

THE **Endocrinologist**

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THE NEWSLETTER OF THE SOCIETY FOR ENDOCRINOLOGY



Osteoporosis: new hope

PLUS...

Reacting to
real-time PCR

Support for
anorchidism

Clinical trials:
get ready for
new guidelines!

When refereeing
gets risky

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Members: Mono - Half page £110 Full page £170
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Deadline for news items for
the Summer 2004 issue: 9 April 2004.
Please send contributions to the above address.

It's changeover time and opportunities for me to hide behind Richard's smiling face, his knowledge of every endocrinologist in the country, and all his hard work are gone. I am sure I speak for all members of the Society when I thank Richard for all his creative and productive work as Editor of *The Endocrinologist* for the last 2 years.

As the new Editor, I would welcome all your comments regarding the content of your newsletter. Does it provide the news, views and updates you need? Would you like more information about Society activities? Should there be a letters page? Any suggestions will be seriously considered. On one specific matter, I am sure you will be keen to get involved. The front cover of the newsletter is a blank canvas, just crying out for your contributions. We currently purchase rights to use cover photographs from a library, but surely amongst our membership hundreds of you must have unique scientific or clinical pictures, or other artwork to grace this space? If so, send a copy to the Bristol office and it could be published in glorious technicolor, free of charge!

And so to this issue. Statistics reveal an explosive fourfold increase in requests to the *Endocrine Abstracts* web site, but less encouraging is the news that 30% of consultant posts in parts of the UK remain unfilled, while the NHS target of a 30% increase in the number of consultants is unlikely to be met (see page 5). Practical help for patients is on hand, and I entreat you to point affected families in the direction of the Anorchidism Support Group (page 6) who offer support for those with this distressing condition.

There's good news, this time for sufferers of osteoporosis, as Neil Gittoes and Peter Selby explain the potential of a novel new treatment on page 7. Teriparatide has an anabolic action on bone and so may even serve to reverse the effects of the disease. Meanwhile, May 2004 will see the implementation of the European Clinical Trials Directive. On page 8, Alan Davies gives us the low down on the effect this might have, particularly on non-commercial or academic trials.

For those whose education involved isolated nerve-muscle preparations rigged up alongside smoke drums to record twitches, grappling with the intricacies of molecular biology has been an uphill task! Fortunately Stephen Bustin is here to provide us with a lucid account of the benefits of real-time PCR over its conventional cousin in the study of gene expression (page 9).

Invariably research papers and grant applications are refereed by colleagues with similar interests, and referee spotting (as opposed to train spotting) is always an interesting challenge. We've all fallen into the trap of trying to identify the 'vindictive/ill-informed/nit-picking' object of our irritation after receiving a report that doesn't give us the warm glow we believe we deserve. Well Hotspur took things one stage further. Read his uncomfortable tale in a case of inadvertent transparency on page 10.

By now you will all be looking forward to a few days beside the seaside at BES 2004. This year's meeting is held jointly with the European Federation of Endocrine Societies and will take place on 22-24 March in Brighton. See the back cover for more details and make sure you register straight away. You can be sure of a meeting laced with hormones that you can soak up with fish and chips!

SAFFRON WHITEHEAD

B R I T I S H
T H Y R O I D
F O U N D A T I O N

RESEARCH AWARD 2004 – £10 000

Research must be directly related to thyroid disorders or the basic understanding of thyroid function.

Up to £10 000 is being offered to enable medical researchers to supplement existing projects or to pump-prime new research ideas. Funds will be awarded for consumables, running costs and equipment.

Further information and application forms are available from
Mrs B Nevens, BTF, PO Box 97, Clifford, Wetherby, West Yorkshire LS23 6XD, UK

Closing date for applications: 31 August 2004

Regional Co-ordinators

Members are reminded that the Society has eight regional co-ordinators, who ensure that Society information is available in all major centres throughout the UK and Ireland. Their aim is to strengthen the specialism by increasing membership and encouraging feedback from members. If you have a view on any of the Society's activities, please contact your local regional co-ordinator.

London: Dr Graham Williams, Hammersmith Hospital
(graham.williams@ic.ac.uk)

Midlands and East Anglia: Dr Rose Bland, University of Warwick, Coventry
(rosemary.bland@warwick.ac.uk)

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(n.a.hanley@soton.ac.uk)

Southwest and South Wales: Dr Bronwen Evans, University of Wales College of Medicine, Cardiff (evansba@cardiff.ac.uk)

Members on the move...

S L Dickson to University of Gothenburg, Sweden; F M Fisher to University of Warwick, Coventry; A Goldstone to University of Florida College of Medicine, Gainesville, FL, USA; A Lyakhovich to Robert Wood Johnson Medical School, New Brunswick, NJ, USA; W A Nieuwlaet to St Elizabeth Hospital, Antwerp, Belgium; L J Seal to St George's Hospital, London; V A Thornton-Jones to The Churchill Hospital, Oxford.

Corporate members

The Society welcomes Sandoz Biopharmaceuticals and Ardana Bioscience Ltd, both of whom have joined as Corporate members.

Sandoz manufacture products for growth hormone replacement, and Ardana manufacture products for testosterone replacement.

Grants, glorious grants!

Travel grants up to £500 available now

Details of all grants can be found at www.endocrinology.org/sfe/grants.htm

Simplified travel grants

If you earn less than £30 000 (excluding London weighting) or you are a clinical fellow not in receipt of any other funding, you are eligible to apply for a grant to attend:

- the BES meeting
- the Molecular Endocrinology Workshop at Summer School
- the Society's November meeting
- an overseas endocrine conference (one per 12 month period)

New deadlines for grant applications (from April 2004)

15 April - for overseas conferences and Molecular Endocrinology Workshop at Summer School

15 August - for overseas conferences and the November meeting

15 December - for overseas conferences and the BES meeting

Lab visit grants

In addition, young endocrinologists can obtain grants to visit other labs to gain experience. Up to £500 is available for visits within the UK and Europe, and up to £1000 for other locations.

Clinical department grants

These enable young endocrinologists to visit clinical departments outside their Calman rotation, to see endocrinology practised in a different setting. Up to £500 is available for UK visits, and up to £1000 for visits elsewhere in Europe.

All these grants are jointly funded by the Society for Endocrinology and the Clinical Endocrinology Trust.



**Society for
Endocrinology**

BioScientifica strengthens European ties

The Society's trading company, BioScientifica Ltd, has been successful in its bid to support the secretariat services of the European Federation of Endocrine Societies (EFES).

EFES is an influential European organisation. Its members comprise 42 European endocrine societies, of which 7 are pan-European. BioScientifica will be responsible for administering the Federation's secretariat services, acting as a general office for its members, supporting its committees, and tracking historical data relating to its meetings and training courses. Furthermore, BioScientifica will publish the Federation's newsletter *EFES News*, provide web support services for the EFES website at www.euro-endo.org, and publish its journal, *European Journal of Endocrinology*.

Grants for medical undergraduates

Awards of £1000 from the Clinical Endocrinology Trust are available to undergraduate medical students to fund a project of up to 3 months' duration on any aspect of endocrinology. The grant is expected to cover laboratory and other expenses.

Research will normally take place in the UK under the guidance of a supervisor.

A 500-word report must be submitted to the Trustees upon completion, and an abstract may be submitted to a future BES meeting. A further £1000 will be awarded for the best report.

See www.endocrinology.org/sfe/grants.htm for further details about how to apply. The deadline for applications is 31 March 2004.

SOCIETY CALENDAR

22-24 March 2004

23rd Joint Meeting of the British Endocrine Societies with the European Federation of Endocrine Societies

The Brighton Centre, Brighton, UK
(see advert on back cover)

13-16 July 2004

Society for Endocrinology Summer School

St Anne's College, Oxford, UK
(see advert on page 6)

9-11 September 2004

Society for Endocrinology Endocrine Nurses Training Course
Wills' Hall, Bristol, UK

1-3 November 2004

195th Meeting of the Society for Endocrinology

Royal College of Physicians, London, UK

Osteoporosis

■ ■ ■ ■ ■
**AND OTHER
METABOLIC
BONE DISEASES**

■ a course for SpRs

31 March – 2 April 2004

Balliol College, Oxford, UK

- for SpRs in rheumatology, endocrinology, care of the elderly and gastroenterology
- will aid management of patients with osteoporosis and other metabolic bone diseases
- especially relevant to trainees who plan to work in these areas
- focus will be on practical issues relating to patient management
- programme devised by the Bone Disease Training Forum, along with the Bone and Tooth Society, the National Osteoporosis Society, the British Geriatric Society and the Society for Endocrinology
- stimulating interactive format combining lectures, panel discussions, debates and workshops
- 3-day course: £300 (residential), £150 (non-residential)

Contact: Tamara Lloyd, BioScientifica Ltd,
22 Apex Court, Woodlands, Bradley Stoke, Bristol BS32 4JT, UK
(Tel: 01454-642231; Email: tamara.lloyd@endocrinology.org)

BioScientifica 

Web spinning

Melissa Westwood highlights the best on the web

It's a scoop!

www.alphagalileo.org

Guest visitors to this resource for European research and health news can browse through the latest press releases from institutions and companies across Europe, search the library for background information on breaking news stories and find out about forthcoming events like seminars, conferences and symposia. The site is managed by the AlphaGalileo Foundation, a not-for-profit company supported by a combination of government grants, commercial sponsorship and advertising.

SERVICES: D, N; STRONG POINTS: Interesting content; WEAK POINTS: Requires registration; RATING: Good.

Interfering molecules

chembank.med.harvard.edu/bioactives

Here's a site that might be of interest to those intent on disrupting the function of receptors - or any other cellular process for that matter. The ChemBank Small Molecule Bioactives Database provides a freely available collection of information (including vendors) for over 2000 drugs and other compounds known to perturb biological systems. Currently, the project is at an early stage, but the authors promise to add new tools and data regularly, so this may be a site to bookmark for future reference. SERVICES: D, L; STRONG POINTS: Simple design; WEAK POINTS: None; RATING: Very good.

Thanks to Kevin Ahern and *Genetic Engineering News*. Don't forget to visit the Society for Endocrinology on the web: www.endocrinology.org; tell us about your favourite web site: melissa.westwood@man.ac.uk.

Receptors-R-Us

receptome.stanford.edu/hpmp

As well as providing another '-ome' for the dictionary, this site allows visitors to use text- and sequence-based search tools to access information on more than 1000 human plasma membrane receptors. Each receptor has an individual page that provides a summary and links to relevant literature and databases, so it's possible to step from sequence data to domain information or OMIM (online mendelian inheritance in man) links at the click of a button. SERVICES: T, D, L; STRONG POINTS: Easy to use; WEAK POINTS: Some broken links; RATING: Very good.

KEY Services provided at web sites:

- T Tools - Analytical computing tools
- D Data - Searchable or downloadable database information
- G Goods - FTP delivery of useful items (e.g. full package, bug fix or demo software)
- L Links - Useful links to other sites
- N News - News of interest
- S Support - Feedback in response to users' enquiries
- O Others - e.g. Innovative use of web tools, appearance, editorial point of view

Ratings: Excellent, Very Good, Good
Nothing below good will be reported here.

Big hits for *Endocrine Abstracts*

Tens of thousands of requests for information were made to the *Endocrine Abstracts* web site last Autumn. Usage statistics have revealed an impressive leap in the number of hits to the site. The surge began in July, with an increase to 7000 requests, and the latest information for October indicates over 24 000 hits that month. The increase may have been due to the run up to the Society for Endocrinology's November meeting, but such a swift rise in popularity is unprecedented.

Endocrine Abstracts is published by BioScientifica and publishes permanent, citeable abstracts for key conferences in endocrinology. The web site provides a searchable list of presentations and gives free access for interested readers worldwide. If *Endocrine Abstracts* could help with a conference you're organising, then make sure to visit the site at www.endocrine-abstracts.org.

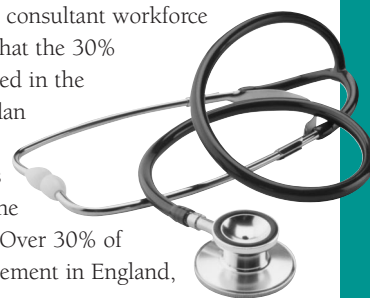
Consultants examined

December 2003 saw publication of the *Census of Consultant Physicians in the UK, 2002*. This followed the UK-wide survey of all consultant physicians which the Royal College of Physicians of London's Medical Workforce Unit has been conducting since 2000.

Placing the spotlight on the consultant workforce and workload, the data show that the 30% increase in consultants envisaged in the Department of Health's NHS Plan (2000) is unlikely to be met. Growth in consultant numbers in UK countries is slow, with the highest being 6% in Scotland. Over 30% of posts are unfilled after advertisement in England, Wales and Northern Ireland.

Concomitantly, admissions to consultants in acute specialities have risen from 49 to 56 per week in the last 2 years. The increasing workload means that few consultants are able to comply with the European Working Time Directive. Interestingly, working hours increase with age, with consultants in their early sixties putting in an additional 5.5 hours per week compared with those in their early thirties. This may indeed influence the data showing that an increasing number intend to take early retirement!

Copies of the census are available from the Publications Department at the Royal College of Physicians (Tel: 020-79351174) and cost £15.



SPOTLIGHT ON...

Anorchidism Support Group

Since its formation in 1995, the Anorchidism Support Group has supported individuals with congenital (or acquired) absence of the testes, as well as parents of boys with this condition. We provide a means of networking for affected families, as well as education and information. We are based in the UK and have members both here and overseas, including America, Italy, Australia, Germany, Ireland and New Zealand.

For any adult, child or parent, the diagnosis of any kind of specific condition or disability can be one of life's most devastating experiences. Many families and individuals comment on how isolating the news makes them feel, and how difficult it can be to find relevant information, no matter what the diagnosis. When a child is diagnosed at an early age, which can be just a few months old, most families want to speak to others who have been through the same experience. They want to know what to expect over the coming years from someone who has the same condition, or from a parent whose child is affected.

As you will be aware, children cannot start medical treatment until the time when puberty should have started naturally, which could be at any point from approximately 10 to 14 years of age. This is a long time to 'sit and wait', with only a yearly or 5-yearly appointment to check their son's height and weight until either testosterone treatment or testicular prostheses can be given.

Unlike many conditions, anorchidism is not noticeable by family and friends. Unless someone is told, they would have no idea that a child is afflicted. Parents feel that it is not their place to speak about their son's condition outside of a very small circle of friends and family. Furthermore, as the child gets older, he may prefer that his parents had not told certain family members and friends. This makes it very hard for parents of anorchic children to speak openly to others who do not have experience of the condition. Other people's lack of knowledge about anorchidism can also result in them saying things that are unintentionally hurtful to the parents.

At the Group's inception, the founders only knew of four other families whose sons had been born with anorchidism. It was unclear how many families would make contact - if, indeed, any. But with the aid of the internet, and other organisations who list our details on their databases and websites, we have been

able to reach out internationally to many more families than we had thought possible. We produce a newsletter three times a year, which keeps members informed and in contact with one other. We also provide an opportunity for families to express themselves, to ask questions and obtain answers. In comparison to other support groups we are still quite small, but no less important to any family that longs to contact another parent who has been in their shoes.

*...it is very hard for
parents of anorchic
children to speak
openly to others...*

Funding has always been one of our main problems, as it is for many large and small support groups. Many parents do not wish to bring attention to themselves or to their sons by organising public fundraising events. Also, as we are not yet a registered charity, we have found that large businesses are less willing to sponsor our group, as we cannot provide the high profile publicity for sponsors that they might receive from a mainstream charity.

We would therefore particularly like to take this opportunity to thank the Society for Endocrinology, who invited us to apply for a small grant last year. Our application was successful and the grant has covered some of our basic expenditure (for example, printing and postage costs), which has made a big difference.

If you would like one of our information sheets for your records, or for a patient that you may see at your clinic, please contact us at the address below. Also note our new web address: <http://freespace.virgin.net/asg.uk>. This replaces any previous address you might have on file.

Anorchidism Support Group
PO Box 3025, Romford RM3 8GX, UK
Email: asg.uk@virgin.net
Web: <http://freespace.virgin.net/asg.uk>

2004
**SUMMER
SCHOOL**



13-16 July 2004

OXFORD, UK

Molecular Endocrinology Workshop 13 July

Advanced Endocrine Course 14-15 July

Clinical Practice Day 16 July

Grants are available for those wishing to attend the Molecular Endocrinology Workshop

Further details will be available shortly
- see www.endocrinology.org/sfe/train.htm



Teriparatide: anabolic action in osteoporosis

Mention possible endocrine causes of osteoporosis, and parathyroid hormone (PTH) and its catabolic actions on bone spring to mind. So the idea of treating this debilitating disease with a recombinant derivative of the human hormone's 34 N-terminal amino acids may seem surprising. But this derivative, teriparatide, has significant anabolic actions that lead to large rapid increases in bone mineral density (BMD) and reductions in fracture risk.

The anabolic actions of PTH were noted around 1930, but interest only grew 50 years later when the sequencing and synthesis of the N-terminus of human PTH (hPTH) allowed Reeve and colleagues to conduct the first formal clinical trial of 'intermittent' hPTH(1-34). Results were similar to those in animal studies, with a mean increase in trabecular bone volume of 70% above baseline. Moreover, the new bone was histologically normal. In 1997, the apparent dichotomy of action of PTH was demonstrated by Dobnig & Turner, who showed that intermittent exposure to hPTH(1-34) increased osteoblast number and bone formation in rats, whereas continuous exposure resulted in hypercalcaemia and abnormal bone histology.

During the 1990s, several large multicentre placebo-controlled randomised trials provided evidence for the prescription of anti-resorptive agents in osteoporosis. Bisphosphonates, HRT and specific oestrogen receptor modulators were all found to primarily inhibit osteoclast function, so reducing the rate of bone remodelling and allowing more complete secondary mineralisation of the existing bone matrix. But while this increased BMD, the bone's macro- and microarchitecture remained unchanged; anti-resorptives do not build new bone.

Previous attempts at anabolic therapy for osteoporosis either failed to show a significant anabolic effect (anabolic steroids) or were limited by increased fracture rates and unacceptable side effects (fluoride). In contrast, teriparatide's novel anabolic mechanism of action has provided a means of modulating and potentially partially reversing the pathology by primarily stimulating osteoblasts via the PTH/PTH-related protein receptor. Osteoblast number and function are increased, while osteoblast apoptosis is inhibited. The net result is increased bone formation, greater bone mass, and improved bone microarchitecture, including increased trabecular connectivity. This leads to a reduced rate of fractures.

A randomised controlled trial of teriparatide in 1637 postmenopausal women with osteoporosis has provided the most robust information about its use in clinical practice. Women who received 20µg daily by subcutaneous injection for around 18 months showed an increase in BMD of 9.7% at the lumbar spine and 2.6% in the total hip, compared with changes of 1.1 and -1.0% following placebo. At a higher dose (40µg daily) the changes were more marked, at 13.7 and 3.6% respectively. New vertebral fractures were seen in 14% on placebo, in contrast to 5% at the low dose and 4% at the high dose. Non-vertebral fragility fractures occurred in 5.5% of women in the placebo group but in 2.6% in each treatment group. The incidence of adverse events, particularly hypercalcaemia, was higher in the 40µg treatment group. Given the two doses' similarity in fracture reduction, 20µg was adopted as the recommended clinical dose. A subsequent subgroup analysis has indicated that bone density improvement and fracture risk reduction are largely independent of the initial bone density and fracture status. Similar changes in bone density are found following treatment of men with osteoporosis and in glucocorticoid-induced bone loss.

All these studies were conducted over a shorter period than usual for studies of osteoporosis treatment, as results of animal toxicology studies became available during the clinical development programme. Rats treated with high doses of teriparatide for most of their lifespan not only gained vast quantities of bone but also developed osteosarcoma. Given the high doses of treatment, the duration of therapy and the difference in bone turnover between rats and humans, these findings are probably not relevant to human treatment. However, this was not realised before the clinical trials had been terminated.

In the USA, teriparatide is licensed for use in both men and women with osteoporosis, whilst in the EU it has only been approved for women with established osteoporosis. The approved duration of treatment has been limited to 18 months, as this reflects the median duration of therapy before the pivotal clinical study was terminated. In addition, the contraindications (see list) reflect the need to avoid risk

factors for bone tumours, in addition to the more obvious exclusion of patients with pre-existing parathyroid activity or risk of developing hypercalcaemia.

The greatest restriction on teriparatide use is likely to be imposed by its cost. At £9.71 per day it costs ten times more than the most expensive conventional osteoporosis therapies. Guidance is being developed to identify patients in whom the extra expense is likely to be justified. In Scotland, the Scottish Medicines Consortium has approved its use for the treatment of severe osteoporosis under the supervision of an appropriate specialist. In England and Wales, the final results of a NICE technology appraisal are currently awaited. Meanwhile, the British Society for Rheumatology is producing guidance regarding the drug's use.

Teriparatide's novel anabolic mechanism provides a new approach for the management of osteoporosis, and its hormonal nature and administration by subcutaneous injection are familiar to endocrinologists. It may offer an opportunity for the speciality to once again become involved in the management of this common and disabling condition.

NEIL GITTOES & PETER SELBY

Contraindications for teriparatide

- Hypersensitivity to teriparatide or any of its excipients
- Hypercalcaemia
- Severe renal impairment (plasma creatinine >160µmol/l)
- Metabolic bone diseases other than osteoporosis (including hyperparathyroidism and Paget's disease of bone)
- Unexplained elevation of alkaline phosphatase
- Prior radiotherapy to skeleton
- Prolonged immobility
- Metastatic bone disease
- Vitamin D insufficiency and/or secondary hyperparathyroidism
- Heterotopic or other secondary calcifying disorder

Clinical trials: Europe's new guidelines

May 2004 will see the enforcement of the European Clinical Trials Directive.

Its greatest impact may be on academic clinical trial procedures, as Alan Davies explains.

The European Clinical Trials Directive (2001/20/EC) comes into force on 1 May 2004. Along with many European academic institutions and research charities, we at Kendle International Inc, an international clinical research organisation (CRO), have been following the Directive's progress for the past few years, and analysing its impact. Processes and procedures will have to change for all clinical trials, including those that are not sponsored by a pharmaceutical company. Across Europe, we are working alongside several organisations to ease their transition to the new environment.

The Directive's main purpose is to simplify the administrative provisions governing clinical trials. It aims to provide an environment where clinical research can flourish, where participants are protected, and which does not hamper the discovery of essential medicines. Currently, clinical trials are not directly regulated under the European Community code relating to medicinal products (Directive 2001/83/EC) but are subject to national legislation. This will change on 1 May.

The Directive covers all investigational medicinal products (chemical, biotechnological, cell and gene therapeutic, plasma-derived, other extractive, immunological medicinal, herbal medicinal, radiopharmaceutical and homeopathic). It does not cover non-interventional trials. The scope of the Directive applies to the design, conduct, recording and reporting of all trials, the protection of subjects and the credibility of the data.

Non-commercial or academic trials will now have to follow the International Conference on Harmonisation guidelines. This will constitute one of the Directive's biggest impacts, as all documentation will need to be maintained and studies monitored and audited in accordance with these procedures. These trials will also have to allocate a named 'sponsor', which may prove difficult if there are many different sponsors, and they will have to register with the European Clinical Trials Database.

Standardisation of the regulatory approval system will be required across Europe, along with standardisation of the manufacture and labelling of drugs, adverse event reporting via the Eudravigilance database and information exchange through the Eudract database of trial information. Importantly, all trials, whether commercial or academic, can be audited by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Agency for the Evaluation of Medicinal Products and be subject to mandatory good clinical practice (GCP) inspections, which will become a legal requirement. It is intended that routine inspections will be carried out by MHRA or their delegated representatives every 3 years.

At the most extreme end of the spectrum, failure to comply could lead to criminal prosecution (potentially a 2-year prison sentence). Assurance has been given that every option would be exhausted before prosecution was considered, and the EU Commission suggests that sponsors will be given an opportunity to address short-falls, illustrating due diligence prior to initiation of any legal action. Ensuring compliance from the outset would appear to be a time-consuming and complex process, with many sponsors requiring assistance from external organisations like Kendle. Advice has to be reasonable, flexible and relevant to the clinical trial environment and the organisation where the audit is conducted.

The protection of the trial subject will require: a legal representative for those unable to give legal informed consent; an emphasis on the Data Protection Directive (95/46/EC); provision for insurance or indemnity to cover the liability of the investigator and sponsor (also required for academic studies); medical care and medical decisions to be the responsibility of a qualified doctor or dentist; all subjects to have a contact point for further information. Two new articles will give additional protection for children and incapacitated adults taking part in research.

Nine GCP Guidance Notes relating to the Directive were released in June 2002. The consultation period ended in October 2002 and five final Notes were issued in April 2003, whilst four Notes will not be issued but will be elevated to Directive status. These four are Principles of Good Clinical Practice Guideline, Qualifications of Inspectors, Inspection Procedures for the Verification of GCP Compliance, and Trial Master File and Archiving.

One of the principal issues is the uncertainty surrounding the Directive's implementation and its impact on non-commercial sponsor-led trials. This is only now raising issues at a time when clarity is essential. Some academic bodies are, belatedly, recognising the implications of the Directive; a group of leading oncology research groups have publicly called for the Directive to be repealed (www.saveeuropeanresearch.org).

'Ensuring compliance would appear to be a complex process...'

On the other hand, the Medical Research Council (MRC) and the Department of Health have established a joint project to address issues raised by the academic trials community about the Directive's implementation in the UK. The MRC has highlighted that over-rigid interpretation of the Directive will halt much important work (www.mrc.ac.uk/current-eu_clinical_trials_directive), a sentiment with which Kendle wholeheartedly agrees.

Uncertainty also surrounds the timescales for establishment of the Eudract and Eudravigilance databases. All trials running from 1 May 2004 and investigational medicinal product should be uniquely identifiable on the Eudract database, but the database is unlikely to be in place before 2005. An interim measure using local member state databases will be invoked, though how is unclear.

The European clinical trials directive will require significant changes to procedures for CROs, pharmaceutical companies, and academic and research charity funded clinical trials, and Kendle are helping organisations to make the transition. For useful, current information see www.medicines.mhra.gov.uk.

ALAN DAVIES

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Reacting in real-time

Stephen Bustin explains the real-time polymerase chain reaction (PCR), and its advantages over conventional end-point PCR assays.

Endocrinology is characterised by its exploration of numerous ligand, receptor and signalling networks that converge on transcriptional regulation in both endocrine and target organs throughout the body. 'Functional genomics' is one of the currently fashionable approaches that are viewed as essential to understanding the resulting molecular and mechanistic details of these complex events at the level of the individual tissue or even cell.

One consequence of this focus is the prominence afforded to techniques that permit whole genome and/or transcriptome analysis. The aim is to ascribe functional significance to polymorphisms and expression signature changes revealed between tissues, disease states or following treatment. While high through-put microarray analysis constitutes the sledgehammer that permits large-scale analysis of expression patterns, the PCR represents the forceps that afford the sensitivity necessary to validate its findings for individual genes. However, conventional end-point PCR is singularly ill-equipped to perform that function, as it is neither robust nor does it easily yield reproducible results.

Real-time PCR technology, with its potential to enhance significantly the specificity and reliability of target discrimination, represents a huge technological advance in the usability and reliability of PCR-based assays. Its use has become ubiquitous in DNA mutation and single-nucleotide polymorphism analysis, as well as the quantification of steady-state mRNA levels. This technology is one of the reasons behind the accelerating shift of much clinical research from epidemiology and physiology to molecular biology and genetics.

Real-time PCR requires a light source of defined wavelength, appropriate excitable fluorophores, and a detection system that can distinguish any emission resulting from the light exciting the fluorophore. The key feature of a real-time assay is the threshold cycle, which is the cycle number in the amplification reaction when amplicon-derived fluorescence amplification is first detected above a defined baseline. It is dependent on the starting template copy number, the efficiency of PCR amplification, efficiency of cleavage or hybridisation of the fluorogenic probe and the sensitivity of detection.

There are two basic types of real-time assay. The simplest approach detects the binding of an intercalating agent, for example SYBR® Green, to the amplification product (amplicon). The accumulation of amplicon during the PCR assay results in increased binding and fluorescence of the intercalator. As with conventional PCR, the specificity of the reaction is determined entirely by the primers; hence its principal disadvantage is that both specific and non-specific products generate a fluorescent signal. Its main advantage is that there is no need for additional, expensive oligonucleotide probes.

The second approach relies on the annealing of a fluorescently labelled probe to its target sequence, thereby incorporating a hybridisation step which provides additional specificity to the assay. The most widely used technique uses a probe labelled with a fluorophore at one end and a quencher at the other. While the probe is intact, the proximity of the quencher greatly reduces the fluorescence emitted by the reporter dye by Förster resonance energy transfer. Successful hybridisation generates a substrate that can be cleaved by the 5' nuclease activity of Taq DNA polymerase. This physically separates the fluorophore from its quencher, permitting the detection of its emission after excitation by light. Thus, with fluorogenic probes, non-specific amplification due to mispriming or primer-dimer artifacts does not generate any signal. The main disadvantage of fluorogenic probes is that each target requires a different specific probe.

Real-time PCR assays have several distinct advantages over conventional assays. Since the assays integrate the amplification and analysis steps of the PCR, they require no post-PCR processing, making them very convenient, as well as giving them potentially high through-put capacity. Furthermore, as results are recorded during the exponential phase of the reaction, end-point related distortions are eliminated. In addition, more than one assay can be carried out in a single tube (multiplexing), as probes can be labelled with different, distinguishable reporter dyes. This can be particularly convenient when analysing splice variants, such as those known to exist for GH or IGF-I.

One of the most exciting aspects of real-time assays is their ability to accurately quantify steady-state mRNA levels. This allows the researcher to measure mRNA levels directly, e.g. in response to the addition of a growth factor or hormone. For example, IGF-I is a well-known survival factor, and its addition to tissue culture cells permits an analysis of the changes in the patterns of putative target mRNAs, such as c-myc, VEGF etc. This allows a rapid and relatively easy assessment of the effects of these factors on parts of the transcriptome of these cells. Similarly, studying the effects of siRNA on target mRNA levels is fairly straightforward, and together with RNA prepared from laser capture microdissected cells, it is possible to localise mRNA expression patterns *in vivo*.

'This technology is behind the shift of clinical research from physiology to molecular biology'

Obviously, it is vital that assays, especially those involving quantification of RNA, are carried out consistently and appropriately. Real-time-PCR assays require high quality RNA, since differences in RNA quality result in significant distortions of any quantitative results. Furthermore, meaningful data normalisation is particularly relevant for the quantification of material derived from *in vivo* biopsies. Finally it should be noted that operator variability has been shown to generate non-reproducible results. Whilst the assay itself is simple, obtaining reproducible and biologically meaningful results is not.

In conclusion, there can be no doubt about the central role that real-time PCR technology has to play as a modern research tool. However, it is important to be aware of the danger of a bandwagon effect, where raised expectations can so typically and abruptly meet with disappointment.

STEPHEN A BUSTIN
BARTS AND LONDON SCHOOL OF MEDICINE,
UNIVERSITY OF LONDON

Refereeing: a humour-free occupation

Sometimes you find yourself in a mess through no fault of your own. On other occasions the problem is self-inflicted, because of character traits that have troubled you in the past and no doubt will do so again in the future. One such character trait that I possess is a tendency to be flippant when relaxed.

Well, I was very relaxed on a lovely summer evening a year or two ago in north America. The day's work was over, and I was in happy hour mode; I sensed upregulation of my flippancy gene. The purpose of my visit was to attend the annual meeting of the American Endocrine Society (AES). As far as I could tell, my presentation had been well-received, and I was now enjoying myself at a dinner held for a small constituent society of the AES that always arranges a social function to coincide with the annual meeting.

I was searching for my second pre-dinner cocktail when I spotted Mike, an American colleague. I had known Mike (the name has been changed to protect the guilty) for years: a lively, intelligent man of strongly held beliefs, and equipped with a great sense of humour. We had sparred many times before in a jocular good-hearted fashion. Furthermore, I was certain that he had just refereed one of our articles for *Clinical Endocrinology*. The style, the manner of expression, and the content of the referee's argument all pointed to Mike.

The article was a tricky one and I have to admit that I was amazed that my research fellow had ever conjured a manuscript out of such raw data. Nonetheless, he had done a very professional job, and no other data on this topic exist in the literature. So we were in the position of the one-eyed man in the land of the blind, and I anticipated that the journal would accept the manuscript.

Referee one, whom I guessed was Mike, started down the first page of his report by not liking the article and by the end of the page he hated it; boy, did he hate it! Vitriol was pouring from his pen as he became more and more agitated by our efforts. The journal behaved impeccably and allowed us to rebut the criticisms/comments, eventually accepting and publishing a revised version of the manuscript.

I had to pass in Mike's direction to get to the bar so I paused to greet him.

'How are you?'

'Fine.'

'Tell me, why did you hate our work with such intensity?' (flippancy in overdrive)

'What are you talking about?' (my pulse rate quickened)

'You know, our recent manuscript for *Clinical Endocrinology* on Schruckelgrüber's disease?'

'I don't know what you are talking about, I have never refereed any manuscript of yours...' (beads of sweat appeared on my forehead) '...but YOU refereed an article of mine recently that had been sent to *JCEM*.' (legs felt leaden)

'Did I?'

I scrambled my thoughts together; was he right? Oh God, I do seem to remember an article, *the* article presumably. I continued, brain no longer driving my side of the conversation...

'What happened to that article?'

'Oh, it was rejected on your recommendation.' (my need for that drink grew desperate)

'How do you know it was me that refereed your article?' (legs no longer capable of movement in any direction)

'The journal sent me the referee's comments with your name on the fax.'

Well for the remainder of the AES meeting, as luck would have it, I ran into Mike every day. Without fail he reminded me that I had rejected his article. Even if on escalators moving in opposite directions, and too far apart for dialogue, he would simply look across at me with a baleful eye and then give me a thumbs-down sign.

I was particularly upset that my ability to referee-spot was not as good as I thought. In the past I used to

recognise the typeset, like the dropped 's' on the typewriter in Middlesex Hospital's paediatric endocrine department. The computer era had rendered this an unhelpful talent, but no matter, as I had always told myself that I could identify writers by their style and language. Thus my illusion was shattered, and my self-esteem reduced.

Some 2-3 months had elapsed when, out of the blue, I received a fax from Mike. 'I have been reviewing my refereeing records and find that I have refereed two articles of yours, including the one on Schruckelgrüber's disease.' My referee-spotting self-esteem was restored instantly. I felt happier than if I had a manuscript of my own accepted. More seriously, I was deeply impressed by his actions. He must have lain awake for a few nights tormented that he had been economical with the truth and driven by his conscience to respond in the manner that he had.

From that whole experience, I advise all readers to avoid any attempt at humour where the refereeing of manuscripts is concerned. Above all else, flippancy inhibitors must be applied whenever appropriate. When an article is 'criticised', pain of varying intensity and duration is felt by the author - however senior or junior.

I still relax after a day's work and I am fonder of Mike, but I now understand that refereeing is a straight-faced occupation.

HOTSPUR



Hormones, brain and behavior

Eds DW Pfaff (Editor-in-Chief), AP Arnold, AM Etgen, SE Fahrbach & RT Rubin, Academic Press 2002, 927pp, 5 vols, £690.00/\$995.95, ISBN 0-12-532104-X

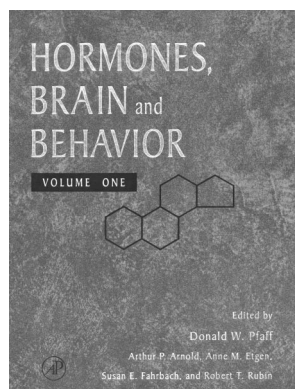
This book is a remarkable achievement. The editors have convinced many of the very best behavioural neuroendocrinologists to contribute to a five volume compendium which is comprehensive, up-to-date, well written and reasonably approachable. Note that the volumes are similar in size and do not correspond to the compendium's sections.

The dangers of editing such a *magnum opus* are threefold. First, some authors may never write their chapters, so rendering the whole enterprise out-of-date. Secondly, lax editorial control can lead to huge and often contradictory overlaps between chapters. Thirdly, poor quality chapters can diminish the overall impact. It is to the editors' great credit that they have largely avoided all these pitfalls.

The first section is very successful in bringing together international experts to cover integrative mammalian behaviour including sexual, affiliative, aggressive, motivational, adaptive and injury response behaviours. The chapter on opioid peptides doesn't fit comfortably, and it is unclear why this is present rather than catecholaminergic, serotonergic or other peptidergic systems. The chapters on olfactory and circadian systems and thyroid and gonadal hormones are not so cohesive.

Comparative neuroendocrinology is covered in an excellent series of chapters in section two. Fish, amphibia, reptiles and birds are followed by exceptional coverage of invertebrates. Since my first interest in neuroendocrinology was triggered by reading about ecdysone whilst still at school, it was a particular pleasure to read the fascinating insights that insects continue to provide in our understanding of neural and behavioural plasticity.

In section three, the focus is on the cellular and molecular mechanisms of hormonal action on behaviour, with coverage of oestrogens, androgens, thyroid hormones, glucocorticoids, mineralocorticoids, progesterone and neurally acting steroids. This is well written and edited. High standards are maintained in the discussion of oxytocin and vasopressin systems, GnRH and CRF. Development of hormone-dependent neuroendocrine



systems features in the fourth section, with excellent treatment of sexual differentiation, early-life stress and puberty and ageing.

Finally, in the last section, the editors emphasise the clinical importance and relevance of all that has gone before, exploring the hypothalamic-pituitary-adrenal, thyroid and gonadal axes, GH and IGF-I and melatonin. Strangely there is a chapter on cholecystokinin, emphasising its effects on appetite. But following the recent insights into the regulation of appetite, it is a pity that there is no chapter on food intake, metabolism and obesity, only a relatively small section in a chapter on the hypothalamic origins of disease. The other clinical sections are rather disparate, but generally well written, and cover sexual differentiation, androgen receptor

mutations, pain, stress, anxiety and affective disorders, diabetes, calcium disorders, ageing and cocaine, heroin and alcohol abuse.

This is really a very well presented and well planned book. It is a major reference source and deserves to be found in all well funded institutional libraries.

STAFFORD LIGHTMAN

Bigger than life

Dir. Nicholas Ray; 1956; 95 mins; cert 12A

Bigger than life tells the story of Ed Avery (James Mason), a high school teacher who becomes dangerously psychotic during treatment with cortisone. Ed initially develops periarteritis nodosa, and is told that without treatment he is likely to die within a year. He gratefully agrees to take the experimental drug cortisone. While he can soon return to work, Ed behaves inappropriately at a PTA meeting, propounds reactionary ideas about the education system and is disagreeably honest about the students. At home, he has periods of manic happiness alternating with bouts of depression. His friend Wally (a very young Walter Mathau) finds an article in a medical journal that describes psychotic reactions to cortisone but, despite the pleading of his wife Lou (Barbara Rush), Ed refuses to see his doctor.

Ed now bullies his son Richie continually, whether teaching him football or helping with his homework. Richie tries to find and destroy the cortisone pills, but Ed catches him and tells Lou that their son is a thief. He reads her the biblical story of Abraham's sacrifice of Isaac and proposes they kill Richie and then themselves. Lou reminds him that God instructed Abraham not to perform the sacrifice, but Ed responds: 'God was wrong.' Wally bursts in and prevents the assault. Ed is returned to hospital and the dilemma of his absolute need for a treatment that may have terrible side effects is recognised.

The medical details are impressively authentic, from the diagnostic work-up to the rapidly evolving mental illness. James Mason gives an inspired account of the oscillations of the acute psychotic from grandiosity and elation to paranoia and depression. Director Nicholas Ray uses the device of a madman's insight to challenge conformist 1950s

America, not least the empty promise of fulfilment through material prosperity. The film also offers a mirror for anyone who has had to face the existential terror of discovering one has a fatal illness - and perhaps too the illusory quality of the panacea offered by medicine.

The film is beautifully shot, the acting and direction superb, the narrative taut and clear, so why has such an excellent film not been seen for almost half a century? Its unavailability on video and its absence from cinemas and TV may have been a consequence of its uncomfortable messages. The film's arrival in consecutive seasons at the National Film Theatre and on tour must, I think, tell us something about our own needs at present, as well as about the quality of the film itself.

HOWARD JACOBS

Details of the Nicholas Ray season and other events at the National Film Theatre can be found at www.bfi.org.uk/showing/nft.

The Society is pleased to have supported the following members in their attendance at these conferences. The next deadline for travel grant applications is 15 April 2004. See www.endocrinology.org/sfe/grants.htm for more information.

194th Meeting of the Society for Endocrinology

London, UK, November 2003

The Asia and Oceania Medal Lecture was the highlight of the meeting for me. Mike Waters gave an excellent talk on new insights into GH action. His lecture introduced me to a number of methods I've not previously used. The mix of *in vitro* and *in vivo* studies really brought home the novel activation signal of the GH receptor.

Phil Lowry's Society Medal Lecture on the placenta's endocrine dilemma was particularly relevant to my research, and again included a number of methods that I hope to use in the future.

A number of delegates visited my poster, stimulating several discussions. I was also lucky enough to be awarded the prize for the best basic science poster, which was a real bonus!

ALISON MOSTYN

I found Fadi Charchar's Basic Science Review Lecture, 'Y are men the weaker sex?', extremely interesting. It combined studies of genetics in men with the epidemiology of cardiac disease. The Young Endocrinologist oral communications session covered a broader spectrum of science, and provided some insights into areas peripheral to my own research, particularly GH replacement.

Ezio Ghigo gave the European Medal Lecture on Ghrelin and synthetic QMS, which was very informative. A number of my colleagues are working in this field and it provided them with some answers - as well as posing several questions!

I was presenting during the Growth and Development session. I enjoyed all the other talks in the session, particularly 'Spontaneous differentiation of mouse embryonic stem cells into an islet phenotype' and 'Over-expression of IGFBP-5 in mice results in compromised muscle development'.

JAYSON BISPHAM

Mother and Infant: Perinatal Influences on Health

Montréal, Canada, June 2003

In 1999, the first conference addressed the maternal brain and the CNS changes that prepare the body for the physiological demands of pregnancy and motherhood. This second conference went further, to address the consequences of the mother's physiology and behaviour on her offspring. It encompassed human and animal studies, ranging from neuroscience and neuroendocrinology to psychology.

In the plenary sessions, Jonathan Seckl spoke on the glucocorticoid programming of adult disorders, Peter Gluckman's talk focused on epidemiological evidence linking adverse fetal environments to disease in adulthood. The final plenary lecture by Seymour Levine covered maternal regulation of the HPA axis in the neonate.

Symposia addressed the long-term effects of the environment during infancy, the plasticity of neural substrates in the brain, the maternal influences on fetal and neonatal growth, the influence of parental behaviour on child health, and the stress axis in mothers, fetuses and infants.

I am already looking forward to the next conference, in Boston in 2006.

SIMONE L MEDDLE

Society for Neuroscience Meeting

New Orleans, LA, USA, November 2003

I presented two posters, and the response provided several suggestions for subsequent experiments. The meeting also introduced me to a number of key people in my area of work.

Several sessions were of particular interest to me, including those on CNS regeneration and retinal damage. These described the latest developments regarding the function of inhibitory molecules and their receptors. There were also several posters on the involvement of protein tyrosine phosphatases in CNS regeneration, and several interesting lectures on the latest technical approaches, e.g. the application of siRNA *in vitro* and *in vivo*. This is a technique that I intend to use to knock down gene expression of protein tyrosine phosphatases in future experiments.

BARBARA LORBER

75th Annual Meeting of the American Thyroid Association

Palm Beach, FL, USA, September 2003

This was my first experience of an international meeting, and also my first oral presentation, so a good learning experience all round! I found the 'meet the professor' sessions particularly valuable; I attended those on RNA silencing and tissue arrays. I really appreciated the relaxed atmosphere which allowed greater interaction and exchange of ideas between the expert and other people who also had experience of the techniques. I hope to be able to use what I learnt during my PhD.

ANNA STRATFORD

The meeting covered both basic science and clinical topics. Of particular personal interest were symposia on the role of the thyroid-stimulating hormone receptor in thyrocyte development, and also the role of thyroglobulin, its antibodies and its defective synthesis and transport in thyroid disease.

It provided a fascinating insight into current developments as well as the perfect opportunity for networking and discussion with collaborators and eminent investigators in the field.

JOANNE COLLINS

I combined my attendance of the American Thyroid Association meeting with the 6th International Workshop on Resistance to Thyroid Hormone. As a final year PhD student, it was a privilege to attend this workshop, which gave me the opportunity to meet and listen to scientists whose names I had only previously seen in print. I particularly enjoyed Thomas Scanlan's talk, which introduced a novel metabolite of thyroxine that acts as a potent agonist of an orphan G-protein-coupled receptor, rather than on nuclear thyroid hormone receptors.

The Thyroid Association meeting provided an excellent opportunity to attend presentations directly relevant to my interests of thyroid hormone and bone development. I was very fortunate to present a plenary oral communication, which was well received and generated useful feedback.

PATRICK O' SHEA

Hot Topics

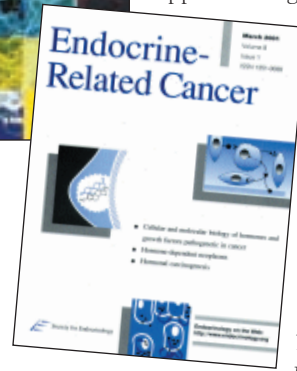
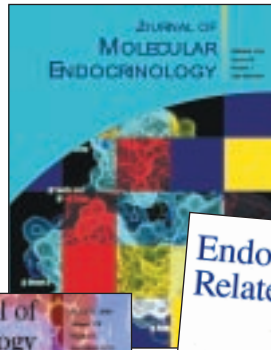
The latest in endocrine research from the Society's journals, courtesy of Mona Munonyara, Jolene Guy, Nathalie Gilmore and Stephanie Barber.

Non-genomic inheritance

Epidemiology has shown a link between low birth weight and the development of diabetes and cardiovascular disease. The relative contributions of genetic and environmental factors to this association have been debated, but remain to be established in the absence of compelling evidence implicating specific candidate genes.

Evidence from human and animal studies suggests that manipulating the fetal environment 'programmes' the fetus to develop chronic diseases in adulthood. This has given rise to the fetal origins hypothesis, which proposes that a stimulus *in utero* may permanently alter tissue structure and function. In this article, Drake and Walker review the evidence extending this hypothesis by considering transmission of fetal programming effects through subsequent generations. Thus, non-genetic mechanisms may contribute to the co-inheritance of a predisposition for low birth weight with cardiovascular disease. **MM**

(See the full article in *Journal of Endocrinology* **180**(1), January 2004)



Insulin resistance and gene expression

Insulin resistance is an early abnormality in the development of type 2 diabetes, the cellular and molecular mechanisms of which are presently unclear. It is generally assumed that increased blood levels of free fatty acids cause peripheral insulin resistance and increased hepatic glucose production. In an attempt to increase understanding, Becker and colleagues studied differential gene expression in a murine model exhibiting severe insulin resistance of hepatic metabolism associated with leptin resistance and obesity, using microarray analysis.

Insulin resistance was associated with a marked upregulation of mRNA transcripts for enzymes involved in lipogenesis, glycolysis and gluconeogenesis - effects enhanced by a high fat diet. This pattern of gene expression provides evidence for a dissociation of insulin effects on glucose and lipid metabolism. The findings support the suggestion that hyperinsulinaemia,

produced by insulin-resistant hepatic glucose output, leads to enhanced insulin- and substrate-driven lipogenesis, which further increases insulin secretion and aggravates insulin resistance, establishing a vicious circle leading to the onset of type 2 diabetes. **SB**

(See the full article in *Journal of Molecular Endocrinology* **32**(1), February 2004)

Signal transduction inhibitors in cancer

Current cancer therapies are not adequately specific to cancerous cells to avoid damaging healthy cells, and cancerous cells often develop resistance to them. This article by Melisi and co-workers discusses promising strategies for cancer treatment that combine conventional cytotoxic drug therapies with novel approaches aimed at inhibiting components of signal transduction pathways. It is hoped that, by specifically interfering with key pathways controlling cancer cell survival, proliferation, invasion and/or metastatic spreading, the side effects and resistance typically associated with conventional therapies can be avoided.

This thorough review summarises the findings of many animal studies and clinical trials, describing the mechanisms behind the cell reactions, and attempting to provide scientific explanations for the clinical results obtained. The authors highlight the importance of identifying patients who are most likely to benefit from this treatment, and the need to investigate the combinations of cytotoxic drugs and signal transduction inhibitors, and the treatment schedules, that are most effective. **NG**

(See the full article in *Endocrine-Related Cancer* **11**(1), March 2004)

GH, IGF-I and bone growth

The roles of IGF-I and GH in bone growth have been investigated in various model systems, with IGF-I regarded as the mediator of GH's growth effects. Wang and co-workers have now provided novel evidence for GH's important contribution to longitudinal bone growth.

Using targeted deletion of the *Igf1* and *Ghr* (GH receptor) genes, the tibial linear growth rates of mice were compared at postnatal days 10, 20 and 40. Long bone growth was more profoundly retarded in mice with *Ghr* deletion when compared with those with *Igf1* deletion. Chondrocyte generation and proliferation remained normal in the *Igf1* null mice, indicating that GH enhances these processes independently of IGF-I. Whether or not GH acts directly on chondrocyte generation remains uncertain, as the authors found an increase in growth plate IGF-II mRNA in the absence of IGF-I, suggesting that IGF-II may mediate this process. The current observations were confirmed by analysis of published data on growth rates with *Igf1* and *Ghr* mutations in other strains of mice. **JG**

(See the full article in *Journal of Endocrinology* **180**(2), February 2004)

Diabetes Mellitus: Molecular Signaling, Genes and Therapeutics and Molecular Control of Adipogenesis and Obesity

Alberta, Canada, 4-10 March 2004.

Contact: Customer Services
(Tel: +1-970-2621230; Fax: +1-970-2621525;
Email: info@keystonesymposia.org;
Web: www.keystonesymposia.org).

Joint International Symposium on Calcitonin Gene-Related Peptide, Amylin and Calcitonin, 4th Symposium on Adrenomedullin and Proadrenomedullin N-20 Peptide

Zurich, Switzerland, 18-20 March 2004.

Contact: Prof. Dr J A Fischer, Research Laboratory for Calcium Metabolism, University of Zurich, Klinik Balgrist, Forchstr. 340, CH-8008 Zurich, Switzerland (Tel: +41-1-3861651; Fax: +41-1-3861652; Email: fischerj@balgrist.unizh.ch; Web: www.symposium2004.ch).

PET/CT and SPECT/CT Imaging in Medical, Radiation, Surgical and Nuclear Oncology

Baltimore, MD, USA, 19-20 March 2004.

Contact: Office of Continuing Medical Education, John Hopkins University School of Medicine, Turner 20, 720 Rutland Avenue, Baltimore, MD 21205-2195, USA (Tel: +1-410-9552959; Fax: +1-410-9550807; Email: cmenet@jhmi.edu; Web: www.hopkinscme.org).

10th Workshop on Cell Biology of Bone and Cartilage in Health and Disease: Frontiers of Skeletal Biology

Davos, Switzerland, 20-23 March 2004.

Contact: Heidi Triet/Rita Maag, Office of Prof. H Fleisch, Effingerstrasse 40, CH-3008 Berne, Switzerland (Tel: +41-31-3899276; Fax: +41-31-3899284; Email: secretariat@hflfleisch.ch).

BES 2004: 23rd Joint Meeting of the British Endocrine Societies in association with EFES

Brighton, UK, 22-24 March 2004.

Contact: British Endocrine Societies, 22 Apex Court, Woodlands, Bradley Stoke, Bristol BS32 4JT, UK (Tel: +44-1454-642210; Fax: +44-1454-642222; Email: conferences@endocrinology.org; Web: www.endocrinology.org/sfe/conf.htm).

New and Emerging Treatments for Skeletal Diseases: from the Bench to the Bedside

Davos, Switzerland, 23-24 March 2004.

Contact: Heidi Triet/Rita Maag, Office of Prof. H Fleisch, Effingerstrasse 40, CH-3008 Berne, Switzerland (Tel: +41-31-3899276; Fax: +41-31-3899284; Email: secretariat@hflfleisch.ch).

What's new in Bisphosphonates? 7th Workshop on Bisphosphonates: From the Laboratory to the Patient

Davos, Switzerland, 24-26 March 2004.

Contact: Heidi Triet/Rita Maag, Office of Prof. H Fleisch, Effingerstrasse 40, CH-3008 Berne, Switzerland (Tel: +41-31-3899276; Fax: +41-31-3899284; Email: secretariat@hflfleisch.ch).

Osteoporosis and other Metabolic Bone Diseases: a course for SpRs

Oxford, UK, 31 March-2 April 2004.

Contact: Tamara Lloyd, BioScientifica Ltd, 22 Apex Court, Woodlands, Bradley Stoke, Bristol BS32 4JT, UK (Tel: +44-1454-642231; Email: tamara.lloyd@endocrinology.org).

2nd International GH-IGF Symposium

Cairns, Qld, Australia, 18-22 April 2004.

Contact: Symposium Managers, c/o Intermedia Convention and Event Management, 11/97 Castlemaine Street (PO Box 1280), Milton, Qld 4064, Australia (Tel: +61-7-38585597; Fax: +61-7-38585510; Email: grs2004@im.com.au; Web: www.ghigf2004.im.com.au).

European Neuroendocrine Association

Sorrento, Italy, 24-27 April 2004.

Contact: Stefania Acanfora, MCM Congressi, Rione Sirignano 5, 80121 Napoli, Italy (Tel: +39-081-668774/7611085; Fax: +39-081-664372; Email: info@enea2004.it; Web: www.enea2004.it).

47ème Journées Internationales d'Endocrinologie Clinique

Paris, France, 29-30 April 2004.

Contact: Dr G Copinschi (Fax: +32-2-5556239; Email: klotz@ulb.ac.be).

Royal College of Physicians (North West) Endocrine Meeting

Manchester, UK, 6-7 May 2004.

Contact: Janice Norton (Tel: +44-151-4301912; Fax: +44-151-4301900; Email: janice.norton@stkhkhealth.nhs.uk).

2nd International Congress on Adult Consequences of Childhood Endocrine Diseases

Athens, Greece, 6-8 May 2004.

Contact: Prof. G E Krassas, Department of Endocrinology and Metabolism, Panagia Hospital, N. Plastira 22, N. Krini 55132, Thessaloniki, Greece (Tel: +30-2310-447444; Fax: +30-2310-447444/+30-2310-282476; Email: krassas@the.forthnet.gr; Web: www.ghsociety.gr).

EFES Regional Postgraduate Course in Clinical Endocrinology

Wroclaw, Poland, 7-9 May 2004.

Contact: Prof Andrzej Milewicz, Department of Endocrinology and Diabetology, Wroclaw University of Medicine, Pasteura 4, PL-56-367 Wroclaw, Poland (Tel: +48-71-3209603; Fax: +48-71-3282349; Email: milewicz@endo.am.wroc.pl).

3rd Regional International Society of Psychoneuroendocrinology (ISPNE) Congress for Central and Eastern Europe

Cappadocia, Turkey, 13-15 May 2004.

Contact: Fahrettin Keleptimur (Email: fktimur@erciyes.edu.tr; Web: www.ispne2004.org).

IOF World Congress on Osteoporosis

Rio de Janeiro, Brazil, 14-18 May 2004.

Contact: Congress Secretariat (Email: info@osteofound.org; Web: www.osteofound.org).

Frontiers in Reproduction: Molecular and Cellular Concepts and Applications

Woods Hole, MA, USA, 16 May-27 June 2004.

Contact: Carol Hamel, Admissions, Marine Biological Laboratory, 7 MBL Street, Woods Hole, MA 02543, USA (Fax: +1-408-2897931; Email: admissions@mbl.edu; Web: www.mbl.edu/education).

11th Annual Meeting of the Psychoneuroimmunology Research Society

Titisee, Germany, 26-29 May 2004.

Contact: Prof. R H Straub and Prof. M Schedlowski (Tel: +49-941-9447120; Fax: +49-941-9447121; Email: rainer.straub@klinik.uni-regensburg.de; Web: www.aknei.de or www.gebin.org).

4th International Workshop on Musculoskeletal and Neuronal Interactions

Chalkidiki, Greece, 28-31 May 2004.

Contact: Susan Clarkson, International Society of Musculoskeletal and Neuronal Interactions, 7 Spiliadou Square, 21100 Nafplion, Greece (Tel: +30-27520-99342; Fax: +30-27520-99343; Email: info@ismni.org; Web: www.ismni.org).

International Course on Laboratory Animal Science

Utrecht, The Netherlands, 1-11 June 2004.

Contact: Prof. L F M van Zutphen or Stephan van Meulebrouck, Department of Laboratory Animal Science, Faculty of Veterinary Medicine, PO Box

80.166, 3508 TD Utrecht, The Netherlands (Tel: +31-30-2532033; Fax: +31-30-2537997; Email: pdk@las.vet.uu.nl; Web: http://las.vet.uu.nl).

16th International Symposium of the Journal of Steroid Biochemistry and Molecular Biology

Tyrol, Austria, 5-8 June 2004.

Contact: Prof. J R Pasqualini, Steroid Hormone Research Unit, Institut de Puericulture, 26 Boulevard Brune, 75014 Paris, France (Tel: +33-1-45399109; Fax: +33-1-45426121; Email: jorge.pasqualini@wanadoo.fr).

31st European Symposium on Calcified Tissues

Nice, France, 5-9 June 2004.

Contact: European Calcified Tissue Society, PO Box 4, Dursley GL11 6YL, UK (Tel: +44-1453-549929; Fax: +44-1453-548919; Email: admin@ectsoc.org; Web: www.ectsoc.org).

13th International Workshop on the Development and Function of the Reproductive Organs

Copenhagen, Denmark, 12-16 June 2004.

Contact: Congress Secretariat (Tel: +45-3946-0500; Fax: +45-3946-0515; Email: repro2004@ics.dk; Web: www.repro2004.ics.dk).

ENDO 2004: 86th Annual Meeting

New Orleans, LA, USA, 16-19 June 2004.

Contact: Beverly Glover, Administrative Assistant, Meetings, The Endocrine Society, 8401 Connecticut Avenue, Suite 900, Chevy Chase, MD 20815-5817, USA (Tel: +1-301-9410220; Fax: +1-301-9410259; Email: bglover@endo-society.org; Web: www.endo-society.org).

9th International Workshop on Multiple Endocrine Neoplasias (MEN 2004)

Bethesda, MD, USA, 20-22 June 2004.

Contact: Constantine Strakatis, c/o Sue Perdue (Tel: +1-301-4964686; Fax: +1-301-4020574; Email: strakac@mail.nih.gov).

20th Annual Meeting of the European Society of Human Reproduction and Embryology

Berlin, Germany, 27-30 June 2004.

Contact: ESHRE Central Office, Van Akenstraat 41, 1850 Grimbergen, Belgium (Email: info@eshre.com; Web: www.eshre.com).

10th International Congress of Auxology: Human Growth in Sickness and in Health

Florence, Italy, 4-7 July 2004.

Contact: Centro Studi Auxologici, Piazza Madonna degli Aldobrandini 1, 50123 Firenze, Italy (Tel: +39-055-290932/212322; Fax: +39-055-290932; Email: congress@auxologia.org; Web: www.auxologia.org).

UK Advanced Diabetes Course

Exeter, UK, 7-9 July 2004.

Contact: Rosemary Sowden, R&D Office, Exeter Postgraduate Medical Centre, Barrack Road, Exeter EX2 5DW, UK (Tel/Fax: +44-1392-403012; Email: rosemary.sowden@rdehc-tr.swest.nhs.uk).

Society for Endocrinology Molecular Endocrinology Workshop

Oxford, UK, 13 July 2004.

Contact: Ann Lloyd, Society for Endocrinology, 22 Apex Court, Woodlands, Bradley Stoke, Bristol BS32 4JT, UK (Tel: +44-1454-642200; Fax: +44-1454-642222; Email: info@endocrinology.org; Web: www.endocrinology.org/sfe/train/htm).

Society for Endocrinology Advanced Endocrine Course

Oxford, UK, 14-15 July 2004.

Contact: Ann Lloyd, Society for Endocrinology, 22 Apex Court, Woodlands, Bradley Stoke, Bristol BS32 4JT, UK (Tel: +44-1454-642200; Fax: +44-1454-642222; Email: info@endocrinology.org; Web: www.endocrinology.org/sfe/train/htm).

Society for Endocrinology Clinical Practice Day

Oxford, UK, 16 July 2004.

Contact: Ann Lloyd, Society for Endocrinology, 22 Apex Court, Woodlands, Bradley Stoke, Bristol BS32 4JT, UK (Tel: +44-1454-642200; Fax: +44-1454-642222; Email: info@endocrinology.org; Web: www.endocrinology.org/sfe/train/htm).

7th International Symposium on Neurobiology and Neuroendocrinology of Aging

Bregenz, Austria, 18-23 July 2004.

Contact: Andrzej Bartke, Director of Research, Geriatrics Initiative, Southern Illinois University School of Medicine, PO Box 19636, Springfield, IL 62794-9636, USA (Email: abartke@siu.edu; Web: www.neurobiology-and-neuroendocrinology-of-aging.org).

International Congress of Endocrinology 2004

Lisbon, Portugal, 31 August-4 September 2004.

Contact: Conference Secretariat, IT GmbH Association and Conference Management Group, Kurfürstendamm 71, D-10709 Berlin, Germany (Tel: +49-30-24603-0; Fax: +49-30-24603-200; Email: info@ice2004.com; Web: www.ice2004.com).

Society for Endocrinology Endocrine Nurses Training Course: the Thyroid Gland

Bristol, UK, 9-11 September 2004.

Contact: Ann Lloyd, Society for Endocrinology, 22 Apex Court, Woodlands, Bradley Stoke, Bristol BS32 4JT, UK (Tel: +44-1454-642200; Fax: +44-1454-642222; Email: info@endocrinology.org; Web: www.endocrinology.org/sfe/train/htm).

43rd Annual Meeting of the European Society of Paediatric Endocrinology (ESPE) 2004

Basel, Switzerland, 10-13 September 2004.

Contact: Congrex Sweden AB, Attn ESPE 2004, PO Box 5619, 11486 Stockholm, Sweden (Tel: +46-8-4596600; Fax: +46-8-6619125; Email: espe2004@congrex.se; Web: www.europe.org/meetings.jsp).

3rd European Congress of Andrology and 16th Congress of the German Society of Andrology

Münster, Germany, 11-14 September 2004.

Contact: Prof. Dr E Nieschlag, Institute of Reproductive Medicine, D-48129 Münster, Germany (Tel: +49-251-8356096; Fax: +49-251-8356093; Email: nieschl@uni-muenster.de; Web: www.3rd-eca.de).

30th Annual Meeting of the European Thyroid Association

Istanbul, Turkey, 18-22 September 2004

Contact: Prof. Gurbuz Erdogan (Email: gurbuz.erdogan@temd.org.tr).

11th World Congress of Gynecological Endocrinology

Florence, Italy, 27-30 September 2004.

Contact: Biomedical Technologies srl, Via Trieste 1, 56126 Pisa, Italy (Tel: +39-050-501934; Fax: +39-050-501239; Email: biomedical@tin.it; Web: www.gynecologicalendocrinology.org).

76th Annual Meeting of the American Thyroid Association

Vancouver, Canada, 29 September-3 October 2004.

Contact: ATA, 6066 Leesburg Pike, Suite 650, Falls Church, VA 22041, USA (Email: admin@thyroid.org; Web: www.thyroid.org).

26th Annual Meeting of the American Society for Bone and Mineral Research (ASBMR)

Seattle, WA, USA, 1-5 October 2004.

Contact: ASBMR, 2025 M Street, NW Suite 800, Washington, DC 20036-3309, USA (Tel: +1-202-3671161; Email: asbmr@dc.sba.com; Web: www.asbmr.org).

60th Annual Meeting of the American Society for Reproductive Medicine (ASRM 2004)

Philadelphia, PA, USA, 16-21 October 2004.

Contact: ASRM, 1209 Montgomery Highway, Birmingham, AL 35216-2809, USA (Tel: +1-205-9785000; Fax: +1-205-9785018; Email: asrm@asrm.org).

Workshop on Reproduction

Caen, France, 21-23 October 2004.

Contact: Dr S Carreau (Email: carreau@ibfa.unicaen.fr).

195th Meeting of the Society for Endocrinology

London, UK, 1-3 November 2004.

Contact: Feona Horrex, Society for Endocrinology, 22 Apex Court, Woodlands, Bradley Stoke, Bristol BS32 4JT, UK (Tel: +44-1454-642210; Fax: +44-1454-642222; Email: conferences@endocrinology.org; Web: www.endocrinology.org).

International Conference on Steroid Hormone Receptor Superfamily and Molecular Signaling

Kerala, India, 18-20 November 2004.

Contact: Raghava Varman Thampan, Rajiv Gandhi Centre for Biotechnology, Thycad PO, Thiruvananthapuram 695014, Kerala, India (Tel: +91-471-2347975; Fax: +91-471-2348096; Email: steroidrgcb2004@yahoo.com).

5th European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis

Rome, Italy, 16-19 March 2005.

Contact: YP Communication, Boulevard G Kleyer 108, 4000 Liège, Belgium (Tel: +32-4-2541225; Fax: +32-4-2541290; Email: yolande@piettecommunication.com).

BES 2005: 24th Joint Meeting of the British Endocrine Societies

Harrogate, UK, 4-7 April 2005.

Contact: British Endocrine Societies, 22 Apex Court, Woodlands, Bradley Stoke, Bristol BS32 4JT, UK (Tel: +44-1454-642200; Fax: +44-1454-642222; Email: conferences@endocrinology.org; Web: www.endocrinology.org/sfe/confs.htm).

1st International Congress on 'Prediabetes' and the Metabolic Syndrome: Epidemiology, Management and Prevention of Diabetes and Cardiovascular Disease

Berlin, Germany, 13-16 April 2005.

Contact: Kenes International (Tel: +41-22-9080488; Fax: +41-22-7322850; Email: prediabetes@kenes.com; Web: www.kenes.com/prediabetes).

16th IFCC-FESCC European Congress of Clinical Chemistry and Laboratory Medicine

Glasgow, UK, 8-12 May 2005.

Contact: EuroMedLab Glasgow 2005 (Tel: +44-141-4341500; Fax: +44-141-4341500; Email: euromedlab2005@meetingmakers.co.uk).

2nd Joint Meeting of the European Calcified Tissue Society and the International Bone and Mineral Society

Geneva, Switzerland, 25-29 June 2005.

Contact: European Calcified Tissue Society, PO Box 4, Dursley GL11 6YL, UK (Tel: +44-1453-549929; Fax: +44-1453-548919; Email: admin@ectsoc.org; Web: www.ectsoc.org).

European Congress of Endocrinology

Göteborg, Sweden, September 2005.

Contact: Congrex Göteborg AB, Ref. ECE 2005, PO Box 5078, SE-40222 Göteborg, Sweden (Tel: +46-31-7086000; Fax: +46-31-7086025; Email: ece2005@gbg.congrex.se; Web: www.ece2005.com).

61st Annual Meeting of the American Society for Reproductive Medicine (ASRM 2005)

Montréal, Québec, Canada, 15-21 October 2005.

Contact: ASRM, 1209 Montgomery Highway, Birmingham, AL 35216-2809, USA (Tel: +1-205-9785000; Fax: +1-205-9785018; Email: asrm@asrm.org).

BES 2006: 25th Joint Meeting of the British Endocrine Societies

Bournemouth, UK, 12-16 April 2006.

Contact: British Endocrine Societies, 22 Apex Court, Woodlands, Bradley Stoke, Bristol BS32 4JT, UK (Tel: +44-1454-642200; Fax: +44-1454-642222; Email: conferences@endocrinology.org; Web: www.endocrinology.org/sfe/confs.htm).

2004
**SUMMER
SCHOOL**

Clinical
Practice
Day

Friday 16 July 2004
St Anne's College, Oxford

This year's cases are on the topics of:

Acromegaly and Cushings

**Management of uncommon
pituitary conditions**

Provides CPD points for consultants

Details can be found at
www.endocrinology.org/sfe/train or
from Ann Lloyd in the Bristol office
(ann.lloyd@endocrinology.org)



23RD JOINT MEETING OF THE British Endocrine Societies

with the European Federation of Endocrine Societies

22-24 March 2004

THE BRIGHTON CENTRE, BRIGHTON, UK

This year's inspirational programme covers both dynamic basic science and modern clinical practice, and integrates the two. Plenary lectures, symposia, workshops and 'meet the expert' sessions will address a broad range of contemporary endocrine topics.

Brighton has much in common with its European neighbours: its café culture, good food, bars, beachfront and relaxed pace of life to name a few. Of the many landmarks in Brighton, the most famous include King George IV's Royal Pavilion, a seaside palace with Indian domes and minarets and a Chinese style interior. And no visit is complete without a stroll along the glorious seafront with its piers, fun and frivolity!

The meeting will be held at the Brighton Centre. This is one of the largest multi-purpose venues in the south of England, with the capacity, experience and flexibility to offer the perfect location for another superb BES meeting.

HIGH PROFILE PLENARY LECTURERS

- J Flier 'The molecular pathophysiology of obesity'
- W Wiersinga 'Prediction and prevention of autoimmune thyroid disease'
- W Vale 'Corticotrophin-releasing factor, the urocortins and their receptors: roles in stress and beyond'
- A B Grossman 'Cycling into trouble'

WIDE-RANGING SYMPOSIA

- Endocrinology of obesity
- Actions of insulin in non-classical target tissues
- The extracellular calcium-sensing receptor in endocrine tissues
- Pituitary adenomas
- Neural migration in neuroendocrine systems
- Hair: too little, too much
- Molecular basis of thyroid disease



KEY WORKSHOPS:

- Electrolyte disturbances
- Insulin delivery systems
- When and how to remove the overactive parathyroid
- Molecular endocrinology

PLUS:

- Focused Science Session 'BRET in endocrinology: application to the study of the insulin receptor'
- Nurses Symposium 'Congenital adrenal hyperplasia'
- Young Endocrinologists Session 'How to compete for grant funding'

SEE THE EXPERTS DISCUSS:

Diabetic retinopathy, Ubiquitin/proteasome, BMPs, Weird thyroid function tests, Myths about short stature, Intellectual property

OPEN SESSION:

Watch out for this session on stem cell research, which will take place on Sunday evening, to mark the end of National Science Week 2004. Further details will be mailed to delegates. Organised in association with 'Sense About Science'.

EXCITING SOCIAL PROGRAMME:

SUNDAY

- BES Golf Tournament (supported by Pfizer Ltd)
- Five-a-Side Football Tournament
- BES Tennis Tournament
- BES Orchestra Practice

MONDAY

- Civic Reception, The Brighton Centre, accompanied by the BES Orchestra
- Champagne and Chips, Brighton Pier

TUESDAY

- BES Banquet, Glyndebourne House, accompanied by the Glyndebourne Opera

Further details from Feona Horrex, BES, 22 Apex Court, Woodlands, Bradley Stoke, Bristol BS32 4JT, UK
(Tel: 01454-642212; Fax: 01454-642222; Email: feona.horrex@endocrinology.org; Web: www.endocrinology.org/sfe/confs.htm)

The Society for Endocrinology thanks its corporate members for their kind generosity. The ordinary members are: Abbott Diagnostics Ltd, Ardana Bioscience Ltd, Endocrine Pharmaceuticals Ltd, Genzyme Therapeutics, Organon Laboratories Ltd, Randox Laboratories Ltd and Schering Healthcare Ltd. The premier members are: AstraZeneca plc, BioScientifica Ltd, Eli Lilly and Company Ltd, GlaxoSmithKline Pharmaceuticals UK, Ipsen Ltd, Novartis Pharmaceuticals UK Ltd, Novo Nordisk Pharmaceuticals Ltd, Pfizer Ltd, Sandoz Biopharmaceuticals and Serono Ltd.