Reviews in Medicine

Endocrinology

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Introduction

In our review of current endocrine literature we have tried to identify areas which are likely to continue to be of interest through the 1990s. This is not simply because of the likelihood of scientific progress but also because in each instance it is probable that our approach to the investigation and management of the relevant clinical problem will alter. Thus the management of Graves' ophthalmopathy, osteoporosis and growth hormone deficiency in adults, and the investigation of thyroid hormone resistance syndromes and hypercalcaemia of malignancy, are continuing problems for all clinical endocrinologists, and in all of these clear progress has occurred recently. We hope and believe that the information will be of interest and relevance to those other than specialist endocrinologists.

The management of Graves' ophthalmopathy

Ophthalmopathy is an autoimmune disorder which may be an integral part of Graves' disease or a closely related but distinct entity. It can be a most distressing and disabling clinical problem, its course is difficult to predict, and treatment is often only partly successful. The temporal relation with Graves' disease is close, since ophthalmopathy first appears in approximately 75% of patients in the year before or the year after the development of their hyperthyroidism. One of the longstanding debates in the thyroid literature is whether anti-thyroid therapy, in particular radioiodine, causes or exacerbates ophthalmopathy. The standard view is that radioiodine therapy should be avoided in patients with eye disease. If this is true there are considerable implications for the current management of Graves' disease since increasingly radioiodine is being used as the treatment of choice, particularly in North America where a recent survey of members of the American Thyroid

Association showed that 69% favoured radioiodine as first treatment in patients with Graves' disease.¹ A recent letter in the *Lancet* entitled 'Radioiodine and aggravation of Graves' ophthalmopathy'² reinforced this view. The authors state that in Denmark (where the study originated) there is an increasing tendency to use radioiodine for Graves' disease and their impression was that this may worsen any associated ophthalmopathy. They describe a small study of 50 patients given radioiodine and followed for 24 months. In 5 patients with pre-existing ophthalmopathy the eye condition worsened and in one patient without eye disease ophthalmopathy developed. These patients were not in any way compared with a control group receiving anti-thyroid drugs and in view of the known close temporal relationship of ophthalmopathy and hyperthyroidism it is difficult to be convinced that this was a direct effect of therapy.

As the authors point out, however, there have been few attempts to evaluate the effects of different treatment modalities on the development and progression of eye disease. A small prospective study some years ago showed a slower progression with surgery or radioiodine than propylthiouracil.³ The most extensive and informative study in the literature has now been published.⁴ Among 288 hyperthyroid patients with no ophthalmopathy who were followed up for 1 to 11 years, eye disease developed in 6.7, 7.1 and 4.9% after antithyroid drug, surgery and radioiodine therapy respectively. In addition, in a prospective study (discussed below) of glucocorticoid therapy⁵ none of 10 hyperthyroid patients with no ophthalmopathy acquired it in the first 18 months after radioiodine therapy. In the study of Sridama and DeGroot⁴ the incidence and degree of progression of ophthalmopathy in patients who already had exophthalmos before treatment were similar in the medically, surgically, and radioiodine treated groups (19.2%, 19.8% and 22.7%, respectively). The incidence of improvement of ophthalmopathy was also similar (14.1%, 12.6% and 12.3% in the medically, surgically and radioiodine treated patients). Although this is a retrospective study, the numbers are large

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(506 patients analysed) and it seems quite clear that there was no influence of the type of therapy for hyperthyroidism on the clinical course of Graves' ophthalmopathy. Previous conflicting reports of the deleterious effects of radioiodine are probably due to the small number of patients studied or because the effects of only one form of treatment were observed. Although this is not likely to be a popular or consensus view it would seem that there is little evidence that any antithyroid therapy, including radioiodine, causes or exacerbates ophthalmopathy. The eye disease and hyperthyroidism usually appear at about the same time and in most patients the ophthalmopathy changes little after that, no matter how the patient is treated. Currently too much emphasis is placed on anecdotal evidence.⁶ Hyperthyroidism should be treated as if ophthalmopathy were not present.

The treatment of Graves' ophthalmopathy is not satisfactory particularly for those patients with moderate eye disease. Treatment of severe eye disease is still best managed with high dose steroids or surgical decompression, areas in which little progress has been made in the last few years other than the suggestion that intravenous methylprednisolone followed by oral prednisolone may be the preferred approach.⁷ The results of orbital irradiation have been quite variable, and so it is not now widely used.

Two recent articles in the *New England Journal of Medicine* have provided information of interest provoking further discussion. In the study of Bartalena *et al.*⁵ 26 patients were randomly associated to treatment with radioiodine alone and 26 to treatment with radioiodine and concomitant oral prednisone. In no patient without ophthalmopathy before treatment did ocular symptoms appear. In patients with eye disease treated with radioiodine alone, eye disease worsened in 56% and was unchanged in 44%; in the second group ophthalmopathy improved in 52% and was unchanged in 48%. The authors concluded that systemic corticosteroid therapy prevented the exacerbations of Graves' ophthalmopathy that occur after radioiodine therapy. In view of the large retrospective study discussed above showing no such deleterious effect specific to radioiodine, and the known side effects of glucocorticoids, the conclusion in an accompanying editorial⁸ was that the routine use of glucocorticoids to prevent progression is unwarranted. A control group of patients treated with antithyroid drugs with or without steroids would have provided important information. The second paper, from Prummel *et al.*⁹ looked once again at the question of the use of cyclosporin which may interfere with the cellular and humoral autoimmune processes thought to have a role in Graves' ophthalmopathy; results of clinical trials, however, are conflicting. In their single blind, randomized

clinical trial in 36 patients they found that single drug therapy with prednisone was more effective than cyclosporin and the combination could be effective in patients who do not respond to either drug alone. These findings are not conclusive, however, since although prednisone was more effective it caused more side effects. A final point of interest – cigarette smoking has been associated with Graves' ophthalmopathy and patients should be advised to stop smoking.¹⁰

Thyroxine replacement therapy and osteoporosis

Thyroid hormone excess has long been recognized as one of several risk factors for osteoporosis. Thyroid hormones accelerate the rate of bone remodelling, and the increased turnover of bone that develops in thyrotoxicosis is characterized by an increase in the ratio of resorptive to formative bone surfaces, the net result being loss of bone. It has long been believed, however, that there is little risk associated with long-term exogenous thyroxine treatment. Thyroxine for replacement therapy in conventional doses (100–200 µg/day) or suppressive therapy for goitre as well as for less clear indications – a recent follow up study of the Framingham cohort in the USA showed that 15% of those taking thyroid hormone did so for conditions such as obesity or fatigue¹¹ – has consequently been administered frequently in 'supraphysiological' doses without regular monitoring of tests of thyroid function. Since the introduction of assays for TSH with improved sensitivity (which are able to distinguish between normal and reduced levels) it has become clear that many patients receiving thyroxine treatment have TSH values which are either below the lower limit of the normal range or are suppressed below detectable levels. These results are argued by some clinicians to represent over-treatment.

Controversy exists as to whether such patients, who usually do not have any symptoms or signs of hyperthyroidism, have adverse tissue effects related to their thyroxine excess. Currently there is a specific argument as to whether exogenous thyroid hormone therapy in excess can predispose to the development of osteoporosis, in the same way as endogenous hyperthyroidism. Many previous studies were confounded by failure to distinguish between pre- and postmenopausal women and by the lack of comparable control populations. Ross *et al.*¹² examined bone density in 28 pre-menopausal women taking routinely prescribed doses of thyroxine for 5 or more years (mean dose 171 µg/day); TSH was found to be suppressed in 23. Women who had taken thyroxine for 10 or more years had a 9% reduction in bone density compared with normal age-matched controls without

any evidence of thyroid disease, leading the authors to conclude that mild subclinical or biochemical 'hyperthyroidism resulting from thyroxine therapy has an adverse effect on bone and that . . . patients should be given the smallest dose of thyroxine to achieve a clinical response'. Paul *et al.*¹³ reported a 12.8% lower bone density at the femoral neck and a 10.1% lower bone density at the femoral trochanter in 31 premenopausal women treated with thyroxine for a minimum of 5 years, compared with matched controls. These authors again concluded that 'it is advisable to employ a dosage of thyroxine that is carefully monitored to avoid the long-term use of dosages that are excessive'. These findings and conclusions prompted editorial comment in the *Journal of the American Medical Association*¹⁴ and extensive discussions at the 1989 meeting of the American Thyroid Association, most discussants being in favour of reduction of thyroxine dosage and repeated biochemical assessment of thyroid hormones and TSH.

Two recent studies came to slightly different conclusions. In the first, forearm bone mineral content (BMC) was measured in 60 women treated with triiodothyronine (T3) or thyroxine (T4) for euthyroid goitre, in 13 untreated goitre patients, and in 2 controls matched for age and menopausal state for each goitre patient.¹⁵ BMC was not different between untreated goitre patients and controls. In 36 premenopausal patients, treated for 1 to 23 years (mean 5.8) a slight decrease in BMC of about 5% compared to controls was observed. In 24 postmenopausal patients treated for 2 to 19 years (mean 10.0) a 20% deficit was found. Whether the difference between the 2 treatment groups was due to menopausal state or duration of treatment is not clear. The authors concluded that thyroid hormone therapy under these circumstances had a clear adverse effect on bone mineral status in postmenopausal patients. In the second study both serial and cross-sectional studies were performed in subjects with thyroid disease.¹⁶ In patients with primary hypothyroidism a mean decrease of 5.4% for vertebral bone mineral density (BMD), 7.3% for trochanter and 7% for femoral neck was observed after one year of treatment with thyroxine (mean dose 135 µg/day). In contrast, in the cross-sectional study, vertebral BMD was not significantly different from age-matched normal values in patients receiving either replacement (mean dose 104 µg/day) or suppressive (mean dose 154 µg/day) doses of thyroxine for at least 2 years. It is suggested that bone mass reduction could be transient and reversible due to new bone formation at the end of the resorptive sequence.

As the authors point out, the apparent reduction in BMD that may accompany exogenous thyroid hormone administration has not been shown to be associated with an increased fracture risk. The lack

of prospective studies of fracture rates in thyroid hormone treated subjects raises the question of the clinical significance of such a decrease in bone density. The risk may not be the same for male patients. Toh and Brown report a 3 year follow-up study of 35 male patients, including 24 patients with hypothyroidism receiving thyroid hormone replacement to the euthyroid state, and 11 patients with treated Graves' disease who were euthyroid.¹⁷ There was no significant difference in bone mineral content of the distal radius between the 2 groups and values were no different from those in 23 age-matched normal males.

If these concerns of an osteoporosis risk are correct then fundamental changes need to occur in our prescribing habits for patients with hypothyroidism, as well as in biochemical monitoring, with considerable implications for cost, time and patient compliance and inconvenience. It is crucial to note, however, that while it is of great importance to avoid any increased risk of osteoporosis and fracture associated with over-zealous thyroxine treatment, the findings pose a number of questions which are as yet unanswered. Are pre- and postmenopausal women equally at risk? Does a preceding episode of thyrotoxicosis, and hence previous accelerated bone loss, exert an effect of any significance and are there clear-cut differences in risk between those given 'suppressive' doses of thyroxine and those given 'physiological' doses? Is the problem only related to thyroxine therapy or are other patients with suppressed TSH secretion (e.g. due to goitre, glucocorticoids, non-thyroidal illness) equally at risk? What is the clinical significance of small but statistically significant decreases in bone density? How realistic are these recommendations on reducing thyroxine doses? The overall prevalence of thyroid hormone use in an unselected population of older adults in the Framingham cohort (94% aged 60 years or older, the remainder aged 58 or 59 years, average age 68.6) was 6.9% (10.0% in women and 2.3% in men).¹¹ Thirty seven percent of those definitely hypothyroid had a clearly elevated serum TSH level (> 10 mU/l) despite thyroid therapy. In our own study of patients over 60 years of age in a single general practice approximately 50% of subjects taking thyroxine had abnormal TSH values.¹⁸ Our view remains the same as that outlined earlier this year.¹⁹ We believe that, given the current state of knowledge, it is wise to avoid prescribing higher than conventional doses of thyroxine for hypothyroidism unless suppression of TSH secretion is important, as in patients with a history of thyroid carcinoma; steps should be taken to ensure long term compliance with thyroxine and to avoid undertreatment, and that means occasional biochemical monitoring with adjustment of thyroxine dose when necessary. It almost goes

without saying that further long term studies are required and are in progress.

Generalized thyroid hormone resistance (GTHR)

Cloning and sequencing of the genes encoding the thyroid hormone receptors have led to a rapid advance in our understanding of the pathogenesis of this apparently rare syndrome, and an appreciation that it may in fact be a more common condition than originally thought:

Thyroid homeostasis is maintained largely by a negative feedback effect of T4 and T3 on TSH synthesis and secretion from the anterior pituitary; primary thyroid failure leading to a reduction in circulating levels of thyroid hormones is associated with an increase in circulating TSH, while increases in T4 and T3 are associated with suppression of TSH secretion. The recent development of TSH assays with improved sensitivity which are able to differentiate normal from reduced values, has led to the recognition of increasing numbers of patients with discrepancies between clinical thyroid status and tests of thyroid function, as well as between circulating concentrations of thyroid hormones and TSH. Patients with thyroid hormone levels above the normal range in association with unexpectedly normal or high TSH levels are said to exhibit 'inappropriate TSH secretion' and patients with resistance to thyroid hormones fall within this category. Inappropriate secretion of TSH from pituitary glands which do not have a TSH-secreting tumour has been described in association with a euthyroid, hyperthyroid and rarely hypothyroid clinical state. Generalized thyroid hormone resistance (GTHR) is the most commonly recognized form of the defect and because the anterior pituitary is affected in addition to the 'peripheral' tissues of the body, the defect is usually compensated in the untreated patient so that a euthyroid state is maintained by high circulating free thyroid hormone levels. In contrast, in the rarer situation of selective pituitary resistance to thyroid hormones, the clinical picture differs in that hyperthyroidism is evident.

Analysis of the familial pattern of the disease suggests that it usually follows an autosomal dominant pattern of inheritance, although recessive inheritance has been reported. The disease affects males and females with equal frequency. Most patients are clinically euthyroid but in children the condition may be associated with deafness or stunted growth and thus thyroid hormone therapy may be indicated. The biochemical hallmark of the condition is the presence of detectable levels of TSH, as well as a normal or exaggerated response to thyrotrophin releasing hormone (TRH), despite elevated thyroid hormones. A

recent report showing that the TSH response to TRH is proportional to the basal TSH level, and that TRH responsiveness is maintained while taking T3, confirms thyrotroph resistance to thyroid hormone.²⁰

There have been considerable advances in our understanding of the mechanisms by which thyroid hormones act to regulate gene expression in recent years, the most important breakthroughs arising from cloning and sequencing of T3 receptor cDNAs (see reviews refs 21, 22). These advances led to the recognition that at least two major classes of T3 receptor proteins exist, termed α and β which are encoded by separate genes on different chromosomes. The precise physiological roles of the two receptors have yet to be elucidated. Activation of gene transcription by thyroid hormones is dependent on the dimerisation of receptor molecules and interaction with specific regulatory DNA sequences in target genes. Attention has focussed on the role of thyroid hormone receptor abnormalities in the aetiology of GTHR. Reduced binding affinity of cell nuclei for T3 was described some years ago but more recently possible linkage of the receptor genes to the syndrome of GTHR has been investigated. The first report revealed the presence of tight linkage of the gene conferring the GTHR phenotype to the T3 receptor β gene locus on chromosome 3.²³ It thus appeared likely that the syndrome resulted from a mutation of the T3 receptor β gene. This hypothesis was supported by a subsequent study using polymerase chain reaction amplification of genomic DNA, describing a single base substitution in exon 8 resulting in a change from proline to histidine, a mutation predicted to alter the secondary structure of the T3 binding region.²⁴ Expression of the mutant receptor *in vitro* revealed that it bound T3 with an approximately 10-fold lower affinity than normal receptor, but was capable of binding normally to thyroid hormone response elements in DNA.²⁵ In similar studies of another affected patient a single base substitution in exon 7 was found resulting in a glycine to arginine substitution in the hormone binding region of one of two β receptor alleles.²⁶ Several similar base substitutions have been described by this group in different families exhibiting a dominant pattern of inheritance, although it is clear that different mutations are present in different kindreds.²⁷ A small number of families with a recessive pattern of inheritance of thyroid hormone resistance has also been reported. The presence of a homozygous mutant T3 receptor β gene allele has been described in one individual from such a family, sequence analysis again indicating the presence of an abnormality in the hormone binding region of the β gene.²⁵ In addition, Southern blot analysis has revealed a major deletion involving several exons of the β receptor

gene including those encoding hormone binding and DNA binding domains in affected subjects in a further family exhibiting a recessive pattern of inheritance.²⁷

These specific T3 gene mutations provide some insight into the functional characteristics of normal and mutated thyroid hormone receptor proteins. In the majority of families showing a dominant pattern of inheritance, only one abnormal T3 receptor allele is present, while presumably both alleles are transcribed and translated. It has been suggested that expression of the abnormal allele results in reduced levels of the normal receptor gene product, the activity of which may be reduced further by competition for binding between the normal and abnormal gene product for thyroid hormone response elements.²⁶ The situation in affected individuals may be similar to that seen in transfection studies of human and rat cells in which the $\alpha 2$ gene product (which does not bind T3 but which is structurally homologous to the functional T3 binding $\alpha 1$ gene product) has been shown to inhibit the cellular response to T3 mediated by either β or $\alpha 1$ receptor proteins.²⁶ This 'dominant negative inhibition' phenomenon may be present in GTHR and may result from the formation of dimeric molecular structures comprising an abnormal and normal β receptor molecule, the 'heterodimer' inhibiting normal receptor activation of transcription.²⁴ This inhibition is probably overcome (as in most of the patients described) by increased T3 saturation of normal receptors consequent on high circulating endogenous hormone concentrations or from administration of exogenous thyroid hormone. The recent description of a family with a recessive pattern of inheritance of GTHR with affected members possessing a major deletion of the T3 receptor β gene extends this hypothesis. Since heterozygous members of the family were unaffected, it is clear that the presence of a single normal allele in the absence of a mutated allele is sufficient for normal T3 receptor function. The presence of the abnormal gene product in the dominantly inherited syndrome, however, interferes with the function of the normal receptor protein.

Thus the introduction of sensitive TSH assays with the recognition of syndromes of 'inappropriate TSH secretion', combined with the advances of molecular biology, resulting in the definition of a variety of mutations in the thyroid hormone receptor genes, has led to an increasing frequency of the diagnosis of the syndrome of GTHR. What is not clear as yet is whether such individuals require treatment with thyroid hormone, particularly in childhood, what the dose should be, and whether the prevalence is sufficiently high for screening programmes to be considered.

The role of growth hormone in adults

The physiological role of growth hormone (GH) in children is well established but its function in adults is less clear. There is as yet no defined clinical syndrome of adult GH deficiency. GH has both anabolic and lipolytic activity and these metabolic effects appear to be mediated by insulin-like growth factor 1 (IGF1) which is produced by the liver in response to GH stimulation. It has been proposed that in adults the metabolic activities of GH may be important for maintaining lean body mass. In 1988 a small study was published on the effects of exogenous GH on the body composition of eight healthy, fit adults aged between 22–33 years.²⁹ The trial was of a placebo-controlled, double-blind, cross-over design. The duration of treatment was 6 weeks and human growth hormone (hGH) dosage 8 mg (2 U/mg) per week. The authors report that GH caused a significant increase in lean body mass (3–7%) and a fall in body fat (1%). IGF1 levels were increased after GH treatment from 0.67 ± 0.09 U/ml to 1.51 ± 0.23 U/ml but this final figure was still within the normal range for the age group studied (upper limit 2.2 U/ml). The authors concluded that supraphysiological levels of exogenous growth hormone can alter body composition.

Salomon *et al.*³⁰ studied the effects of growth hormone treatment in adults with biochemical growth hormone deficiency. Subjects, who had all previously undergone pituitary surgery, were selected on the criterion of sustained GH deficiency for 12 months or more, with peak GH levels of less than 3 mU/l on a formal insulin tolerance test. IGF1 levels were also depressed in these patients (0.41 ± 0.5 U/l). There were 12 subjects in both treatment and placebo groups and their average age was 39 years, all were obese according to their ideal body weights $131 \pm 7\%$. The treatment group received 0.07 U/kg (0.19 mg/kg) of hGH daily, a much higher dose than in the previously discussed study. After 1 month of therapy, lean body mass increased by 10.8% and body fat levels had fallen by 2.2%. The study continued for 6 months and although the major increase in lean body mass was seen within the first month, a small effect was apparent throughout the study [52.0 ± 3.5 kg (0); 56.1 ± 4.1 kg (1 month); 58.2 ± 4.8 kg (6)]. A similar time course was observed for the effect of GH on total body fat [30.5 ± 3.3 kg (0), 28.3 ± 2.7 kg (1 month) and 25.5 ± 3.6 kg (6 months)]. These coordinated changes in body composition meant that after 6 months of hGH therapy, lean body mass increased to $104 \pm 3.4\%$ of the predicted ideal value. Compliance in the trial was high ($96 \pm 2\%$ in treatment group) with only one patient withdrawing because of non-specific side effects. Three patients required a reduction in

GH dose because of oedema or hypertension. Five patients reported mild arthralgia which settled within the first 3 months of the trial. Although there was some increase in insulin resistance during treatment (blood sugar 4.6 ± 0.2 mmol/l to 5.3 ± 0.2 mmol/l) no patient developed overt diabetes mellitus. There also seemed to be a potentially beneficial lowering of serum cholesterol in the treatment group from 5.8 ± 0.3 to 5.1 ± 0.3 mmol/l. These authors suggest that the role of GH in adults may be to maintain lean body mass. Jorgensen *et al.*³¹ performed a similar study on 22 growth hormone-deficient adults and made identical conclusions.

Rudman *et al.*³² extended this idea by looking at the effects of GH therapy in men over the age of 60 years. It is argued that as people age there is a physiological fall in lean body mass and increase in adipose tissue. It is also known that GH and IGF1 levels fall with age, 5% of men between the ages of 20 and 40 have IGF1 levels below 350 U/l but this figure rises to 30%, even in healthy men, over 60 years of age. It is proposed that the fall in serum GH/IGF1 concentrations and the age related changes in body composition may be mechanistically linked. The study initially recruited 95 men by age, of these only 33 had IGF1 levels less than 350 U/l. The final study population was 21 and divided into a treatment ($n = 12$) and control group. The test subjects received hGH, 0.03 mg/kg three times weekly, which is approximately half the dose used by Salomon *et al.*³⁰ After 1 month of GH therapy IGF1 values became markedly elevated (230 ± 66 mU/l to 830 ± 339 mU/l). Lean body mass increased by 8.8% and adipose mass fell by 14.4%. Cholesterol levels were unaffected by GH in this study. The authors argue that the data support the hypothesis that GH helps maintain lean body mass and further suggest that the changes in body composition associated with aging are a reflection of declining GH and IGF1 levels.

These claims have been highlighted by the lay press who proclaimed that GH therapy in the elderly may promote prolonged youthfulness and vigour and could therefore become a standard treatment for the future. An editorial in the *New England Journal of Medicine* highlights³³ the possible ethical, logistic and financial problems which could be generated if GH therapy was advocated on a large scale in the elderly population. However, even before such arguments are entertained, some questions concerning these studies need to be addressed. The reported studies when taken together, provide a strong argument that supraphysiological doses of hGH may increase lean body mass in healthy, young, slim subjects,²⁹ GH deficient obese subject,^{30,31} and elderly male subjects.³² The study of Soloman³⁰ and Jorgenson³¹ also suggests that in adults, prolonged GH

deficiency may cause alterations in body composition. However, claims that the increases in adipose tissue mass which occur with aging are a function of diminished GH/IGF levels are less easily established. Firstly, Rudman *et al.*³¹ state that 30% of men over 60 have IGF1 levels outside the normal range. The 'normal range' used may not be valid for this age group as the distribution of values is clearly severely skewed to the left of the mean. This suggests that an age-related normal range for IGF1 needs to be employed. Secondly, by definition 70% of the 60 + year old population have 'normal' IGF1. There are no data presented to show if the high and low IGF1 populations are significantly different in respect of body weight, body composition, overall health, level of normal activity or exercise habits. If these sub-populations are similar then the observed difference in IGF1 becomes less significant. If the populations differ, it becomes important to determine if altered IGF1 levels are in fact the cause or effect of such differences. Thirdly, measurements of IGF1 can be technically difficult and the possibility of changes in the concentration of binding and transport proteins needs to be excluded in the apparently IGF1-deficient population. It is probable that a physiological role for GH in adults has been found and that a clinical syndrome of GH deficiency is about to be defined. However, the widespread use of hGH in the general or aged population seems unlikely at the present time.

Growth hormone and Turner's syndrome

The use of hGH in Turner's syndrome appears to be slightly less contentious. Rosenfeld (1989)³⁴ reviewed the available trial data including the Genetech Collaborative Study. It is pointed out that hGH doses in all trials have been randomly selected and that no data are available which would allow the optimum hGH dosage regime to be determined. Despite this shortcoming it is concluded that hGH therapy does produce a significant increase in growth rate in patients with Turner's syndrome. Although the studies have yet to achieve completion it is predicted that hGH therapy will also lead to an increase in final adult height. The augmentation of hGH with anabolic steroids or low dose oestrogens is also discussed. Oxandrolone appears to cause a significant increase in growth velocity. One study reports a 3.2 cm/year increase in growth velocity with the group treated with hGH and oxandrolone when compared to the hGH alone treated group.³⁵ Similarly the data from the Genetech study suggests that while hGH treatment alone leads to 82% of patients exceeding the 50th centile for untreated patients with Turner's syndrome, the addition of oxandrolone led to 41%

exceeding the 90th centile, while 33% were in fact above the 10th centile growth curve for normal girls.³⁴ Worries concerning premature epiphyseal fusion appear to be unsubstantiated and it is predicted that the final adult height in the combined treatment group will be similar to hGH alone.

The use of low dose oestrogens is less clear. Vanderschueren³⁶ has argued that the use of hGH does allow the early introduction of low-dose oestrogen therapy therefore assisting the induction of normal maturation. These studies suggest that all girls with Turner's syndrome should be treated with hGH $\pm$ anabolic steroids to allow them to maximize their adult height. Additionally low dose oestrogens should be introduced at an early stage to minimize the period of oestrogen deficiency and allow maximum maturation.

Growth hormone and ovulation induction

Attempts to increase the efficiency of artificially-induced ovulation has led to the discovery that hGH treatment can increase the sensitivity of the ovarian follicles to human chorionic gonadotrophin (HCG). Therapeutically hGH treatment allows significant reductions in both the dose and duration of HCG therapy. Homburg *et al.*³⁷ reported the use of hGH in 7 patients who were 'resistant' to HCG therapy. The use of hGH 20 IU/day dramatically reduced the dosage of HCG required to induce ovulation. A larger trial by the same authors³⁸ studied 16 women who required induction of ovulation. The test group ($n = 8$) received HCG and hGH while the control group received HCG and placebo. The test group showed a 30% reduction in HCG requirement. After 1 cycle of therapy, 2 patients in the test group became pregnant, with one pregnancy occurring in the placebo group. A single case report³⁹ has also suggested that hGH therapy may augment the use of pulsatile gonadotrophic releasing hormone (GnRH) treatment. This paper describes the induction of a twin pregnancy after two cycles of pulsatile GnRH and hGH therapy (10 μ g/90 minutes and 0.1 U/kg/day from day 1 to 12) in a patient with hypothalamic amenorrhoea. These authors suggest that hGH may have a physiological role in ovulation and could have a significant effect on the treatment of some forms of infertility.

Parathyroid hormone related peptide (PTHrP) and the hypercalcaemia of malignancy

The occurrence of hypercalcaemia in certain malignancies has been recognized since the 1920s. It was initially argued that this reflected metastatic spread

of the disease to bone. The observation that hypercalcaemia can occur in the absence of skeletal metastasis and that the number of bone metastases does not correlate with the degree of systemic hypercalcaemia suggested that the physical presence of tumour alone does not stimulate osteolysis. This led to the suggestion that two separate mechanisms may be involved in the generation of hypercalcaemia. The first reiterated the idea that hypercalcaemia could be produced by the local osteolytic action of bone metastasis, additionally it was speculated that certain tumours produced a systemic humoral agent which, like parathyroid hormone (PTH), could elevate serum calcium. The identification of a number of local paracrine agents which stimulate osteoclast activity and mediate hypercalcaemia (interleukin 1, tumour necrosis factor α ; β , cytokines and prostaglandins) strengthened the argument for local metastasis but suggested that the hypercalcaemia of malignancy is basically humorally driven either at a paracrine or endocrine level.

The continued search for a systemic humoral agent responsible for malignancy related hypercalcaemia has now identified a candidate peptide, parathyroid hormone related peptide (PTHrP).⁴⁰ This peptide is a product of a gene on the short arm of chromosome 12, unlike PTH and calcitonin which are coded for on the short arm of chromosome 11. However, these chromosomal segments are products of duplication and it is possible that all these peptides are telologically closely related. Active PTHrP is composed of 141 amino acids. Although the N-terminal 13 amino acids of PTHrP are identical to those of PTH, the peptides share little homology over their remaining sequence. The N-terminal sequence contains the active site of both PTH and PTHrP and the homology in this area probably explains the similarity in physiological function of the two peptides. It is also argued that the dissimilarity of the remaining sequence explains why there is little or no cross-reactivity between the two peptides in conventional radioimmunoassays. The PTHrP appears to be expressed in both malignant and normal tissue, particularly those of epithelial origin.

A recent report,⁴¹ using *in vitro* hybridization, has shown that mRNA for PTHrP was present in all 7 tumours taken from patients with hypercalcaemia of malignancy. These tumours were histologically malignant and none were of parathyroid tissue origin. Malignant tumours from 14 normocalcaemic patients were also studied. PTHrP mRNA was found in all 3 squamous cell carcinomas of the lung, one hepatocellular carcinoma and one of four adenocarcinomas of the lung. None of the 4 colonic adenocarcinomas were positive for PTHrP mRNA. It is suggested that tumours which are commonly associated with

clinical hypercalcaemia frequently appear to express mRNA for PTHrP. The authors point out that the expression of mRNA does not necessarily indicate that translation into active peptide occurs. However, the demonstration that biological active PTHrP was extracted from one of the bronchial carcinomas and that high peripheral blood concentrations of PTHrP were found in 2 of the study patients (one with a malignant pheochromocytoma and the other with an islet cell tumour) argues strongly for the involvement of PTHrP. Similarly, the hypothesis that a humoral agent is controlling the hypercalcaemia in these patients is supported by the observation that 3 patients were rendered normocalcaemic following removal of the primary tumour.

The exact relationship between PTHrP and hypercalcaemia is complex and may depend on factors such as the rate of mRNA translation, peptide secretion and the relative activities of other calcium homeostatic mechanisms. Considerable research remains to be done in this area. The recognition that PTHrP is also expressed in normal tissue presents the exciting problem of determining the physiological function for this novel peptide.

Bisphosphonates and the treatment of hypercalcaemia of malignancy

Hypercalcaemia of malignancy is a significant clinical problem. It affects 10% of all cancer patients, is the commonest cause of hypercalcaemia in hospital practice and contributes significantly to the morbidity of malignant disease. While basic medical research continues to give an insight into the underlying mechanisms of the disorder, applied research has provided data suggesting a rational treatment regime for patients in the clinical situation. A recent study⁴² reports the effects of intravenous bisphosphonates on the serum calcium of patients with hypercalcaemia of malignancy. Forty-eight patients who had a corrected serum calcium in excess of 2.8 mmol/l and were symptomatic from their hypercalcaemia were recruited to one of the 3 study arms. All patients initially received 6 litres of normal saline intravenously over 48 hours. Sodium repletion caused a significant fall in mean serum calcium from 3.45 mmol/l to 3.25 mmol/l ($P < 0.001$; $n = 48$). The subsequent treatment limbs of the study consisted of either (i) pamidronate (30 mg in 0.9% saline over 4 h i.v.), (ii) clodronate (600 mg in 500 ml 0.9% saline over 6 h i.v.), or (iii) etidronate (7.5 mg/kg body weight in 500 ml 0.9% saline over 2 h i.v. on 3 consecutive days). All three bisphosphonate therapies produced a significant fall in serum calcium concentrations. However, pamidronate induced a more rapid fall, a lower nadir value (2.45 mmol/l) and a

more protracted suppression of serum calcium (up to 29 days) than the other agents. It is argued that pamidronate is the superior agent and this might reflect the unique *in vitro* action of the drug on osteoclast synthesis and recruitment.⁴³ There has been some criticism of the study in relation to the relative doses of bisphosphonates chosen. However, these drugs in general and perhaps pamidronate in particular, now seem to be established as first line agents for the treatment of hypercalcaemia in malignancy.

Bisphosphonates and postmenopausal osteoporosis

Bisphosphonates may have also found a role in the treatment of postmenopausal osteoporosis.⁴⁴ This costly and disabling condition is currently treated by a number of agents including oral oestrogens, parenteral calcitonin, sodium fluoride, thiazide diuretics and calcium supplemented diets. The number and variety of therapies reflects the fact that none is entirely satisfactory. Expense, routes of administration, safety and lack of proven efficacy limit their widespread use. Bisphosphonates inhibit osteoclast activity thus reducing bone reabsorption⁴⁵ and appear theoretically to be logical therapeutic agents for osteoporosis. A large number of small, short term uncontrolled studies have produced conflicting results on the efficacy of bisphosphonates in osteoporosis.⁴⁴ Recently, however, the results of a large, 2 year prospective, multicentred, placebo controlled, double-blind, randomized trial assessing the efficacy of intermittent oral etidronate on postmenopausal osteoporosis has been published.⁴⁶ The study recruited 429 women by media announcement. They were below the age of 75 years and had body weight between 40 and 80 kg. All patients were white or Asian with postmenopausal osteoporosis defined radiologically as vertebral osteopenia with 1 to 4 vertebral compression fractures. Women who had received therapy within the preceding 12 months were excluded and none of the subjects had previously taken sodium fluoride, bisphosphonates or calcitonin. All patients were counselled to increase dietary calcium intake to 700 mg daily, in addition they also received calcium supplements (500 mg) to be taken on days when no other drug therapies were given. The subjects were randomized to treatment groups. Initially patients received either placebo or phosphate tablets (250 mg phosphate) twice daily for 3 days. This was followed by 14 days of treatment with either placebo or etidronate (400 mg). All patients then received calcium supplementation (500 mg) for the next 74 days. Treatment cycles were repeated every 91 days for 2 years. This protocol generated 4 study groups namely: placebo-placebo, placebo-eti-

dronate, phosphate–placebo and phosphate–etidronate. Three hundred and sixty-three patients completed the study (86%), of the 60 patients who withdrew only 7 (1.6%) claimed adverse side effects of therapy.

The study recorded the effects of treatment on bone mass and fracture rate. In both groups receiving etidronate (placebo–etidronate; phosphate–etidronate), there was a significant increase in vertebral bone density after 12, 18 and 24 months of therapy. Increase in bone density in other sites was less pronounced and it is suggested that trabecular bone may be preferentially affected by etidronate treatment. Review of fracture rates was performed by comparing the cumulative fractures in the groups treated with and without etidronate. This showed a striking reduction of 50% in the fracture rates of the etidronate treated group (29.5/1000 patient years compared to 62.9/1000 patient years). This cumulative figure, however depends heavily on the markedly lower fracture rate in the etidronate–phosphate group (14.8/1000 patient years) which is significantly different from the etidronate–placebo group (44.2/1000 patient years). In fact the fracture rate in the etidronate–placebo group is very similar to the non-

etidronate treated groups (68.0 and 57.7/1000 patient years). This point is not discussed in the report. The authors also state that phosphate therapy confers no additional benefit to etidronate treatment. This statement is only correct if the data on bone density and fracture rates are considered together. The authors do, however, stress that there does appear to be a substantiated inverse relationship between bone density and fracture rates which probably makes the combined analysis valid.

A similar but smaller trial of the effects of cyclical oral etidronate therapy in postmenopausal osteoporosis was also reported in the *New England Journal of Medicine*.⁴⁷ Sixty-six patients were treated with 400 mg of etidronate orally each daily for 2 weeks in 15 week cycles over 3 years. The results of this study were identical to that of Nelson *et al.*⁴⁴ showing that etidronate therapy produced significant increase in the mineral content of trabecular bone and a dramatic fall in vertebral fracture rates (6 vs 54 fractures per 100 patient years). The results from these studies are encouraging and it appears that oral etidronate may have an important and significant role in the future treatment of postmenopausal osteoporosis.^{44,46,47}

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