SPECIAL ISSUE

Genetics: brave new world?

PLUS...

Special Interest Groups: time to make your mark
Consensus on hormone replacement therapy
New possibilities for POMC
Growth hormone: the NICE conclusion
Genes, new blood and facts are central to this special issue of The Endocrinologist. As Gradgrind said in Hard Times, when asking for a definition of a horse, ‘Now, what I want is facts.’ To which the boy answered, ‘quadruped, graminivorous, 40 teeth, namely 24 grinders...’ But we now know a lot more about our equine companions, according to Paul Kelso (page 10). Did you know, for instance, that all thoroughbreds stem from three stallions brought to England in the late 17th century? If you’re a betting man, this article is essential reading, as Paul considers the possibility of predicting the Derby winner at birth by cloning the equine genome.

If you think this mission is irrelevant to man, then it’s time you knew that we share 40% of the genome of even the humblest worm! For more information on your genetic make up, turn to page 8, where George Orphanides has answered ten of the most frequently asked questions about the human genome. But one of the facts in this issue that really surprised me was Paul Rodgers’ prediction (page 9) that we can soon expect growth hormone to be derived from tobacco plants and sunflowers rather than from E. coli.

And so to new blood. In a previous editorial I questioned whether SIGs (Special Interest Groups) would fly, and I am delighted to report that they are now on the tarmac! If you want to play a part in this exciting new venture, please turn to page 3. In addition to SIGs, there are various opportunities to join Committees within the Society and become involved in broadening its appeal. The request for nominations can be found on page 5, and I do hope that members will play an active part in nominating colleagues.

This is my last issue as Editor, and I must come clean. Anyone who works with the Society for Endocrinology will know that the real work is done at the Bristol office. The commissioning, editing, drafting and illustrations are all inspired by Ailsa Bailey and her team and it has been a real honour and pleasure to work with the group. The product, The Endocrinologist, is a high quality publication which would compete with any of the top class magazines at your local newsagent.

My final round of thanks goes to my Associate Editor, Saffron Whitehead, who has had a major impact on this newsletter. If you wondered who that sneaky paparazzo was that stole your image at the BES, it was Saffron behind the lens. Saffron now takes over as Editor, and I hope you derive as much satisfaction as I do whilst reading this packed volume.

RICHARD ROSS
WANTED – enthusiastic key people to lead Special Interest Groups

Earlier this year, we asked for your views on creating Special Interest Groups (SIGs) within the Society, and outlined how these might operate. Thank you to all who responded to the email questionnaire. This has enabled us to identify a number of areas in which groups may be established.

Based upon the level of interest, the Society is keen to set up four pilot SIGs, covering reproduction, steroids, pituitary and neuroendocrinology. The existing expert group on endocrine disruptors would become the fifth SIG. We realise that the subjects may need refining, and volunteers will be encouraged to take soundings from their colleagues and propose the final coverage of each SIG. The creation of each group depends on finding at least one enthusiastic volunteer to lead it.

The aim of a SIG will be to:

- provide a focus for sub-specialties within endocrinology - this will strengthen the overall discipline and provide a framework for different groups to come together in a community and promote interdisciplinary interests within the Society
- organise small meetings for focused groups - these could either be stand-alone meetings or form a day of parallel SIG-related programmes on the third day of the annual November meeting
- increase the profile of endocrinology as a specialty
- improve communication and promote endocrinology as an interdisciplinary subject that interfaces with other biomedical subjects. The Society will provide a web page for each group, publicity on the group’s aims and activities, discussion list facilities if required and limited assistance with meeting arrangements.

Each group will be required to:

- set up an informal committee and constitution
- initiate and manage communication between its members
- organise any desired activities on a cost-neutral basis

If you would like to be part of this exciting new development, please email julie.cragg@endocrinology.org.

Simplified travel grants

The rules are now more straightforward. If you earn less than £30 000 (excluding London weighting) in any 12-month period, 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

New deadlines for grant applications (with effect from April 2004)

- 15 December - for overseas conferences
- 9 January - for BES 2004 Meeting
- 15 April - for overseas conferences and Molecular Endocrinology Workshop at Summer School
- 15 August - for overseas conferences and the November Meeting

Grants for lab visits and clinical departmental visits

In addition, young endocrinologists can obtain grants to visit:

- labs to gain experience
- clinical departments outside their Calman rotation

Up to £500 is available for lab visits within the UK and Europe, and up to £1000 for other locations. Up to £500 is available for UK-based clinical departmental visits and up to £1000 for Europe-based visits.

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

Grants, glorious grants!

Up to £500 available for members now

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

Society for Endocrinology

Fellowships and studentships

Council’s review of travel grants concluded that more members would benefit from the channelling of grant funds into travel grants. The Society’s fellowships and studentships will therefore be on hold for the time being.
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
- Electrolyte disturbances
- Insulin delivery systems
- When and how to remove the overactive parathyroid
- Molecular endocrinology
- 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’
- Diabetic retinopathy, Ubiquitin/proteasome, BMPs, Weird thyroid function tests, Myths about short stature, Intellectual property
- Watch out for this session on a topic of public interest, which will take place on Sunday evening, to mark the end of National Science Week 2004. Further details will be mailed to delegates in due course. Organised in association with ‘Sense about Science’.

EXCITING SOCIAL PROGRAMME:

- BES Golf Tournament (supported by Pfizer Ltd)
- Five-a-Side Football Tournament
- BES Tennis Tournament
- BES Orchestra Practice
- Civic Reception, The Brighton Centre, accompanied by the BES Orchestra
- Champagne and Chips, Brighton Pier
- BES Banquet, Glyndebourne House, accompanied by the Glyndebourne Opera
Council and Committees

At the recent 2003 AGM, Steve Bloom (Chairman), John Wass (General Secretary) and Ann Logan (Programme Secretary) were all re-elected for their second year of office, and Anne White was re-elected for her third year as Treasurer. We welcome two new Council members, Steve Atkins (Hull) and Neil Gittoes (Birmingham). They replace Ieuan Hughes and John Monson, who are both retiring after completing 4 years of service. In July, Paul Stewart became Chairman of the Awards Committee in place of Julian Davis, and, in January, Barry Brown will take the Chair of the Science Committee from Ian Henderson, who was the inaugural Chairman of this committee. Our thanks go to all retiring Council and Committee members.

Letters of support

On request the Society will provide any retiring committee member with a letter of support to assist with their career progression. Contact Julie Cragg for details.

Committees - nominations needed!

Send your nominations now to fill vacancies left by retiring members of the following committees:

- **Awards Committee**
- **Science Committee**
- **Clinical Committee**

Nomination forms are available under the relevant committee at www.endocrinology.org/sfe/commit.htm or from Christine Davis in the Bristol office (christine.davis@endocrinology.org). Please return them by **31 January 2004**.

Medal and prize winners

The Society is delighted to announce the following winners of its medals for 2004-2005.

- **Society for Endocrinology Medal 2004**: Richard Eastell (Sheffield)
- **European Medal 2004**: Kjell Oberg (Uppsala)
- **Asia & Oceania Medal 2004**: Peter Leedman (Perth)
- **Dale Medal 2005**: Ron Kahn (Boston)
- **Transatlantic Medal 2005**: Ken Korach (Research Park Triangle)

The following won prizes at the Society’s November meeting.

- **Best Basic Science Oral Communication**: Steven Harmer, Reading
- **Best Clinical Oral Communication**: Serena Tolhurst-Cleaver, Altrincham
- **Best Young Endocrinologist Oral Communication**: Fiona Lovett, Cambridge
- **Best Basic Science Poster**: Alison Mostyn, Nottingham
- **Best Clinical Poster**: Angela Paisley, Manchester

Members on the move...

- **M Clark** to British Antarctic Survey, Cambridge; **P Driver** to Centre for Reproductive Biology, Edinburgh; **I Evans** to Rayne Institute, London; **T Higgins** to Tralee General Hospital, Ireland; **E J Johns** to University College Cork, Ireland; **W Leadbeater** to Birmingham University; **M I McCarthy** to Oxford Centre for Diabetes, Endocrinology and Metabolism; **B Mukhopadhyay** to Royal Infirmary, Glasgow; **R Poole** to Queen Alexandra Hospital, Portsmouth; **V Taylor** to Imperial College London; **C M Thomas** to University Hospital Aintree, Liverpool; **C Wright** to University of Edinburgh.

Charity Commission review

In October, the Society was randomly selected for a review visit by the Charity Commission. We are awaiting the official report, but the reviewers commented on the good management practices in place, reflecting sound management over a number of years.

Money for nothing - and info for free!

Yes - that’s exactly what you can expect as a Young Endocrinologist member of the Society. The Young Endocrinologist Steering Group aims to support the interests of younger endocrinologists in the early part of their career (normally up to 35 years old and up to 6 years postdoc). It encourages them to get actively involved in the Society’s activities.

The Society’s new travel grant policy (see page 3 for details) means that, as a Young Endocrinologist member, you’ll be able to apply for a grant to attend the BES or annual Society meeting even if you don’t have data to present, and you can apply for grants for the Molecular Endocrinology Workshop and an overseas endocrine conference. This gives you the chance to listen to plenary lectures from internationally recognised endocrinologists as well as cutting edge talks from young investigators.

The Steering Group is starting a cycle of educational seminars, with the first at BES 2004, where the session is ‘How to compete for grant funding’. Subsequent sessions will include presentation skills, writing skills and experimental design - all crucial at any stage in your career! So, have a look at the Young Endocrinologist web site and see just how many ways you can benefit from the Society: www.endocrinology.org/sfe/yepage.htm.
Adult GH: the NICE conclusion

The National Institute for Clinical Excellence (NICE) has recently reached its final conclusion regarding use of human growth hormone (GH) therapy in adults. It has decided that the NHS should fund treatment of the most badly affected patients. Using the QoL-AGHDA score to measure quality of life, patients with a score greater than 11 should be allowed to start a GH replacement therapy trial. To be allowed permanent treatment, they must then show an improvement of 7 points. Full guidance can be found at www.nice.org.uk/cat.asp?c=83406.

As many members will be aware, the Society for Endocrinology has devoted considerable resources to this appraisal over the last 3 years. In June 2002, NICE concluded that GH replacement therapy could not be recommended to the NHS, and only strong representation from the Society for Endocrinology and other stakeholders persuaded them to revisit the evidence. The Society, including the Clinical Committee, the Bristol office and those GH specialists who contributed to the NICE appraisal, can be congratulated on their work in persuading NICE to adopt a more positive view. This process has really shown the value of the Society in representing patients and clinicians.

At the same time, the final decision by NICE is not as positive as we would have hoped. The barriers to entering and continuing treatment mean that it will be difficult for many new patients to be accepted for therapy. Difficulties will arise, for instance, where a patient sees the benefit of GH treatment during a trial, but then has funding withdrawn because they have not shown a 7 point improvement. The issue of withdrawing treatment from patients who are making the transition to adulthood, and allowing their condition to deteriorate before starting a trial, also raises difficult ethical problems.

Clinicians will often recommend treatment only to find that NHS funding is unlikely because of the NICE guidance. NICE clearly states that ‘This guidance does not ... override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer’. In these cases, the clinician must continue to manage the patient’s condition according to their clinical judgment and ethical principles.

The NICE decision will be reviewed in July 2006. Meanwhile, we would appreciate your feedback on how it works in practice: is it effective or a matter of concern?

JOHN WASS

Alfred Cowie

It is with sadness that we mark the passing of Alfred Cowie, one of the Society for Endocrinology’s longest-standing supporters. He had been a member since the Society’s formation in 1946, and was on the Committee from 1971 to 1974. He was also a member of the Editorial Board of Journal of Endocrinology from 1966 to 1972, and Editor from 1981 to 1984.

After qualifying as a veterinary surgeon from Edinburgh in 1938, he entered research, studying fetal physiology in sheep in the Cambridge laboratory of Sir Joseph Barcroft. In 1941, he took up a post at the National Institute for Research in Dairying, receiving a PhD in 1947 and DSc in 1959 from Reading University. He succeeded Professor S J Folley as Head of the Department of Physiology in 1970, and retired in 1981.

At Reading, he soon became interested in Folley’s work on lactation, which marked the beginning of his lifelong enthusiasm. During the war, he undertook field trials using oestrogen implants to improve the productivity of dairying by inducing lactation in barren cattle. The erratic success of these trials led to his research on the relative roles of oestrogen and progesterone in mammary growth. He also identified the hormones necessary to initiate and maintain the secretion of milk in dairy goats, and found that species differ in the minimum hormone combination that will support lactation. It was his combination of skills as a veterinary surgeon with meticulous laboratory work that made his research so successful. As a Head of Department, he remained active in research and provided generous support to colleagues, visitors and students.

Alfred Cowie wrote with great lucidity and style, producing two very readable and comprehensive books, The Physiology of Lactation (with J S Tindal, 1971) and Hormonal Control of Lactation (with I C Hart and I A Forsyth, 1980). His kindness, good humour and common sense judgments made him many lasting friendships. He was a proud Scot and his Hogmanay dinners (subsequently lunches) were a great joy to all who attended. He sadly died on 3 July 2003, at the age of 86.

ISABEL FORSYTH
Life on the net
www.bio.com/index.shtml
Bio.com claims to be the ‘most reliable and up-to-date information resource for today’s time-pressed professionals working in life sciences’. The web site provides live panel discussions, topical reviews, interviews with leading scientists and daily news updates from academic and industrial labs. On a more practical note, there’s an extensive range of laboratory protocols and an impressive collection of internet links and web-based tools. SERVICES: L, O (protocols); STRONG POINTS: Well-organised information, hierarchical organisation; WEAK POINTS: None; RATING: Excellent.

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.

HRT: a consensus
Reviewing the role of HRT was the focus of the Consensus Conference on Hormone Replacement Therapy, hosted by the Royal College of Physicians of Edinburgh in October. This exercise was particularly timely, given recent publication of results from the Women’s Health Initiative and the Million Women Study.

Distinguished speakers presented review papers on all aspects of the clinical roles of HRT. The evidence of benefits and risks was subjected to rigorous analysis by a multidisciplinary audience of around 250, including an invited panel, whose main role was to facilitate the drafting of a consensus statement on when and how HRT should now be used. The Society for Endocrinology was represented at the conference. The full draft statement is at www.rcpe.ac.uk/esd/consensus/hrt_03.html.

Key recommendations are as follows:
- The prime role of HRT is the relief of menopause-related symptoms (vasomotor, urogenital and associated mood change), and the appropriateness of its use should be considered on an individual basis.
- The absolute risks and benefits of HRT need to be explained to each woman considering HRT.
- The lowest effective dose of oestrogen should be used, and potential users should undergo assessment of cardiovascular risk (with risk-reduction lifestyle and therapeutic intervention as required if that risk is increased, prior to starting HRT).
- The use of HRT should be reviewed annually to respond to changes in risk with continuing use.
- In the absence of clear evidence, it is reasonable for HRT to continue to be given until the age of 50 years to women with premature menopause.
- Use and potential benefits of HRT must be offset against the small increase in absolute risk of breast cancer, cardiovascular disease and stroke. The risk of breast cancer, for example, equates to an extra 2-6 cases per 1000 women treated with HRT for 5 years, depending on the age of the patient and the preparation used (greatest risk with combined HRT, but also to a lesser extent with oestrogen alone and tibolone).
- There is no evidence to justify using HRT for the primary or secondary prevention of coronary artery disease or stroke, or in the prevention of Alzheimer’s disease.
- Oral oestrogen is associated with increased risk of venous thromboembolism. When potential users have risk factors for this, transdermal preparations should be considered as they may carry a lower clotting risk.
- The benefit of fracture risk reduction is, for most women, outweighed by the risks of HRT. Bisphosphonates are the first-line treatment of osteoporosis. HRT is among the alternatives that could be considered when bisphosphonates cannot be used.

ALASTAIR R MCLELLAN
As an introduction to this special issue on genetics, George Orphanides takes a look at the human genome.

Never mind charades, get your colleagues and family answering the questions that really matter this Christmas! Read on to find out what every human should know about their DNA...

How big is the human genome?
Our genomes contain approximately 3.2 gigabases (3.2 x 10^9 bases) of DNA. Less than 2% of the human genome encodes protein, while more than half is made up of parasitic, ‘selfish’ sequences that use our DNA as a host.

How is the genome packaged into the nucleus of a cell?
If the DNA of a single human cell were stretched out, it would be more than 2 metres long. Packing the genome into a cell nucleus therefore requires remarkable compaction. This is achieved by proteins that mediate successive orders of DNA folding to form a highly ordered nucleoprotein structure termed ‘chromatin’.

How many genes does the human genome encode?
This is a controversial question that has occupied computational biologists since the draft human genome sequence was published in 2001. Gene prediction algorithms designed to find human genes in the sea of As, Cs, Gs and Ts differ in how they classify a true gene, leading to estimates that vary from 20 000 to 100 000 genes. Some genes are so short that many algorithms do not detect them. Accurate counting is also confounded by the presence of ‘pseudogenes’, extinct DNA sequences that have all the features of a true gene but are no longer active. A panel of gene-counting experts estimated recently that the human genome has around 24 500 genes.

How many genes do we have in common with other species?
About 40% of predicted human genes are similar to genes found in worms and flies. Not surprisingly, we share more genes (around 80%) with our closer evolutionary relative, the mouse. Many geneticists are surprised that there is little correlation between a species’ biological complexity and its number of genes: humans, flies, worms and plants are predicted to have 24 500, 13 000, 19 000 and 25 500 genes respectively. The extraordinary biological complexity of humans may be due to a higher level of alternative gene splicing, resulting in a more diverse complement of proteins.

How many genes are expressed in each cell type?
A study of human cell lines suggests that the number of genes expressed varies with cell type. Most cells contain 10 000-15 000 different gene transcripts. Cells derived from the brain appear to have the most diverse complement of gene products (23 500 genes), presumably reflecting a higher degree of specialisation. A core set of 1000 genes is expressed in all cell types and may be essential for minimal cell functioning.

How are genes regulated?
The master regulators of gene expression are sequence-specific DNA-binding proteins known as ‘transcription factors’. More than 2000 of these are encoded by the human genome, making them one of the largest families of human proteins. Transcription factors bind to specific sequences in the regulatory regions of genes and, with the help of a plethora of accessory factors, promote the local decompaction of chromatin so that gene sequences can be transcribed by RNA polymerase II.

How much variability exists between the genomes of different individuals?
Approximately 0.1% of the human genome varies in sequence between individuals. Much of this variability is in the form of single base pair differences known as single nucleotide polymorphisms (SNPs). A large public consortium has published the results of a comprehensive analysis of human polymorphisms. This revealed that SNPs occur with an average frequency of one in every 1000-2000 base pairs.

What are the functional consequences of genome variability?
Although only 1% of SNPs will alter biological activity, some have severe consequences for an individual’s health. The genetic bases for many inherited disorders have now been identified and some conditions not previously considered to be influenced by polymorphisms, like obesity and cardiovascular disease, may have genetic components.

In some cases, allelic variability is believed to be of considerable importance. Extensive polymorphism at a locus encourages heterozygosity (that is, inheritance of different allelic forms of the gene from the mother and father). This may confer important selective advantages. For instance, a reduced chance of homozygosity at a locus where a recessive disease-conferring allelic form of the gene exists would be advantageous. In addition, heterozygosity at loci encoding proteins that are known to influence protective immune responses to infectious micro-organisms (like the major histocompatibility complex) provides a basis for ensuring a more diverse repertoire of specificity.

How can we use genome sequence information to benefit human health?
The sequencing of the human genome has the potential to revolutionise the diagnosis, prevention and treatment of human disease. Novel, genome-based diagnostic methods will enhance prediction of susceptibility to genetic diseases and the response of patients to drugs. Identification of the entire complement of human genes will facilitate discovery of new drug targets by allowing researchers to map new genes and pathways involved in disease. As we enter the ‘post-genomic’ era, the focus will be on understanding the complex regulatory networks that function in human cells, a field of study that has come to be known as ‘systems biology’. We must also understand more fully the relationships between genome variation, disease and the influence of environmental factors.

What are the ethical implications surrounding human genomics?
The new knowledge generated by the human genome project comes with a responsibility to use it in a manner that benefits mankind. Possible ethical issues relating to the use of genetic data must be acknowledged and debated. For example, should individuals be tested for genetic disorders? Should this information be made available to potential employers or insurance companies? How can we prevent unfair discrimination based on genetic data?

GEORGE ORPHANIDES
SYNGENTA CENTRAL TOXICOLOGY LABORATORY
A healthy crop?

Genetically modified (GM) plants seem to hit the headlines almost on a daily basis. Environmental or safety concerns about cultivating GM plants or eating foods derived from them are top of the European political agenda. But you may (or may not) be surprised to know that 58.7 million hectares of GM crops were grown in 2002, principally in the USA, Canada and Argentina.

The current range of GM crops was designed to make life easier for farmers by reducing the need for pesticides through the incorporation of insecticide- or herbicide-resistance genes. Today, a whole new generation of GM crops is being developed for the production of therapeutic proteins for medicinal use.

You will be familiar with recombinant human proteins such as growth hormone and erythropoietin that have been in clinical use for many years. More recently, a range of recombinant antibodies has been approved for clinical use (e.g. infliximab for the treatment of rheumatoid arthritis and Crohn’s disease), and there is a large pipeline of other therapeutic proteins in clinical development. These products are currently manufactured using micro-organisms or animal cells in fermentation processes not dissimilar to those used to produce beer and wine. The cost of producing proteins in this way is high and manufacturing facilities are expensive to construct, so there is a shortage of capacity.

Scientists are consequently turning to GM plants as a low cost, high capacity, alternative production system. A wide variety of plants can be used to make pharmaceutical proteins. Companies have received permits for field trials using alfalfa, corn (maize), duckweed, rice, safflower and tobacco. The following are examples of pharmaceutical proteins that have been produced in plants.

**Human proteins** - growth hormone (in tobacco, sunflower), serum albumen (in tobacco, potato), erythropoietin (in tobacco), α1-anti-trypsin (in rice)

**Recombinant antibodies** - anti-herpes simplex virus (HSV) IgG (in soybean), anti-Streptococcus mutans adhesion protein IgA (in tobacco)

**Recombinant subunit vaccines** - hepatitis B envelope protein (each in potato), *Escherichia coli* enterotoxin - travellers’ diarrhoea (in tobacco, potato), Norwalk virus antigen (in potato)

One of the biggest challenges facing the companies that hope to develop pharmaceutical proteins in plants is the way that the proteins are glycosylated, i.e. the pattern of sugars attached to the surface of many proteins. These sugar residues are integral to the structure of complex proteins and essential to the protein’s functionality. When a therapeutic protein is manufactured in a plant, the sugar pattern may not be identical to that observed when the protein is produced in a mammalian cell. There are several possible consequences of a changed sugar pattern. First, the recombinant protein may be rendered immunogenic. If it causes an immune response in a patient, its utility and usefulness are reduced over time. Secondly, the protein may exhibit a decreased circulating half-life and accelerated clearance from the bloodstream. Lastly, as sugars are critical for the interaction of many proteins with their receptors, altered protein patterns could result in decreased therapeutic effectiveness of the protein.

Perhaps surprisingly, where they have been studied, the circulating half-life and receptor interactions of plant-produced proteins do not differ markedly from those for the same protein produced in animal cells. However, this is an area that warrants more attention, and a clearer picture will emerge as more clinical studies are performed. The results of therapeutic evaluation of plant-produced proteins can be summarised as follows.

**E. coli** enterotoxin, Norwalk virus antigen, Hepatitis B envelope protein (each in potato) - phase I trial of edible vaccine showed that ingestion of raw potato elicited antibodies against the toxin, antigen or envelope protein respectively

**Avicidin**: antibody against epithelial cellular-adhesion molecule (in corn) - phase II trial showed some side effects due to cross-reactivity that were not unique to the plant-derived antibody

**CaroRx**: antibody against *S. mutans* adhesion protein (in tobacco) - phase II clinical trials showed that topical application, after bacteria were removed from the mouth, helped to prevent recolonisation by *S. mutans* for several months

**T84.66**: monoclonal antibody that recognises carcinoembryonic antigen - tested for cancer imaging and therapy

**Anti-HSV IgG** (in soybean) - prevented vaginal HSV-2 transmission in mice after topical application

**PIPP**: monoclonal antibody that recognises human chorionic gonadotrophin (hCG) (in tobacco) - inhibited the hCG-stimulated production of testosterone in cultured Leydig cells and delayed uterine weight gain in mice

There remain many challenges to be overcome, particularly with regard to increasing yields, removing processing bottlenecks and dealing with the regulatory and clinical testing hurdles that all pharmaceuticals must address. However, there are grounds for optimism that plant-produced therapeutic proteins will be approved for before the end of this decade.

Paul Rodgers
Racing ahead

Great racehorses have traditionally been produced by a combination of guesswork and experience, but today science may help to replace hope with certainty.

Advances in fertility technology in the past decade have helped to turn the thoroughbred into an efficient breeder. More than 90% of mares covered at stud now go on to full pregnancy, and the use of heat, lights and hormone injections has enabled breeders to bring forward the mares’ season from May to February or March.

But the most recent advance in this sport obsessed with pedigree is the discovery of the doctrine of DNA. Geneticists are mapping the equine genome, and their profound aim is to identify the causes of common thoroughbred infirmities in order to treat them or breed them out. Others harbour more profitable ambitions, hoping to decode the genetic secrets of speed and stamina that create a champion, and thus pave the way to thoroughbred perfection.

In Newmarket, heartland of British horse racing, the Animal Health Trust has produced the first map of the equine genome. Dr Matthew Binns, a veterinarian turned geneticist has led the project. He explains why thoroughbreds provide an exceptionally well-defined field for genetic research.

‘The equine genome is unique in genetics because of the singular population it seeks to define,’ he says. ‘All thoroughbreds stem from 3 stallions brought to England in the late 17th century. These ‘origin stallions’ stand at the head of the family tree of every thoroughbred that has ever raced, and the distant cousins who contest races today bear the marks of three centuries of attempts at improvement by selective breeding.’

The entry of the 3 origin stallions into England is well recorded, and nearly every covering since 1701 has been recorded by Weatherbys (the Jockey Club’s agents). The family is traceable back to just these 3 stallions and about 75 mares. There is also a huge archive of paintings, illustrations and literature that tells us about white faces, stockinged feet and other little inherited traits traceable to these founders.

The quality of his material gave Matthew Binns an advantage. In the early 1990s, the Equine Fertility Unit at Cambridge University, run by Professor William ‘Twink’ Allen (father-in-law of jockey Frankie Dettori), produced two pairs of identical twin mares by splitting embryos. The four twins were then repeatedly impregnated by the same stallion, with the resulting embryos flushed out after 32-34 days and retained. The process was repeated until, in the space of 4 years, Binns had DNA samples from three generations of two full sibling families, a process that would have been impossible by natural means. ‘Other genome projects need 400 half-siblings to compile the same amount of genetic material,’ William Allen explains.

This material enabled Binns to publish a partial map of the genome in March 2000. Since then, he has identified the genetic relationship with grey coat colour, which has been linked to the incidence of melanomas, and is now widening his research. ‘There’s a feeling that the thoroughbred has a high degree of unsoundness,’ he says, ‘respiratory disease, weak bones, that sort of thing, and we are looking at whether this is due to underlying genetic problems.’

News reports after publication of Binns’ partial map predicted that the genome would identify Derby winners at birth, and that discovery of the ‘speed gene’ was only a matter of time. While he is anxious not ‘to hype this project’, even Binns cannot conceal his excitement at where it might lead. He talks of publishing DNA sequences alongside the pedigree charts that appear in bloodstock books, and is thrilled at having received a phial of blood from a recent champion. He is, however, sceptical about isolating performance genes.

‘There is no speed gene,’ he says. ‘Just as I don’t think there is a single gene for sprinting, or hurdling, or chasing. I think those sorts of differences in performance are marginal. The lesson of the human genome is that all traits are fabulously complex. Speed might be the ultimate complex trait, but it probably requires an enormous number of genetic elements to be in balance.’

But even if Binns were to discover a speed gene, he wouldn’t be unable to do much with it. Artificial insemination is forbidden in racing; cloning, transgenics and other related techniques are for the moment purely hypothetical.

Binns maintains that, as long as artificial insemination is prohibited, performance will not be his priority. Instead, he is intrigued by the prospect of testing traditional theories about breeding, and is currently examining the effect of grandpaternal DNA on performance, a subject of centuries of debate among pedigree experts, with received wisdom placing primacy on the grandmaternal line.

The practicalities of breeding dictate that a smaller percentage of stallions than of mares go on to breed; far fewer are needed. ‘Only the very best 1% of stallions go to stud, while 50% of mares produce foals, so it follows that males have a better history of performance,’ Binns explains.

‘Horses inherit equal amounts of DNA from their parents, but when the proportions inherited from each grandparent are examined, it is not equally split. Given the excellence of
stallions, it might follow that, of two siblings, the one with the greater proportion of grandpaternal DNA is the better, and therefore more valuable, horse.’

Miles Littlewort, chief executive of the National Stud, is sceptical about the value of the genome project. ‘Much of this stuff is science fiction, and you do have to worry what these advances might lead to,’ he says. His scepticism is shared by many in an industry that accepts, even relishes, the role of chance in producing champions. While established practices may be more art than science, they have continued to produce winners. Science’s stock is not high in racing; too many faddish theories have come and gone, many of them based on bad science.

The independent New England Stud’s Peter Stanley is also dubious about the genome, fearful perhaps of the ban on artificial insemination. ‘I struggle to see the relevance of genetics for our industry, because of the ban on artificial insemination. It’s terrific that we are at the forefront in this country, and many people in my position are grateful that much of what they are doing is centrally funded by the racing industry. That means many of the dilemmas about who owns information, and who can use it to their advantage, are in the hands of everybody, rather than a few.’

‘It is such a lottery, the breeding game, and you use what you’ve got to make it work. There is still space for people like us, the smaller guy, because if it wasn’t unpredictable, then no one would go racing. It is the unpredictability that makes it fascinating.’

That unpredictability is not about to disappear - even with the advances being made at the Animal Health Trust. And, while genetic research has the potential to transform both equine health and the mechanics of the breeding industry, it is unlikely to uncover the genes for luck and optimism, two properties that racing really cannot do without.

PAUL KELSO

This article originally appeared in The Guardian on 7 June 2003, and is reproduced with permission in substantially edited form.

UNITED KINGDOM

POMC: unleashing possibilities

Interest in the biology of pro-opiomelanocortin (POMC) certainly shows no signs of abating. The melanocortin peptides that are derived from this 31 kDa precursor have a hugely diverse range of key roles, in the regulation of food intake and energy metabolism, depression, skin pigmentation, adrenal development and the hypothalamic-pituitary-adrenal axis. Here, Gillian Hart considers valuable new applications for the latest research...

Evidence that adrenocorticotropic hormone (ACTH) is synthesised as a precursor dates back as far as the mid-1970s. ACTH is now known to be synthesised as part of that suprermo of precursor polypeptides, POMC, which is cleaved by prohormone convertase-1 (PC1) at the N- and C-termini of ACTH, thus also yielding β-lipotrophin (βLPH) (see flowchart). Cleavage of both ACTH and βLPH to give smaller peptides occurs by the action of PC2. Further post-translational modification produces α-melanocyte-stimulating hormone (αMSH).

In cells, this processing forms part of a regulated secretory pathway where specific hormones or neurotransmitters act to regulate release of these peptides from secretory granules. POMC itself can also be released directly from cells, and it may be that this is via a constitutive pathway where it is not exposed to post-translational processing mechanisms.

In the anterior pituitary lobe in humans, the presence of PC1 and absence of PC2 results in ACTH as the major secretory product. ACTH stimulates the release of glucocorticoids from the adrenal gland via the melanocortin 2 receptor (MC2R). In the skin, processing of POMC to MSH peptides is important for regulation of pigmentation. In the hypothalamus, POMC is processed to MSH peptides, which are involved in the regulation of food intake and energy metabolism.

A central role of POMC in the hypothalamus was indicated by inactivating mutations in humans and in mice, which resulted in extreme obesity. POMC’s role in appetite and obesity is largely due to interactions between POMC-derived peptides and the neuroendocrine receptors MC3R and MC4R. It is possible to detect POMC, ACTH and αMSH in hypothalamic extracts, although only POMC and ACTH levels change in response to fasting. This suggests that processing of POMC to ACTH and αMSH is regulated as a means of controlling the melanocortin pathway. Numerous studies directly implicate POMC in melanocortin-mediated energy homeostasis. It is therefore important that the mechanisms by which the POMC gene is regulated and post-translationally processed are understood, since this determines the net effect in controlling food intake and energy metabolism.

continued on page 12

POST-TRANSITIONAL PROCESSING OF POMC
To understand how POMC is processed, we must specifically measure the concentration of the precursors and the peptides derived from them. Professor Anne White at the University of Manchester has developed an assay for ACTH precursors using antibodies to N-POMC and ACTH. This assay detects pro-ACTH and POMC but does not recognise any of the smaller peptides (see flowchart). Interestingly, these precursors are found in the circulation of normal subjects at 5-40 pmol/L, slightly higher than the concentration of ACTH itself.

In ACTH-dependent Cushing's syndrome (excess release of glucocorticoids), the exact nature of the POMC-related peptides secreted by the tumours will depend on the processing pathway in the tumour cells. While most tumours are located in the pituitary, about 15-20% of cases have ectopic tumours, most commonly small cell lung carcinoma. Many tumour cells are less differentiated than their normal counterparts, and the presence of the regulated secretory pathway will vary depending on the degree of cell differentiation. In the ectopic ACTH syndrome, it is unlikely that the extra-pituitary tumour cells will have the same regulated secretory pathway for processing POMC as the anterior pituitary. Therefore an increased prevalence of ACTH precursors in the circulation can be expected.

The advent of immunometric assays has made it possible to measure the large excess of ACTH precursors in the circulation of patients with the ectopic ACTH syndrome. In a study comparing patients with pituitary and ectopic tumours causing Cushing's syndrome, ACTH precursors were elevated in all patients with ectopic tumours when compared with pituitary microadenomas. In contrast, ACTH levels in the two patient groups did not differ significantly. In a subsequent study, the measurement of ACTH precursors as a simple diagnostic test for the differential diagnosis of Cushing's syndrome compared favourably with inferior petrosal sinus sampling.

Clearly, further studies are required to determine fully the role and regulation of ACTH precursors such as pro-ACTH and POMC before their biological significance and clinical relevance are fully appreciated. However, the successful collaboration between Professor White and IDS Ltd means that an enzyme immunoassay for the quantitative determination of POMC and pro-ACTH is now available commercially. Could a similar approach help you examine the possibilities for POMC?

GILL HART
EXTERNAL PROJECTS MANAGER, IDS LTD

See page 15 for further details of the immunoassays available from IDS Ltd.

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Osteoporosis
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Hot Topics

More cutting-edge endocrinology from the Society's journals, brought to you by Jolene Guy, Mona Munonyara and Nathalie Gilmore.

Galanin in pituitary hyperplasia

Found in the central and peripheral nervous systems, galanin is reported to regulate anterior pituitary hormones, and has also been implicated in pituitary hyperplasia. Perumal & Vrontakis now present new evidence of galanin’s role, demonstrating variations in serum galanin, prolactin and growth hormone (GH) in transgenic mice that oversecrete and sequester galanin. Mice carrying rat preprogalanin cDNA showed a significant increase in serum galanin and prolactin levels, while an increase in serum GH was only recorded in male mice.

Previous studies have demonstrated galanin upregulation by oestrogens in the anterior pituitary. Now the authors prove for the first time that the peptide acts as a growth factor in the pituitary, causing hyperplasia and adenomas in an oestrogen-independent manner. This was demonstrated in older transgenic male and female mice, and suggests that galanin mRNA levels correlate with tumour formation. The cause for the late onset of adenoma, despite early overexpression and oversecretion of galanin, remains unclear.

This is an intriguing study that not only supports previous work but also details the novel finding of oestrogen-independent galanin function. JG
(See the full article in Journal of Endocrinology 179(2), November 2003)

Fetal adipose tissue linked to maternal nutrition

Uncoupling protein 1 (UCP1) is found exclusively in brown adipose tissue of rodents and some mammals. It is involved in non-shivering thermogenesis, and is activated rapidly at birth to ensure effective adaptation to cold exposure in the extra-uterine environment. In this review, Symonds and colleagues discuss the endocrine and nutritional factors that affect UCP1 expression and function in the fetus.

In rats, maternal prolactin administration throughout gestation increases UCP1 expression in the fetus, while in sheep, postnatal administration of lepin promotes UCP1 function. Raised maternal food intake also results in a higher fetal plasma prolactin, so increasing UCP1. In sheep, reduced maternal nutrition at 20-80 days of gestation increases adipose tissue deposition and UCP1 expression, whilst restricted food intake in late gestation results in smaller fat depots with less UCP1.

The apparent sensitivity of adipose tissue growth to both increased and decreased maternal nutrition may not only have consequences in the peripartum period, but could persist into later life. MM
(See the full article in Journal of Endocrinology 179(3), December 2003)

GLUT4 key to diabetic heart disease

The cardiac pathology associated with diabetes may result from a difference in nutrient supply to the heart, leading to changes in cardiac morphology. In this study, Kaczmarczyk and colleagues have investigated the metabolic and structural consequences for the heart of a decrease in glucose transporter-4 (GLUT4).

Using the CreLoxP system, murine GLUT4 expression was reduced to 15-30% of wild type levels, or to almost undetectable levels in the heart tissue of mice that also expressed Cre recombinase. These differences in GLUT4 expression allowed the authors to study the threshold at which GLUT4 levels have a phenotypically detectable effect on the heart. Cardiac glucose uptake and the development of hypertrophy were examined. Glucose uptake was normal in mice expressing 15% of normal GLUT4 levels, but reduced drastically in mice exhibiting only slightly lower GLUT4 levels. It was also found that as little as 5% of the normal GLUT4 levels were sufficient to prevent cardiac hypertrophy, a finding that is potentially of great significance to diabetic patients suffering from cardiac abnormalities. NG
(See the full article in Journal of Molecular Endocrinology 31(3), December 2003)

ER corepressors in breast cancer

The role of oestrogen receptor (ER) corepressors in breast cancer comes under review in this article by Dobrzycka and co-workers. The authors support the hypothesis that corepressors are crucial regulators of ERα-mediated action, and that their absence may promote the development of breast cancer and resistance to endocrine therapy.

Presenting evidence from tissue culture, animal and clinical studies, they propose that ERα corepressors control the magnitude of the oestrogen response, mediate antioestrogen inhibition of ERα, repress DNA-bound ERα in the absence of the ligand, and confer active repression of ERα-downregulated genes. They give a comprehensive overview of the mechanisms by which corepressors may act, including formation of multiprotein complexes that affect transcription, competition with coactivators, interference with DNA binding and ERα homodimerisation, alteration of ERα stability, sequestration of ERα in the cytoplasm, and effects on RNA processing.

ERα signalling pathways are much more complex than was once thought, and the ERα repressor proteins may have diverse functions, such as a role in DNA repair. Further research is essential if our knowledge of ERα repressors is to lead to improvements in breast cancer therapy. NG
(See the full article in Endocrine-Related Cancer 10(4), December 2003)
Meeting of the European Neuroendocrine Association
Sorrento, Italy, 24-27 April 2004
Contact: Stefano Acarrosa, MCM Congressi,
Rome Sirignano 5, 80121 Napoli, Italy (Tel: +39-081-6687747/6611085; Fax: +39-081-6643722; Email: info@enea2004.it; Web: www.enea2004.it).
47ème Journées Internationales d’Endocrinologie Clinique
Paris, France, 20-30 April 2004
Contact: Dr G Copinschi (Fax: +32-2-5562309; Email: klotz@bulh.ac.be).
Royal College of Physicians (North West) Endocrine Meeting
Manchester, UK, 6-7 May 2004
Contact: Janece Norton (+44-151-4301912; Fax: +44-151-4301000).
2nd International Congress on Adult Consequences of Childhood Endocrine Diseases
Athens, Greece, 6-8 May 2004
Contact: Prof G E Krassa, Department of Endocrinology and Metabolism, Panagia Hospital, N Plastira 22, N Kriti 53132, Thessaloniki, Greece (Tel: +30-2310-447444; Email: krassas@he.forthnet.gr; Web: www.ghclin.org).
EFES Regional Postgraduate Course in Clinical Endocrinology
Wrocław, Poland, 7-9 May 2004
Contact: Prof Andrzej Milewicz, Department of Endocrinology and Diabetology, Wrocław University of Medicine, Pasteura 4, PL-56-367 Wrocław, Poland (Tel: +48-71-3209603; Fax: +48-71-3282349; Email: milewicz@endo.am.wroc.pl).
10th Workshop on Cell Biology of Bone and Cartilage in Health and Disease
Contact: Tim Soper, MRC Laboratory of Molecular Biology, University of Cambridge, Hills Road, Cambridge, CB2 1QH, UK (Tel: +44-1223-336520; Fax: +44-1223-336521).
11th Annual Meeting of the Psychoneuroimmunology Research Society
Tübingen, Germany, 20-29 May 2004
Contact: Congress Secretaries (Email: info@oenfoud.com; Web: www.oenfoud.org).
IOF World Congress on Osteoporosis
Rio de Janeiro, Brazil, 14-18 May 2004
Contact: Congress Secretarial (Email: info@iofed.org; Web: www.iofed.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@ic.sdu.dk; Web: www.repro2004.ics.dk).
ENDO 2004: 66th Annual Meeting of the Endocrine Society
New Orleans, LA, USA, 16-19 June 2004
Contact: Beverly Glover, Administrative Assistant, Meetings, The Endocrine Society, 8401 Connecticut Avenue, Suite 930, Chevy Chase, MD 20815-3817, USA (Tel: +1-301-9410220; Fax: +1-301-9410299; Email: hglover@endo-society.org; Web: www.endo-society.org).
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Have you wondered how your endocrine service compares with services in other centres?

If the answer to one or more of these questions is YES, you may be interested in volunteering your centre for the Society's new Peer Review Visitation Scheme. The scheme's main aim is to improve services for endocrine patients. It is hoped that all UK endocrine centres will become involved in due course.

VISITS
Two reviewers from different areas of the country will undertake each visit, one from a teaching centre and the other from a district general hospital (DGH). The visit will take 2 days, the first of which will be spent in the teaching centre and the second in one of the "linked" DGHs. Each visit will:
- be on a voluntary basis
- aim to support endocrinologists in the various centres
- focus on basic standards for endocrine care and service provision
- facilitate an exchange of ideas and experiences
- allow areas of concern to be voiced
- be summarised in a report

REPORTS
The visit report should provide 'levers for improvement' (e.g. highlighting needs for consultant expansion, specialist nurse provision, etc) and assist in negotiations with management. The report will also provide useful information for clinical governance and consultant revalidation purposes. The visit documentation is currently being finalised and will be made available on the Society's web site.

PILOTS
The Clinical Endocrinology Trust has generously provided a grant to cover the expenses of the early pilot visits. If you would like your centre to be considered for one of the two pilot visits in the first quarter of 2004, or if you would like to gain experience as a reviewer, please contact John Bevan (details opposite).

BACKGROUND
The Society's Clinical Committee endorsed the idea of peer review of UK endocrine units in 2001, and the first visit (to Sheffield) took place at the end of 2002. The British Thoracic Society has been operating peer review visits for over 10 years, and the scheme is widely regarded to be highly beneficial to both the centres visited and to the reviewers themselves.