LESSONS FROM A SYMPOSIUM ON CONTROVERSIES AND DILEMMAS IN ENDOCRINOLOGY HELD IN THE COLLEGE ON 4 MARCH 1999

*H.K. Gleeson**

This Symposium, held at the College on 4 March 1999, highlighted issues in endocrinology which are subject to either controversy or advance. Specialists reviewed the evidence and expressed their opinions on the management of thyroid disease, the controversial use of growth hormone replacement and the unproven benefit of sex hormone replacement. The advances in the understanding of the molecular basis of osteoporosis, insulin resistance in polycystic ovary syndrome and obesity were also explored.

CONTROVERSIES IN THYROID DISEASE

The use of radioiodine for the treatment of thyrotoxicosis is growing in popularity. There are concerns about its effect on thyroid associated ophthalmopathy (TAO) and cancer mortality.

Ten years ago, in a randomised trial of the treatment of thyrotoxicosis comparing radioiodine alone with radioiodine with corticosteroid cover, the radioiodine alone group experienced a worsening of TAO.[1] In the absence of a control group it was unclear whether the conclusion should be that radioiodine worsened or whether corticosteroids improved TAO. In 1998 Bartalena *et al.* published a repeat of their original study but with the addition of a control group treated with antithyroid drugs. Deterioration of TAO occurred in:

- 15% of patients treated with radioiodine alone;
- 3% of patients treated with antithyroid drugs;
- 0% of patients treated with radioiodine and corticosteroids.[2]

The speaker's recommendation is, therefore, that radioiodine should be avoided in patients with TAO. If this is unavoidable such patients should be covered with corticosteroids.

In the last five years there have been three surveys looking at mortality following radioiodine. The surveys involve over 50,000 patients and cover 15 to 21 years of follow up. Using standardised mortality ratios the surveys consistently demonstrate an early increase in mortality due to cardiovascular disease and endocrine problems, particularly thyroid storm, which declines with longer follow-up. This suggests that the increase in mortality may be due to thyrotoxicosis itself rather than radioiodine. There was no overall increase in cancer mortality.[3,4] One survey looked at individual cancers and found a significant increase in mortality from thyroid cancer, standardised mortality ratio 2.8 (CI 1.9-4.0).[5] The speaker's recommendation is that radioiodine should be avoided in children and adolescents.

**Specialist Registrar (LAT), Metabolic Unit, Western General Hospital, Edinburgh, at the time of the Symposium. Now Specialist Registrar in Diabetes and Endocrinology, Royal Preston Hospital, Preston.*

The incidence of agranulocytosis with antithyroid drugs such as the frequently used carbimazole and propylthiouracil, is 3/10,000 patient years of treatment.[7] Current usual practice is still to warn patients of the side effect and to advise them to stop taking the medication should they experience a sore throat, fever or mouth ulcers. This is despite the recommendations in 1997 from the Drugs and Therapeutic Bulletin which suggested fortnightly full blood count screening for the first three months of treatment. This advice was apparently based on information from a single uncontrolled trial from Japan.

An algorithm for the treatment of subclinical hypothyroidism has been devised based upon information from the Whickham survey. The relative risk of developing hypothyroidism is eight in patients with an elevated TSH or in those with positive thyroid antibodies. If patients have both an elevated TSH and positive thyroid antibodies the relative risk increases to 38.[7] Using these findings thyroxine replacement should be started if:

- the TSH is greater than ten;
- the TSH is raised with positive thyroid antibodies;
- the patient is symptomatic despite negative antibodies and a raised TSH of less than ten (a three month trial of thyroxine should be instituted to be continued only if symptoms improve).

Patients on thyroxine replacement should be maintained at a normal TSH. The most convincing evidence to support this came from a study looking at the development of atrial fibrillation in 2,007 patients above the age of 60. The arrhythmia developed in 28% of patients with a suppressed TSH and 11% of those with a normal TSH.[9] A meta-analysis of 13 studies looked at the development of osteoporosis and fracture rates in patients treated with thyroxine in TSH suppressive doses. There was no increase in fracture rates and only postmenopausal women with previous thyrotoxicosis had an excess annual loss in bone mineral density.[8]

GROWTH HORMONE UPDATES

Aspects of growth hormone therapy in children

The process of growth is a complicated interaction involving auxology, endocrinology and psychology. Throughout childhood organic and psychological insults can result in problems with growth. Predicting which children with constitutional short stature and no hormone deficiency will benefit from growth hormone treatment is difficult. The best end point to monitor success of this treatment is final height (linear growth over a short period does not predict final height) therefore the outcome of trials is not known for many years. There are also important quality of life issues to be considered.

The features of GH deficiency in children are well described and there are numerous tests to diagnose this

condition, each with varying sensitivities and specificities; the gold standard is the insulin tolerance test, which is not without risk. Urinary GH could be used as a screening test. There is significant overlap between patients with GH deficiency and short stature, but a high circulating concentration of GH would exclude the diagnosis and obviate the need for more invasive testing.

Patients with constitutional short stature are a heterogeneous group; consequently, the 14 trials in this area have shown varying results on final height from an additional five to six centimetres to a loss of nine centimetres.

Short stature in Turner's syndrome is a problem of end organ resistance to GH. The trials using final height as an end point are difficult to compare because of varying GH treatment regimens. Trials including anabolic steroids demonstrate good increments in height, but the studies were reported before final height was reached and many patients were lost to follow up. Delaying puberty is beneficial for height but can be detrimental for bone mineral density and the psychological well being of the patient who may remain prepubertal at the age of 15. The overall average height gained in these trials is four to six centimetres after four years of treatment.

There are no evidence-based guidelines for the management of short stature in the absence of GH deficiency. The studies performed are often poorly designed, include too few patients and very few have randomised controls. Even if statistical significance is shown for a treatment, this does not necessarily reflect clinical benefit for patients; in particular quality of life should be considered when making treatment decisions. Large high quality trials with randomised control groups and a range of end points are needed. These however would be difficult to organise. There are also concerns that allowing patients with intrauterine growth retardation to catch up may exacerbate their predisposition to develop cardiovascular disease and type 2 diabetes.[10,11]

Adult growth hormone deficiency

The symptoms of GH deficiency in the adult are non-specific but may include a decrease in psychological well-being and a reduction in maximal exercise capacity and muscle strength. The evidence that these symptoms are directly caused by GH deficiency is that they are reversible with GH treatment. The signs attributed to GH deficiency in all studies are as follows: increased central fat mass and decreased lean body mass, decreased bone mineral density (BMD), reduced left ventricular function, an increase in atheroma, insulin resistance and impaired thermoregulation.

A survey of patients with adult onset GH deficiency performed in 1989 discovered that they had a significant deficit in energy levels and emotional reaction and an increase in social isolation.[12] The Pharmacia & Upjohn International Metabolic Database (KIMS), which holds data from 3,500 patients from 22 countries, had shown that receiving GH results in an improvement in quality of life after six months of therapy and a further improvement at 12 months, by which time there is no significant difference from the normal population.

Mortality data in surveys of patients with hypopituitarism have shown an increased risk of death in both men and women. In Swedish studies cardiovascular disease was shown to be the cause of excess mortality,[13] but this was not shown in the UK studies, probably due to the prevalence of cardiovascular disease in the general population.[14] Cardiovascular risk factors from the KIMS database compared to normal population studies show that body mass index (BMI), the prevalence of diabetes (in women) and the plasma cholesterol concentrations are higher in patients with hypopituitarism. There is no evidence to show that increased cardiovascular risk is related to GH deficiency in isolation or whether other physiological or iatrogenic factors are important such as inadequate or excessive replacement of glucocorticoids, thyroxine or sex hormones. GH treatment however results in:

- a decrease in central fat as measured by waist circumference, which is sustained after six months of GH therapy;
- a reduction in total plasma cholesterol in young and old patients as well as LDL cholesterol in young patients;
- an increase in insulin sensitivity which was found to be possibly associated with the changes in obesity rather than treatment of hypopituitarism itself.

Review of data shows no excess mortality in patients treated with GH, but the proper dosage of GH is important because of the knowledge that acromegaly predisposes to colonic dysplasia and left ventricular hypertrophy. Dosing with GH should be titrated against IGF1 levels. In patients with pre-existing hypertension treated with GH there tends to be a reduction over time in diastolic blood pressure, which is hypothesised to be due to GH mediated nitric oxide formation. Any recurrence of a pituitary tumour is likely to occur in the first four years after first surgery in patients with non-functioning pituitary adenoma; patients receiving GH treatment show a similar distribution of pituitary tumour recurrence to historical control data with no increased incidence in 5,000 patient years of follow up.

As yet there is no evidence that GH treatment decreases mortality and a longer time period is needed to assess this. There is evidence that GH improves cardiovascular risk factors but this could possibly be achieved with other pharmacological measures such as optimising other hormone replacement as well as the use of drugs to treat diabetes or dyslipidemia. The significant increase in quality of life shown during GH treatment may play an important role in the future use of GH therapy. At least the current data indicates that the treatment is safe, allowing further exploration of its clinical benefit.

SEX HORMONES

Benefits and risks of male sex hormone replacement

A decline in serum testosterone concentration is a functional change of aging. There are no specific symptoms or markers of androgen deficiency, but several functional changes in aging men may be attributable to decreasing testosterone levels (decreased sexual interest and activity, low mood, decreased stamina, decreased muscle mass, osteoporosis and increased central fat mass). Androgen replacement will improve the functional changes in these cases. Unfortunately androgen therapy is accompanied by the risk of worsening cardiovascular and prostate disease, which are already highly prevalent in the aging general male population.

There have been 13 trials examining the effects of testosterone replacement in the elderly, but these contain less than 500 patient years of treatment. The preliminary

results of an as yet unpublished study by Tenover are presented below.

70 men between the ages of 65 and 83 were randomised to receive testosterone alone, testosterone and finasteride, a 5 alpha reductase inhibitor (acts by preventing the metabolism of testosterone to the more poweful androgen, dihydrotestosterone, it is currently used in benign prostatic hyperlasia), and placebo over three years.

Both placebo and testosterone alone resulted in a significant rise in prostatic specific antigen (PSA) within the normal range and also an increase in prostate size. There was no significant change with testosterone and concurrent finasteride. These results are similar to other studies and suggest that there is no significant increase in risk of prostate cancer with unopposed testosterone replacement when compared with a normal elderly population with untreated androgen deficiency.

The effect of testosterone on cardiovascular risk factors and BMD was as follows:

- lean body mass increased by 4 kgs in six months and was maintained;
- body fat decreased by 5%;
- serum total and LDL cholesterol concentrations were reduced with no effect on HDL cholesterol;
- BMD increased by 8% in the lumbar spine and 3% in the hip in a progressive fashion over three years.

In the normal elderly current available data for androgen replacement are cross-sectional; more placebo controlled studies are needed to assess potential therapeutic effects, long term safety and benefits on quality of life. Hormone replacement therapy in elderly men should be given only after a careful individual evaluation of risks and benefits.

The following working guidelines for the management of hypogonadism in the elderly male have been suggested. In a patient presenting with symptoms suggesting androgen deficiency plasma testosterone concentration should be measured. A total testosterone level of less than 7 nmol/l is diagnostic of hypogonadism and warrants thorough investigation. If the total testosterone concentration is between 7 and 12 nmol/l a free testosterone assay is required to establish deficiency.

If the diagnosis of androgen deficiency is established, testosterone replacement is to be instituted. Before treatment, and after a period of three months on testosterone replacement, a man over the age of 50 should undergo a digital prostate examination, a plasma PSA measurement, haematocrit and serum lipid profile.

Contraindications to androgen replacement are as follows:

ABSOLUTE	RELATIVE
• prostate cancer	• benign prostatic hyperplasia
• breast cancer	• hyperlipidaemia
• sleep apnoea	• polycythaemia
	• cardiac, liver and renal failure

The ideal preparation for the elderly man is a daily testosterone patch because of the ease of discontinuation, but skin reactions are common. Intramuscular and oral testosterone are less suitable for the elderly because of the peaks and troughs of testosterone. Oral testosterone is also poorly absorbed and so requires large doses to achieve adequate circulating levels. Implants are not generally suitable because of the long duration of action.[15,16,17]

Hormone replacement therapy, a cardio-vascular panacea?

In the Western world, coronary heart disease (CHD) is the most common fatal disease with a virtually universal male excess. This is best explained by an intrinsic female advantage usually attributed to oestrogen.[18]

Oestrogen produces favourable changes in lipoproteins, apolipoproteins, LP(a), PAI-1, antithrombin III, homocysteine, endothelial function, vascular reactivity and blood flow, as well as being an antioxidant and having calcium channel blocking activity.

Many observational studies of postmenopausal hormone therapy and heart disease have shown a 30-34% reduced risk of heart disease in women taking oestrogen. The benefits appear to be even greater in current than in past users and in women with known CHD.

The Heart and Estrogen/progestin Replacement Study (HERS) was a randomized, double-blind, placebo-controlled trial of 2,763 women with documented CHD using the active treatment, continuous combined conjugated equine oestrogen plus medroxyprogesterone acetate (CEE plus MPA).

After four years of follow up, CHD rates did not differ by treatment assignment, and no differences were found in all-cause mortality or cardiovascular endpoints including revascularization. This occurred despite the expected favourable effects on lipids. The most unexpected finding was the 50% increase in CHD risk observed during the first year after randomisation to the active treatment. In a *post-hoc* analysis there was a significant trend to better prognosis with longer therapy. Despite compliance and the incidence of new CHD events being lower than predicted there was adequate power in the study to have detected a less than 20% reduction in CHD. Women assigned to active treatment or placebo were also well matched at baseline.[19]

It is possible that the early mortality from coronary artery thrombosis seen in HERS may be an arterial manifestation of excess venous thrombosis, and only later did oestrogen-mediated lipid lowering decrease coronary artery thrombosis. An alternative suggestion is that women susceptible to an unknown oestrogen effect developed CHD, leaving behind only women who might benefit. However both explanations imply that oestrogen's immediate effects either on endothelial function and vascular activity did not occur in HERS women or were completely masked by other effects which resulted in an increased risk. Another explanation for the results is that CEE plus MPA is known to have the least favourable effects when compared with other HRT preparations on HDL cholesterol and fasting glucose.[20] MPA has been shown to reduce oestrogen's favourable effects on endothelial function as well as on atherosclerosis in nonhuman primates.

At present there are no controlled trial data showing that the risk of CHD is reduced by oestrogen. As HERS was a secondary prevention trial it does not exclude the possibility that hormone therapy may be useful for primary prevention of CHD. This question is being addressed by the Women's Health Initiative (WHI) in the United States, and by the Women's International Study of long Duration Oestrogen after Menopause (WISDOM) in the United Kingdom.

A new family of drugs, Selective Estrogen Receptor Modulators (SERM), are currently under assessment. Raloxifene benefits from the experience gained from the oestrogen replacement studies, which demonstrated that good quality prospective trials should be performed early in the lifetime of a new drug. RUTH (Raloxifen Use for The Heart) is to study 10,000 patients from 26 countries with similar end points to HERS.

RATIONAL APPROACHES TO THE OSTEOPOROSIS EPIDEMIC

Predicting the risk of osteoporosis

Osteoporosis is defined as low bone mineral density (BMD) greater than 2.5 standard deviations below the mean for young sex-matched adults. Fracture however is the important clinical end point of osteoporosis. The lifetime risk of fracture for women is between 11% and 14% and for men between 2% and 3%. The cost to the National Health Service is significant.

The pathogenesis of osteoporotic fractures involves the interaction of peak bone mass, bone loss and bone quality with trauma. There are four currently recognised methods to assess the risk of having an osteoporosis-related fracture. The predictive value of each test is less than 40%, increasing if tests are combined. They are as follows:

- clinical risk factors: the factors associated with significant risk are age, benzodiazepine use, falls, maternal history of fracture, smoking and corticosteroid use;
- dual energy X-ray absorbitometry (DEXA) assesses BMD and has a high specificity but a low sensitivity for predicting fractures;[21]
- ultrasound provides both information on BMD and bone quality;
- markers of bone resorption, such as collagen telopeptides (CTX) and deoxypyridine (DPD), have a similar predictive value as BMD.

(Both ultrasound and resorption markers are useful research tools but within individuals are not currently accurate enough to supplant DEXA.)

Genetics play a role in osteoporotic fracture risk. A twin study has shown that BMD correlates more in monozygotic than dizygotic twins despite sharing the same environment. Other aspects of fracture risk such as ultrasound properties and hip axis length are also inherited. A survey of risk factors in 1,800 women found that a positive family history of osteoporotic fracture is a stronger predicter of fracture than either being postmenopausal or having had a previous fracture and BMD or ultrasound measurements.

The collagen type 1 gene appears to be involved in regulation of bone mass and may act as a marker for fracture prediction. Collagen type 1 is a complex protein combining two alpha 1 and one alpha 2 chains encoded by COL1A1 and COL1A2 genes. A protein coding mutation in these genes results in a severe form of osteoporosis called *osteogenesis imperfecta* whereas other polymorphisms may be associated with osteoporosis. One such polymorphism, in intron 1 of the COL1A1 gene, has been strongly associated with low BMD and increased risk of osteoporotic fracture. This intron involves the binding site for Sp1 which is a transcription factor important in regulating the amount of RNA produced. Population studies of caucasians have shown that 70% are homozygous for the G allele (SS), 5% are homozygous for the T allele (ss) and 25% are heterozygous (Ss). The SS genotype is associated with higher BMD and fewer fractures than Ss and ss. The T allele has been shown to bind the Sp1 molecule more tightly than the G allele resulting in more transcripts. The genotype Ss results in over production of the alpha 1 chain relative to alpha 2 in the ratio of 2.3 to 1, whereas the SS genotype results in a ratio of 1.96 to 1. This overproduction may result in alpha 1 homotrimers which are unable to cross link, causing mechanical weakness and therefore osteoporotic fracture independent of BMD. A meta-analysis of studies looking at COL1A1 and fracture in over 3,000 individuals shows a pooled increased fracture risk with an odds ratio of 1.6 per copy of the T allele. The risk was independent of BMD suggesting that the COL1A1 gene may be involved in bone quality. In small numbers of patients low BMD and the presence of the T allele resulted in all patients suffering a fracture.[22]

Current treatment for osteoporosis: which drug and when?

There are numerous therapeutic options for the prevention and treatment of postmenopausal osteoporosis. Positioning of these therapies is difficult because of the variable evidence of efficacy. Most agents have a figure of 40-50% reduction in fracture rates. Observational data on HRT reveal that:

- the greatest increase in BMD is in those who took it from the time of the menopause long term;
- the effect of HRT wears off with increasing time since stopping;
- after five years of discontinuing HRT the risk of a hip fracture is the same as a woman who has never taken HRT.

This information along with the increased risk of breast cancer, unwanted vaginal bleeding and poor compliance makes HRT a less attractive therapeutic option for some women.

Bisphosphonates act predominantly by inhibiting bone resorption. Both etidronate and alendronate increase BMD in the hip and spine by between 5% and 8% over three years. Alendronate was tested in the Fracture Intervention Trial (FIT) study for its anti-fracture efficacy in over 2,000 women. The reduction in relative risk at all sites was, on average, 50%. Unfortunately a similar study with etidronate was not adequately powered to show reductions in fractures. The Fosamax International Trial (FOSIT) study of 2,000 women after one year of alendronate demonstrated a significant reduction in all new fractures particularly in non vertebral fractures. This suggests that short term interventions can produce worthwhile reductions in fracture rate. Data from etidronate studies suggests that after cessation of treatment BMD reduces fairly quickly to placebo levels. Bisphosphonates are in general safe and well tolerated.

Raloxifene has been subjected to rigorous clinical trials. The Multiple Outcomes of Raloxifene Evaluation (MORE) study which included 7,000 women on two doses of raloxifene and a placebo group showed a significant reduction of 40%-50% in vertebral fracture rate in raloxifene treated patients, which is similar to the results for alendronate. The power of the study was not great enough to show a decrease in non vertebral fractures.

The use of calcium and vitamin D in the elderly was

examined in a French study of 3,000 women with a mean age of 84 living in sheltered accommodation. This showed that after 12 to 18 months there was significant protection against hip and other non vertebral fractures. A recent study looking at a cohort of free living elderly randomised to calcium and vitamin D supplementation or placebo suggests the effect may hold in this population as well, although the number of hip fractures was too small to show any statistical significance.[23] Further studies are needed looking at vitamin D alone in the primary prevention of hip fracture. A trial comparing calcitriol and calcium showed a statistically significant fall in vertebral fractures but only in comparison to a sharp rise in the calcium group and therefore the results are unclear. There is no convincing evidence for benefit of calcium alone in fracture prevention.

In summary the first line of treatment of osteoporosis should be bisphosphonates or HRT because of their accepted efficacy in fracture reduction in the spine, hip and wrist. Raloxifene should be used as second line therapy for the prevention of vertebral fractures when the patient is unaccepting or intolerant of HRT and bisphosphonates.[24,25]

POLYCYSTIC OVARY SYNDROME – MECHANISMS AND MANAGEMENT

The classic presentation of polycystic ovary syndrome (PCOS) is anovulation with features of hyperandrogenism. It can be further defined by polycystic ovary (PCO) morphology on ultrasound and the presence of markers such as raised circulating lutenising hormone (LH) and testosterone concentration. Polycystic ovary morphology is present in 20% of the normal population, so ultrasound is not specific enough to be used as a single investigation to diagnose the condition. The syndrome requires symptoms of either anovulation or hyperandrogenism as well as one of the endocrine markers for diagnosis.

Using the ultrasound appearance the prevalence of PCOS in a gynaecological endocrine clinic was:

- 32% in patients with amenorrhoea;
- 87% with oligomenorrhoea;
- 87% with regular cycles and hirsutism.

A similar prevalence of PCOS was found using endocrine markers.

The main treatments for hirsutism are cosmetic and anti-androgen therapy. Cyproterone acetate is the most widely used anti-androgen and it also acts as a progestogen suppressing gonadotrophins release. Other medical therapies include the oral contraceptive pill and long acting gonadotrophin releasing hormone; five alpha reductase inhibitors are currently being studied; corticosteroids have little effect. Weight loss is important as it reduces circulating concentrations of total and free testosterone.

Studies have found that the prevalence of impaired glucose tolerance or undiagnosed diabetes is 13-40% in women with PCOS and that PCOS is associated with lower HDL 2 cholesterol concentrations. Data from patients with ovarian wedge resection showed no increase in mortality from cardiovascular disease despite an increased incidence of diabetes.

There is an association between anovulation and hyperinsulinaemia. Patients with PCOS and anovulation have markedly decreased insulin sensitivity. It has been suggested that insulin either augments LH mediated increase in the terminal differentiation of granulosa cells thus causing premature arrest of follicular growth,[26] or that it stimulates the growth of ovarian stromal cells.

The evidence for using insulin sensitising agents to improve the metabolic and reproductive consequences of hyperinsulinaemia is inconclusive. However, one controlled study has shown improved ovulation rates and androgen levels in response to clomiphene therapy but did not have power to detect an increase in pregnancy rates.

Studies looking at insulin sensitivity and its relationship with increasing BMI and incidence of PCOS have shown a more marked decline in sensitivity to insulin in those with PCOS compared to those without. After correction for waist:hip ratio there was no difference in insulin sensitivity in those with and without PCOS suggesting that insulin resistance is related to centripetal fat distribution. Insulin sensitivity is restored almost to normal with weight loss, but there is no change in the abnormal first phase of insulin secretion, implying the presence of a primary abnormality of beta cell function in PCOS. This has lead to genetic studies. The variable number tandem repeat (VNTR) locus is upstream of the insulin gene and has been shown to regulate insulin expression. Polymorphisms in the VNTR locus are associated with central obesity, hyperinsulinaemia and type 2 diabetes. There is an odds ratio of eight for developing PCOS if homozygous for the class 3 allele in the VNTR.[27,28]

NEW INSIGHTS INTO OBESITY AND APPETITE REGULATION

Obesity is a common endocrine disorder and causes decreased well being as well as increased morbidity and mortality, particularly from cardiovascular disease and diabetes. The prevalence of obesity is increasing due to our changing dietary and exercise habits, but adoption and twin studies do suggest a strong genetic component.

Coleman in 1975 examined mice with the spontaneous genetic mutations of ob/ob and db/db using the technique of parabiosis:

db/db mouse + normal mouse =	db/db mouse unchanged	+ normal mouse starves
ob/ob mouse + normal mouse =	ob/ob mouse thinner	+ normal mouse unchanged
db/db mouse + ob/ob mouse =	db/db mouse unchanged	+ ob/ob mouse starves

The conclusion was that the db/db mouse was resistant to a circulating factor that was present in high amounts, whereas the ob/ob mouse was missing this factor that was eventually named leptin. Two families have been found with children that have a homozygous frameshift in the leptin gene resulting in undetectable leptin levels, hyperphagia and obesity.[29] The children have now been receiving leptin for 18 months resulting in decreased appetite, increased physical activity and weight loss.

Leptin takes part in a classic endocrine feedback loop involving fat and the hypothalamus. Fat mass is one determinant of leptin secretion. It also falls precipitously during starvation hence it was hypothesised that leptin is not a fat preventer but rather a signal of nutritional status and has a role also in the reproductive functions of the hypothalamus. This is observed in anorexia nervosa and

has been confirmed experimentally in fasting normal and ob/ob mice. Patients who are homozygous for a mutation in the leptin receptor have hyperphagia, obesity and hypogonadotrophic hypogonadism.

The lateral hypothalamus is an eating centre controlled by neuronal output from the medial hypothalamus, which inhibits feeding. Leptin sets the level at which the medial hypothalamus will respond with the assistance of other mediators such as pro-opiomelanocortin (POMC) which is the precursor of adrenocorticotrophic hormone (ACTH) and a large number of other molecules such as alpha melanocyte stimulating hormone (MSH). Alpha MSH is produced in the hypothalamus and is increased in response to leptin. Genetic mutations have been described in humans showing the importance of POMC. A patient with a mutation in prohormone convertase 1 has been found. She was obese, had high levels of POMC and low levels of ACTH and also failed to make numerous other hormones.[30] Two children with null mutations in the POMC gene have pale skin and red hair because of the lack of local MSH, cortisol deficiency because of lack of ACTH and obesity due to hyperphagia. The receptor involved in this mechanism is melanocortin 4 receptor (MC4R). This phenotype has also been observed in six families with a dominantly inherited frame shift mutation in MC4R who have primary obesity.

These families have shown that there are subtypes of severe obesity. Each genetic defect discovered provides more information about the control of body mass and appetite and helps to focus therapeutic efforts in tackling the wider problem of obesity.

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