COMMENTARY

Endocrinology: the next 60 years

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Abstract

Advances in clinical chemistry, molecular biology and information technology have brought about major changes in the field of endocrinology. The future practice of endocrinology will be influenced by secular health trends, consumer expectations and the globalisation of health. Pharmacotherapy will remain the backbone of endocrine therapy led by developments in drug delivery technology, pharmacogenomics, combinatorial chemistry and

paracrinology. The endocrine-related consequences of obesity and ageing will be major health problems, demand for anti-obesity and anti-ageing treatments will escalate. There will be increased blurring between endocrine disease and non-disease. The future clinical endocrinologist must continue to practice evidence-based medicine to improve the treatment of genuine endocrinopathies.

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Introduction

The founding of the Society for Endocrinology 60 years ago marked the beginning of the specialty field of hormones and chemical messengers. This was the period of steroid biochemistry and bioassays. The field has metamorphosed; major changes have occurred from applications of advances in other fields. The development of immunological, receptor-binding and phosphorylation assays consolidated the principles of endocrinology, providing the means of identifying and quantifying hormone status and action. The tenets of hormone deficiency, excess and resistance belong to this era. Endocrinology continues to be one of the most dynamic disciplines in biomedical science and among the most quantitative of the specialties in which the marriage of clinical and basic science is very strong (Wilson 2005).

This period also began with the discovery of the genetic code, heralding the dawn of molecular biology and culminating in the sequencing of the human genome 50 years later. The molecular revolution has led to the discovery of new receptors, signalling molecules and chemical messengers acting within complex networks. The new insights gained from studying the molecular basis of hormone action and interactions have already changed, and will continue to change, concepts of disease causation and treatment. The last few decades have also seen an evolution in information technology, knowledge engineering and

bioinformatics, advances that have catalysed the development of high-throughput technology, expanding the databases of catalogued knowledge for biomedical research. These advances will have an unstoppable impact across all fields of medicine.

How will these advances impact on clinical endocrinology in the next 60 years? In this review, I will confine my crystal ball gazing to the pituitary and metabolic areas. The practice of endocrinology will be influenced by secular health trends, demographics and consumer expectations. I will foreshadow major health issues confronting the clinical endocrinologist, new treatments and changes in the landscape of endocrine practice.

The next 60 years

Secular trends

The world is getting older. Life expectancy at 65 years increased from 12 years by more than 50% over the 20th century and this trend is continuing. According to the World Health Organization, the numbers over 60 years of age will increase from 600 million in 2000 to 1.2 billion in 2025 and 2 billion in 2050 with the greater increase occurring in the developing world (WHO 2006). In the US, the population older than 65 years increased from 12 million in 1950 to 26 million in 2004 and there will be a further 50% increase by 2050 (National Center for Health Statistics 2005).

The world is also getting fatter. At present, obesity ranks fourth as a major cause of morbidity and mortality by death-and-disability adjusted life years (Powles & Day 2002). Many leading journals have pointed out the pandemic in obesity, which is fuelling the alarming increase in the prevalence of metabolic syndrome and diabetes, both in the developed and developing world (McLellan 2002, Hedley *et al.* 2004, Yanovski 2005). The East is also catching up. A recent survey in China indicates that approximately 30% of the population are overweight and that 9·8% of men and 17·8% of women have metabolic syndrome (Gu *et al.* 2005), a problem that may well get worse.

These demographic trends have clear implications for the endocrinologist. First, there is a predictable escalation in the societal burden of diabetes and associated micro- and cardiovascular diseases and the associated challenge of controlling these. Secondly, the endocrinological management of ageing will be an even bigger area. There will be strong demands in the traditional areas of hormone replacement and osteoporosis, albeit with newer drug formulations and approaches. However, endocrine care of the aged will be increasingly blurred by endocrine treatment for ageing.

Consumer trends

The rejuvenists are of course going back to the future, driven by consumer demand for eternal vigour and youth. There will be increasing exploitation of the psychology of dissatisfaction and the promise of hormones to fix the woes of an unhealthy lifestyle or an unfulfilled life (Lamberts *et al.* 2003). The present day net-wise consumers are expert patients (Tattersall 2002); their wireless descendants will be more expert. They know that hormones control growth, metabolism, fat, muscle, weight, mood and sexual function; when these are not right, they expect endocrinology to provide the solutions. A quick surf of the World Wide Web reveals over 2 million sites for growth hormone (GH) and over 1.2 million sites for dehydroepiandrosterone use for anti-ageing therapy. These are only a fraction of the field of 'cosmetic endocrinology', which promises to offer much more.

Therapy of endocrine disease

What about mainstream endocrinology? Following the sequencing of the human genome, the complex path from genotype to phenotype will have been largely paved (Strohman 2002). The new era will bring novel solutions to the present problems from drug-delivery technologies, combinatorial chemistry, pharmacogenomics, gene regulation and manipulation.

Pharmacotherapy will continue to be the backbone of endocrine treatment. Time-regulated formulations of steroid hormones will have replaced the clumsy regimens of the past (Romijn *et al.* 2003), allowing the endocrinologist to practise truly physiological hormone replacement therapy (HRT). Twenty-four-hour formulations of hydrocortisone for

normal and stress situations will be available. Thirty-day formulations of female hormones for HRT and higher dose preparations for contraception will be the preferred alternatives to the oral preparations of the 20th century.

Pharmacogenomics will come of age and will have a major impact across all endocrine-based therapies. Genetic variations that affect the responses to hormones and drugs and their disposition within the complex endocrine network of the body will be characterised (Wilke *et al.* 2005). At the patient level, this will bring rationalisation and individualisation of therapy, achieving optimal response with minimal side effects. Women can be identified for safe treatment with oestrogens, the hypoadrenal patient prescribed accurate dosage of steroid with confidence and the susceptible diabetic patient identified for preventative treatment against renal disease.

Combinatorial chemistry will bring treatment selectivity, versatility and convenience. It will exploit knowledge gained from understanding how closely related hormones act on similar classes of receptors to exert a range of effects. Somatostatin receptor subtypes have already been shown to exert differential effects on secretion and cell proliferation in the pituitary (Shimon *et al.* 1997, Zatelli *et al.* 2004). In the hypothalamus, a family of YY peptides interact with different Y receptor subtypes with overlapping and distinct functions regulating appetite, energy homeostasis, behaviour and reproduction (Lin *et al.* 2004). Synthetic compounds selective for particular receptor subtypes will be available to target treatment of selected tissues for different effects. Small non-peptide oral mimetics will begin to replace insulin, GH, gonadotrophins and parathyroid hormone and revolutionise the treatment of many endocrine diseases.

This era will also see the maturation of paracrinology, the science of fine-tuning hormone requirements at the tissue level brought about by drugs regulating prohormone conversion to, or inactivation of, active hormone. Tissue specific regulators of deiodinase, aromatase, 11 β -hydroxysteroid dehydrogenase (HSD) and 5 α -reductase activities will emerge. Cardiac function in the severe hypothyroid patient with coronary artery disease will be protected by cardiac-specific 3'-deiodinase inhibitors during thyroid hormone replacement. Tissue-specific 11 β -HSD inhibitors will be available to protect against the catabolic, adipogenic and diabetogenic effects of chronic hydrocortisone and prednisolone treatment.

In the battle against obesity, several classes of centrally acting drugs controlling hypothalamic function will have been developed. The major appetite-regulating pathways and those regulating basal energy expenditure will have been elucidated, with ligands and receptors identified. Chimeric compounds harbouring multiple properties are under active development.

The global health system and the endocrine patient

The next 60 years will bring about a 'googlelisation' of health with establishment of a Global HealthNet, evolved

from the rudimentary beginnings of eHealth (Wyatt & Sullivan 2005). The traditional boundaries of personal health information available only to the practitioner or local institution will have long disappeared. A global Cybernet repository of medical knowledge from drug and patient trials will be available. There will be parallel platform systems, public and private, holding vast information on millions of people with enabling bioinformatics technology to guide treatment based on the patient's health profile. Patients will be empowered and carry health information on a chip. Access to these global health information systems will be variable depending on public or private health subscription. Personalised genome screening will be realised but at a cost. Genome-system screening will have been established to provide a profile of risks for various body systems. Combined with proteomics, these technologies will define a whole range of risk and outcomes from which therapeutic decisions will be made.

What does this mean for the patient with endocrine disease? There will be individualisation of hormone replacement needs, tailored approaches to the therapy of functional endocrine tumours and endocrine cancers. The appropriate dose of glucocorticoid will no longer be a guesstimate, HRT will be safely prescribed based on personalised genomics.

In the area of endocrine-disease prevention, it is envisaged that more effective management will emerge from an approach combining risk identification, lifestyle and therapeutic intervention. In the area of obesity, the energy homeostatic regulating pathways will have been elucidated, with ligands and receptors identified. A polypharmacy approach will combine the use of anti-orexigenic (e.g. leptin analogues, neuropeptide Y antagonists) (Lin *et al.* 2004) and anorectic (e.g. melanocortin receptor agonists and cannabinoid receptor antagonists) agents (Ellacott & Cone 2004, Despres *et al.* 2005) with new classes of olfactory receptor modulators, which remove pleasant taste from food. There will have been successful development of safe agents that enhance basal energy expenditure by activating brown fat development and activity. Their introduction into the clinic will result in a downturn in the prevalence of obesity and diabetes midway through the 21st century, at least in the Western world.

Cosmetic endocrinology will flourish under the guise of improving health. Unscrupulous health clinics will provide gene profiling and gene modification therapies for longevity and improved satisfaction with life. They will offer a slippery cocktail of myth and fact, as has been occurring through the history of medicine. There will be therapies to slow down the genetic clock or to correct gene profiles destined for short stature, flabbiness, hirsutism, baldness or hyposexuality. The realm of re-tuning one's glands in search of an elusive health will be a zillion dollar industry.

Summary

There are exciting times ahead in endocrinology, as are occurring across all fields of medicine, with an increasing blurring between disease and 'non-disease' (Smith 2002). There are genuine challenges ahead to win the battle against obesity and diabetes, and to manage the consequences of frailty in a progressively aged society. To protect the charter of endocrinology, we must not confuse our goal to improve the treatment of genuine endocrinopathy with the medicalisation of the problems of life and lifestyle. The practice of evidence-based medicine must be followed regardless of the degree of technological advancement. The future generation should be reminded that HRT did not improve health-related quality of life, contrary to the predictions several decades earlier (Hays *et al.* 2003).

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