily an index of body weight) is not helpful. It is recommended that obese women with PCOS should have a fasting glucose measurement at least once a year because of the increased risk of NIDDM and, in view of the associated dyslipidaemia, there may also be some merit in checking the lipid and lipoprotein profile at the same time.

Management

The physiological basis of PCOS is unknown, so treatment is largely symptomatic. Patients with anovulation may require induction of ovulation. The anti-oestrogen, clomiphene, is usually effective, but even this 'simple' treatment should be monitored at a specialist centre because of the risk of ovarian hyperstimulation and multiple pregnancy. For those not concerned about fertility, menstrual regulation by means of oral contraceptives or cyclical progestogens should be considered. Non-androgenic progestogens (e.g. medroxyprogesterone acetate, desogestrel, gestodene) are obviously preferable to norgestrel and norethisterone in women who may already have symptoms of androgen excess.

Symptoms of hyperandrogenism can be managed by anti-androgens such as cyproterone acetate. In women with acne and/or mild or moderate hirsutism, this can usually be given in the form of Dianeette (cyproterone acetate, 2 mg + ethinylestradiol, 35 mg). Cosmetic advice about removal of hair should not be forgotten, whether or not anti-androgens are given. Obese subjects with PCOS require particular attention. Calorie restriction greatly improves the chances of ovulation and reduces the risk of NIDDM.

Further reading

1 Franks S. Polycystic ovary syndrome. N Engl J Med 1995;333:853–61.
2 Jacobs HS (ed). Polycystic ovary syndrome. Baillière's Clin Endocrinol Metabol 1996;10:193–321.
3 Franks S, Gharani N, Waterworth D, Batty S, et al. The genetic basis of polycystic ovary syndrome. Hum Reprod 1997;12:2641–8.
4 Dunail A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 1997;18:774–800.

New treatments for acromegaly

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Acromegaly is a clinical diagnosis, occasionally helped by consulting old photos to look for bony and facial changes. Men and women of all ages are equally affected, with a peak age of diagnosis between 30 and 50 years1. With increasing awareness, the diagnosis is made earlier now: in the 1930s, 30% of patients presented with visual field defects due to their pituitary tumour, whereas now the figure is nearer 10%2.

Key Points

- In over 99% of patients acromegaly is caused by a growth hormone-secreting pituitary adenoma
- Acromegaly is associated with increased mortality due to cardiovascular and respiratory disease and probably malignant disease
- The aims of treatment are to decrease or remove tumour mass, reverse symptoms and normalise growth hormone hypersecretion
- Surgical cure may be achieved by an experienced surgeon in acromegalic patients with a microadenoma. The majority of patients are left with growth hormone hypersecretion
- Somatostatin analogues offer the most effective medical treatment for acromegaly, resulting in symptomatic improvement and a fall in growth hormone levels in the majority

Patients most frequently notice increasing hand and foot sizes (akron = extremity, megas = great), headaches, and excessive perspiration (Table 1). The diagnosis is often made by chance at a medical encounter for another reason or at presentation to a diabetic, neurology or urology clinic.

Aetiology

In over 99% of patients acromegaly is caused by a pituitary adenoma secreting either growth hormone alone or both growth hormone and prolactin (35% of cases); very rarely, the pituitary adenoma may secrete thyroid stimulating hormone (TSH) as well as growth hormone, in which case there is hyper-
thyroidism accompanied by a normal or elevated, but not suppressed, TSH®. Pituitary carcinoma has caused acromegaly in a handful of cases. An ectopic tumour, usually pancreatic or lung carcinoma, which is secreting growth hormone—releasing hormone (GHRH) may also cause acromegaly by stimulating pituitary growth hormone secretion®. In these circumstances, pituitary histology by an experienced neuropathologist will reveal somatotroph hyperplasia rather than an adenoma. The tumours secreting GHRH may be clinically detectable, but not always.

**Adenomas**

Adenomas are quite often large in young patients with acromegaly, and likely to extend out of the pituitary fossa. In those presenting over the age of 50, tumours are usually small and intrasellar. Overall, 30–40% are microadenomas (<1 cm in diameter) and good results for these tumours can be obtained using surgery, radiotherapy or drugs. However, small tumours are in the minority, and good results therefore cannot be achieved across the whole range of patients presenting with acromegaly. The tumours are monoclonal, and 10–40% have a G-Sst mutation which results in a continuous cell cycle of growth hormone production which is unaffected by the normal stimulatory and inhibitory influences of GHRH and somatostatin respectively (Fig 1). This mutation is less frequent in the Japanese than in Caucasians.

**Diagnosis**

The biochemical diagnosis is made with an oral glucose tolerance test (OGT) in which growth hormone fails to be suppressed below 2 μu/l (1 ng/ml). In most normal subjects the level falls below the limit of detection of the assay (normally ≤0.5 μu/l) during an OGT. The diagnosis should not be based on random growth hormone levels because growth hormone is a stress hormone. The OGT will reveal that a third of patients with acromegaly have frank diabetes mellitus or impaired glucose tolerance®. A not uncommon cause of diagnostic uncertainty is a tall adolescent, thought possibly to have acromegaly, whose growth hormone is not suppressed to less than 2 μu/l during an OGT. This is most frequently due to the higher growth hormone pulses that occur during peak growth. Insulin-like growth factor (IGF)-1, the growth hormone-dependent growth factor, which is elevated in virtually all patients at presentation with acromegaly, will be normal (Fig 1). Other causes of failure of growth hormone suppression, namely renal failure, hepatic failure and Laron dwarfism due to a growth hormone receptor abnormality, are unlikely to cause diagnostic confusion.

| Table 1. Presentation of acromegaly. |
|-------------------------------------|
| **Presenting complaint**            | **Frequency (%)** |
| Menstrual disturbance               | 13                |
| Change in appearance of acral growth| 11                |
| Headaches                           | 8                 |
| Paraesthesiae/carpal tunnel syndrome | 6                 |
| Diabetes mellitus or impaired glucose tolerance | 5 |
| Heart disease                       | 3                 |
| Visual impairment                   | 3                 |
| Decreased libido & impotence        | 3                 |
| Arthropathy                         | 3                 |
| Thyroid disorder                    | 2                 |
| Hypertension                        | 1                 |
| Gigantism                           | 1                 |
| Fatigue                             | 0.3               |
| Sweating                            | 0.3               |
| Somnolence                          | 0.3               |
| Other                               | 5                 |
| Chance detection                    | 40                |

(Reproduced from Ref 2 by permission of WB Saunders Company Limited).

IGFBP-3, being growth hormone-dependent, are frequently (80%) but not invariably elevated at diagnosis®.

**Effects of acromegaly on life expectancy**

It has long been known that acromegaly increases mortality from cardiovascular and respiratory disease®. The cardiovascular disease is related to both hypertension and diabetes because of the effects of growth hormone: increasing total body sodium and insulin resistance as well as, in the early stages, insulin levels. More recently it has become clear that acromegaly is also associated with an increase in death from malignant disease, particularly from carcinoma of the colon®. Pre-malignant colonic polyps are frequently found on colonoscopy, occurring in 30% of patients aged over 65. The mechanism for their development is unclear and does not correlate with levels of either growth hormone or IGF-1. A rational policy for surveillance in this group has yet to be developed.

**Objective of treatment**

The aim of treatment for acromegaly should be to remove the pituitary tumour in its entirety and to reverse the clinical effects of growth hormone hypersecretion without causing hypopituitarism, thus rendering life expectancy normal. In practice, this is difficult to achieve and growth hormone levels and dynamics are returned to normal in only 10–20% of subjects. A small but important study looking at the effects on mortality of different growth hormone levels suggests that growth hormone levels of 5 μu/l (2.5 ng/ml) or less are associated with a normal mortality but that mortality is higher at values above this®. More work is needed in larger numbers of patients to investigate the efficacy of different treatments, and the effects of hypertension and diabetes, the induction of hypopituitarism and, in particular, the induction of growth hormone deficiency by surgery and radiotherapy.
Growth hormone deficiency in adults has recently been shown also to be associated with increased mortality, again from cardiovascular disease associated with increased insulin resistance.

Earlier papers claiming 'cure' of acromegaly have to be viewed with circumspection. Cut-off levels of 20 mu/l or 10 mu/l have been used; these are now known to be too high and to be associated with an increased mortality. This has led to the view of a 'safe' growth hormone level which, on current evidence, should have a target value of 5 mu/l. This avoids spurious claims of cure.

**Treatment of acromegaly**

Treatment of acromegaly is usually achieved surgically using the trans-sphenoidal approach to the pituitary fossa. Radiotherapy is only rarely carried out as primary therapy. More recently drugs, particularly somatostatin analogues with a long duration of action, have been used successfully.

**Surgery**

The target of a growth hormone level of 5 mu/l or less after surgery can be achieved in 50–60% of patients. The size of the tumour is important in determining outcome: this 'safe' level may be achieved in up to 90% of surgically treated microadenomas, but in only 40–50% of larger tumours. High growth hormone levels prior to treatment are correlated with adverse surgical outcome.

Surgery may induce hypopituitarism, particularly during operations for macroadenomas, and surgery for acromegaly causes loss of one or more anterior pituitary hormones in 10–15% of patients. The operation is safe, however, even in the elderly, with a mortality of considerably less than 1%. Occasionally, cerebrospinal fluid rhinorrhoea and meningitis occur, and very occasionally haemorrhage, which may result in reduction in visual fields.

Results vary widely between surgical centres, and only the best tend to get reported. The surgeon's experience has a significant influence on the achievement of safe growth hormone levels and on rates of improvement in pituitary function after surgery. To judge by literature reports published in the last two years, optimal surgical outcome is achieved when one surgeon per centre specialises in pituitary surgery.

**Radiotherapy**

Radiotherapy is indicated most frequently in patients with large pituitary tumours in whom surgery has been unsuccessful and who have not responded well to medical treatment with the somatostatin analogue, octreotide. It is most usually administered from an external beam using a linear accelerator. Fraction dose per day and total doses determine side effects. Growth hormone levels fall exponentially after radiotherapy, the maximal fall occurring in the first 1–2 years, but they continue to fall for 10–15 years. It takes longer for patients with higher growth hormone levels (>60 mu/l) to achieve safe levels, but they are eventually achieved in 60% of patients.

The commonest side effect of radiotherapy is hypopituitarism, and 25–40% of patients so treated need replacement therapy at five years. Hypopituitarism can continue to develop for at least 10 years, so regular assessment of pituitary function is necessary. In the period between administration of radiotherapy and effective reduction of growth hormone secretion, somatostatin analogues can be used to lower excessive growth hormone levels. Regular withdrawal at one- or two-yearly intervals allows the effects of radiotherapy to be assessed.

Very rarely, visual field defects can
occur after radiotherapy. This complication has, however, been described only six times in the literature when the tumour was not in contact with the optic chiasma at the time of irradiation and the correct doses were administered.

Second tumour formation in the region of administered irradiation is a theoretical possibility. The risk is low (1–2%), and not all studies report this increased risk.

**Medical treatment**

**Somatostatin analogues.** The most effective medical treatment of acromegaly is with analogues of somatostatin, the hypothalamic peptide which is the major inhibitory hormone for growth hormone. Long-acting analogues, originally shown to be effective in the early 1980s, have a circulating half-life of about 120 minutes, while native somatostatin has a half-life of only 3–4 minutes. Somatostatin also inhibits many gastrointestinal hormones, including insulin, and affects gastrointestinal motility and blood flow. The analogue used most often is octreotide (Fig 2); it is usually administered subcutaneously three times daily and suppresses growth hormone for 6–8 hours.

A new galenical form of the somatostatin analogues has been developed and will soon be commercially available. Octreotide, absorbed on to microspheres, is slowly released and can suppress growth hormone levels for up to 28 days.

lanreotide, a similar preparation which is currently available, can suppress growth hormone levels for 14 days in its sustained-release form. A 28-day preparation will shortly be available.

These new forms of administration appear to be as safe and efficacious as multiple subcutaneous octreotide injections, and will undoubtedly improve patient compliance.

In addition to producing symptomatic improvement, these drugs cause growth hormone levels to fall to 5 mu/l in about 35% of patients. This contrasts with more than 90% of patients in whom safe levels of growth hormone has been achieved after initial surgery.

If surgery is unsuccessful, the effects of long-acting somatostatin analogues should be assessed. If safe levels are achieved by this means, it may be satisfactory to continue treatment. However, there is unlikely to be remission, and growth hormone levels will rise again if treatment is stopped.

If the somatostatin analogues are ineffective or do not reduce growth hormone levels to 5 mu/l or less, external beam radiotherapy should be considered.

Long-term follow-up should be in a tertiary referral centre or shared between tertiary and secondary care.

**References**

1 Melmed S. Acromegaly. N Engl J Med 1990;322:966–77.
2 Molitch ME. Clinical manifestations of acromegaly. Clinics Endocrinol Metab 1992;21:597–614.
3 Lowe DG. Pathology of tumours of the pituitary and related structures. In: Sheaves R, Jenkins PJ, Wass JAH (eds). Clinical Endocrine Oncology. Oxford: Blackwell Science, 1997:168–75.
4 Penny ES, Penman E, Price J, Rees LH, et al. Circulating growth hormone releasing factor concentrations in normal subjects and patients with acromegaly. Br Med J 1984;289:453–5.
5 Melmed S. Acromegaly. In: Melmed S (ed). The pituitary. Boston: Blackwell Science, 1995:413–42.
6 Wass JAH, Cudworth AG, Bottonato GF, Woodrow JC, Besser GM. An assessment of glucose intolerance in acromegaly and...
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