50th St Andrew's Day Festival Symposium: Five decades of medical progress

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ADVANCES IN THE DIAGNOSIS OF ANGINA

Professor Adam Timmis, Professor of Cardiology, The London Chest Clinic

Angina is a symptom of myocardial ischaemia that is usually caused by obstructive coronary artery disease. It is the most common initial manifestation of coronary artery disease and the only manifestation that is not declining substantially in incidence. Diagnosis is important because treatments are available to ameliorate symptoms and improve prognosis. Rapid access chest pain clinics are now available for this purpose in almost every UK hospital, enabling patients with recent onset chest pain to receive prompt specialist attention to confirm the diagnosis and initiate treatment.

In many cases the diagnosis is clear from the history, which allows angina to be confirmed or excluded with confidence without the need for diagnostic testing. However, in ≥50% of cases the diagnosis based on clinical criteria remains uncertain with probability estimates of coronary artery disease ranging from 10–90% depending on typicality of symptoms, risk factor profiles and the age and gender of the patient. In this group diagnostic testing is required, an abnormal test often increasing diagnostic probability to a point that effectively confirms a diagnosis of angina, a negative test allowing its exclusion and consideration of alternative diagnoses.

For more than half a century the preferred diagnostic test in this group of patients has been the exercise electrocardiogram (ECG), but other tests are now available that offer greater diagnostic value and cost-effectiveness, rendering the exercise ECG effectively obsolete for diagnostic purposes in the modern era. These newer tests provide either functional evidence of ischaemia (stress echo, single photon emission computed tomography [CT], magnetic resonance perfusion imaging) or anatomical evidence of coronary artery disease (CT angiography, invasive angiography).

Like all tests, diagnostic value is critically dependent on the likelihood of disease in the population of interest and this has led to recommendations for CT imaging in patients at the lower end and functional imaging at the higher end of diagnostic uncertainty. Indeed, for patients in whom revascularisation is considered appropriate direct referral for invasive angiography is now recognised as being cost-effective. This approach represents a true revolution in diagnostic strategy that turns its back on more than half a century of dependence on the exercise ECG. It will require a fundamental change in the attitudes of clinicians who now need to embrace the exciting potential of current imaging technology, which offers greater diagnostic value and a means of further improving clinical outcomes in patients with recent onset angina.

OUR GENETIC INHERITANCE: A DECADE ON FROM SEQUENCING THE HUMAN GENOME

Professor David Porteous, Head of Section, Medical Genetics, University of Edinburgh

The Human Genome Project (HGP) – unravelling the complete sequence of the human genome – was a collective tour de force of the highest technical and scientific achievement. The HGP held great prospects for improved understanding of the genetic underpinning of human disease, biological mechanisms and potential novel treatment strategies. Ten years on, we can reflect upon what has and what has yet to be achieved by way of decoding the information content of the human genome. This is an altogether more difficult and challenging task than acquiring the sequence in the first place.

By way of notable past recipients of the Ballantyne Prize, I will set out some of the key advances made as a direct consequence of the HGP, and, not insignificantly, the many spin-offs that have accrued. The main focus of the talk will be to survey, albeit superficially, some of the more medically relevant advances, illustrated, at least in part, by our own work at two ends of the genetic spectrum – developing gene therapy for cystic fibrosis, and discovering biological pathways in major mental illness through genetic studies. I will end with some speculations about what to expect over the next decade, as the first products of the HGP mature and move from bench to bedside.

TREATMENT OF RENAL ANAEMIA

Professor Iain Macdougall, Consultant Nephrologist, King's College Hospital, London

The advent of recombinant human erythropoietin in the late 1980s transformed the management of anaemia associated with chronic kidney disease, freeing many dialysis patients from the burden of repeated red cell transfusions, and significantly improving their quality of

life. The early clinical trials reported extremely positive effects in patients whose haemoglobin concentrations were actively increased from around 5–6 g/dl up to around 11–12 g/dl, with a seemingly favourable safety profile. Observational studies suggested that patients with normal haemoglobin concentrations had a much greater survival than patients with haemoglobin concentrations around 9–10 g/dl.

As a result, several randomised controlled trials (RCTs) were initiated to treat the anaemia more aggressively, aiming for complete normalisation of the haemoglobin concentration, with the hypothesis that 'a little was good' and therefore 'a lot must be even better'. These trials adopted hard endpoints, including mortality and cardiovascular events, but, paradoxically, serious concerns about the safety of these products then emerged, with regard to an exacerbation of both arterial and venous thromboembolism at higher haemoglobin concentrations.

The strongest of these RCTs was the TREAT study, published in November 2009, and this double-blind placebo-controlled study suggested a doubling of stroke and venous thromboembolism in the active compared to the placebo arm. Thus, although nephrologists still greatly value having erythropoiesis-stimulating agents available to treat their patients, in recent times they have learned to use these drugs more cautiously, balancing the obvious benefits against potential harm.

RENAL PROTECTION: PREVENTING ACUTE KIDNEY INJURY – THE FUTURE

Dr Andrew Lewington, Consultant Renal Physician, St James's University Hospital, Leeds

Acute kidney injury (AKI) has replaced the term acute renal failure as part of a strategy to raise the awareness of the disease. The new term has been accompanied by newly proposed definitions, which are currently being finalised by the International guideline group, Kidney Disease: Improving Global Outcomes (KDIGO, www.kdigo.org). The development of new definitions of AKI has been supported by an increasing number of publications that have demonstrated the association between small rises in serum creatinine and increased patient morbidity and mortality. The change in terminology and new definitions represent a concerted effort to promote the concept that AKI is a spectrum of injury rather than an absolute failure of the organs. It is hoped that this will prompt healthcare professionals to recognise and respond to the development of AKI at an earlier stage in the spectrum of injury when preventative and management strategies may prove more effective.

Over the past four decades there have been no significant advances in the treatment of AKI and the mainstay of therapy remains supportive care in the form of renal replacement therapy. It is therefore essential to prevent patients developing AKI. Disappointingly, the recent National Confidential Enquiry into Patient Outcome and Death (NCEPOD) reports *Adding insult to injury* and *An age-old problem* demonstrated severe deficiencies in the identification of both medical and surgical patients who are at risk of AKI (www.ncepod.org.uk).

On a more positive note, there has been a growing interest in the identification of new biomarkers for AKI, which may further refine our ability to identify patients at risk. The development of this technology may allow more precise targeting of therapeutic agents at an earlier stage in the disease process.

50 YEARS OF VENTILATION: FROM ITU TO THE HOME

Dr Ian Grant, Consultant Physician, Home Ventilation Service, Western General Hospital, Edinburgh

It is more than 50 years since the 1952 Copenhagen poliomyelitis outbreak, during which mechanical ventilation of the lungs was first introduced as a life-saving therapy. Over subsequent years the technology of ventilation has developed hugely, and a distinct specialty of intensive care medicine has consequently emerged.

While survival benefit from ventilation was self-evident, ventilation also allowed the emergence of new medical syndromes such as acute respiratory distress syndrome (ARDS) and multiple organ dysfunction and failure (MODS, MOF). Complications of ventilation also emerged: ventilation-induced lung injury and ventilation-associated pneumonia.

Observations that over-vigorous ventilation worsened outcome from ARDS prompted a large multicentre RCT (ARDSnet), which demonstrated a survival benefit for low tidal volume ventilation in ARDS, and the concept of lung protective ventilation was born. New forms of ventilation such as high frequency oscillation and extracorporeal gas exchange have been introduced, but absolute proof of efficacy is arguably still lacking.

The problem of ventilator-associated pneumonia has prompted a move away from invasive to non-invasive ventilation (NIV) in a number of situations, a move aided by the development of the bi-level ventilator. Use of bi-level ventilation via a facemask or nasal interface is now proven as effective therapy in acute type II respiratory failure due to chronic obstructive pulmonary disease (COPD) or neuromuscular disease, and in weaning from invasive ventilation. Continuous positive airway pressure/NIV also has a role in critically ill immunocompromised patients in managing hypoxic respiratory failure.

Long-term, usually nocturnal, use of NIV has led to home ventilation for patients with chronic respiratory failure secondary to neuromuscular disease, chest wall restrictive disorders and, controversially, COPD. Survival in Duchenne muscular dystrophy and motor neuron disease patients is prolonged with good quality of life.

50 YEARS OF PNEUMONIA: CAN WE IMPROVE PREVENTION AND TREATMENT?

Dr Stephen Gordon, Reader in Tropical Respiratory Medicine, Liverpool School of Tropical Medicine

Pneumonia is common and satisfying to diagnose. The causes of pneumonia today are much as they were in 1960, but the population profile of the patients has changed. In the UK, hospital admission rates for community-acquired pneumonia and the age of inpatients are rising, but globally the burden of disease falls on children and adults with HIV. Each year, pneumonia kills more children under five years of age than HIV, tuberculosis and malaria combined.

The past 50 years have seen radical change in pneumonia vaccination success and there is potential for major advances in the near future. In particular, conjugate vaccination has transformed the epidemiology of pneumococcal disease in many parts of the world and protein vaccination offers further potential.

Treatment in the past 50 years has not enjoyed the same success – we still lack diagnostic precision and have weathered a storm of antibiotic-related complications as a result of widespread use of broad-spectrum antibiotics. The next 50 years offer considerable promise in diagnostic precision, targeted antibiotic therapy and adjunctive treatment, but these developments have not yet arrived.

Important clinical and basic research opportunities exist in the study of pneumonia that are relevant both to UK practice and global health.

50 YEARS OF END-OF-LIFE CARE

Professor Scott Murray, St Columba's Hospice Chair of Primary Palliative Care, University of Edinburgh

> 'A society which shuns the dying must have an incomplete philosophy'
> – Dame Cicely Saunders, 1961

The modern hospice movement dates back to 1967 when Cicely Saunders founded St Christopher's Hospice in London. St Columba's Hospice, led by Dr Derek Doyle, FRCP Edin, followed ten years later in Edinburgh. In 1974 Professor Balfour Mount in Montreal coined the term 'palliative care'. In 1987 palliative medicine was recognised as a specialty in the UK and the first UK journal in this field was launched. There are now more than 200 hospices, over 350 hospitals with palliative care services and many community support and day care teams throughout the UK.

Palliative medicine is now recognised as a medical specialty in over 20 countries, and palliative care has grown internationally. Dr Anne Merriman OBE, FRCP Edin, has been central to the development of palliative care throughout Africa and currently leads Hospice Africa's international programmes.

Palliative care specialists in 2010 are now working with hospital and primary care clinicians to address five important challenges facing palliative care:

1. To be available for people with all progressive life-limiting illnesses according to need, not by diagnosis or indeed prognosis;
2. To be considered at diagnosis of a life-limiting illness rather than only in the terminal stages;
3. To meet all dimensions of need, including emotional and existential distress;
4. To be available in all care settings, delivered by hospital and primary care staff; and
5. To reach less economically developed countries.[1–3]

Palliative care has come of age at a crucial time to help our patients with life-threatening illnesses live and, in due course, die well.

References

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FROM APOPLEXY TO BRAIN ATTACK VIA STROKE AND CVA

Dr John Bamford, Consultant Neurologist and Cerebrovascular Physician, Leeds General Infirmary

There are few areas of medicine where, in the past few years, the therapeutic pendulum has swung so dramatically from nihilism to enthusiasm as stroke medicine. This has not occurred because of the discovery of a single 'golden bullet', although many advances have been underpinned by the ability to image the brain in vivo that came with CT and magnetic resonance imaging.

The early, enthusiastic involvement in academic clinical trials, particularly in the UK, provided a robust evidence base that has transformed the patient journey, with the substantial benefits of stroke unit care, in particular, prompting major organisational change throughout the NHS. In turn, stroke units have provided a platform for

increased involvement in research across the whole stroke pathway despite a relative paucity of research funding.

Both apoplexy and brain attack emphasise the sudden, unpredictable and potentially serious nature of the condition. However, the brain attack era has a treatment of proven benefit in thrombolysis, with the greatest potential benefit accruing the earlier treatment is started. Sceptics doubted that the public and professionals (and particularly neurologists!) would react quickly enough for thrombolysis to add anything other than marginal benefit, but the recent experience in London appears to disprove this.

In the immediate future we need to ensure equitable access to established treatments, perhaps using technologies such as telemedicine. There will also be increased interest in targeting therapies to those patients most likely to benefit. High-profile interventions such as intra-arterial therapy need to be properly evaluated and there are still many unanswered, yet fundamental, questions about early management which need to be addressed.

DOING ACUTE NEUROLOGY BETTER... AND BETTER

Dr Ed Dunn, Consultant Neurologist, Leeds Teaching Hospitals

Traditional neurology services have often revolved around the 'ivory tower' approach. If presenting acutely to hospital with a neurological problem, a neurologist might only be involved some days or weeks later. The acute liaison neurology model puts the neurology specialist close to the 'front door' on the acute medical unit, with significant improvements for the patient in terms of time to diagnosis and treatment. The model makes financial sense for Leeds Teaching Hospitals as well, since the savings through reduction in length of stay are considerable.

Before the post was introduced in 2004, the median length of stay for such patients in acute medicine was eight days. In 2005 this was halved to four days and by 2009 halved again to just two days. Patterns of referrals have also changed over this period, suggesting that the quality of care on the acute medical unit has improved through the experience of working up similar patients in the past. Supporting this inpatient service are fast-track outpatient services, which again allow earlier discharge in the knowledge that patients will get specialist input within a fortnight. Despite the innovative delivery, the traditional bedside skills of history and examination underpin the success of the service rather than tests – as was the case for the neurologist of 50 years ago.

FROM SALK AND SABINE TO SWINE FLU: 50 YEARS OF MASS VACCINATION

Dr Philip Minor, Head of Virology, National Institute for Biological Standards and Control, Potters Bar

In 1960, vaccines against whooping cough had only just been introduced, smallpox had not been eradicated and the range of vaccines now available was undreamt of. It is possible that the presence of such diseases meant that there was not today's sensitivity to adverse events, real or imagined. The beneficial effect of vaccines is demonstrable at the level of public health surveillance but philosophically impossible to demonstrate for an individual patient. The possible effects of vaccination are well illustrated by the polio eradictaion initiative of the World Health Organization, which has all but eliminated the disease from the world, although it poses interesting problems for the end game. On the other hand, the nature of the influenza virus makes vaccination a more frantic and reactive effort, as was illustrated in the pandemic events of 2009/2010.