SQU Med J, August 2010, Vol. 10, Iss. 2, pp. 287-295, Epub. 19th Jun 10

Advanced General Medicine Conference

Joint Conference of the Royal College of Physicians UK, Ministry of Health, Oman and Sultan Qaboos University

20th - 23rd February 2010

مؤتمر الطب العام المتقدم

مؤتمر مشترك بين كلية الجراحين الملكية البريطانية ووزارة الصحة العمانية وجامعة السلطان قابوس

20 – 23 فبراير 2010

Recent Advances in Chronic Obstructive Pulmonary Disease (COPD)

Prof. Peter MA Calverley

School of Clinical Sciences, University of Liverpool, UK. Email: pmacal@liverpool.ac.uk

The last decade has seen major changes in our understanding of the clinical importance, causes and treatment of COPD. Systematic epidemiological studies, such as the Burden of Obstructive Lung Disease (BOLD) study, have shown that the prevalence of this disease is around 9% of adults and is much commoner in developing countries than expected. Persistent inflammation secondary to oxidative stress and corticosteroid resistance seem to drive both airway thickening, fibrosis and contribute to emphysema. Reliance on a fixed forced expired volume (FEV) 1/ forced vital capacity (FVC) ratio may lead to misdiagnosis in some circumstances while bronchodilator responsiveness is not a feature of stable COPD. COPD persists even after smoking cessation, but a long-acting inhaled bronchodilator, if combined with inhaled corticosteroids, reduces exacerbation numbers, improves health status and probably decreases the decline in lung function and the risk of dying from COPD. Systemic problems often accompany advanced COPD which increases the risk of lung cancer cardiovascular disease and osteoporosis irrespective of background treatment. Exacerbations often cluster in periods of disease instability and are driven by a range of viral and bacterial pathogens, persistent lower respiratory tract colonisation being particularly important. Respiratory failure can be managed more effectively with non-invasive ventilation (NIV), but preventing the development of severe disease is the major public health goal and will require earlier intervention in at risk populations if we are to move forward from simply managing advanced symptomatic COPD.

Asthma Management: The Guidelines–Practice Gap

Dr. Omar Al-Rawas

Department of Medicine, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman. Email: orawas@squ.edu.om

Asthma is a major global public health problem. In recent years, a large number of national and international asthma management guidelines have been published and disseminated. However, there is evidence that health care providers have not widely adhered to these guidelines. This poor adherence to guidelines appears to be universal and span the spectrum of physicians in public and private practice as well as in teaching and tertiary referral hospitals. The problem is compounded by poor patient compliance. As a result of these factors, many asthma patients receive inadequate care and have poor asthma control. The available data indicate a need for further educational programmes directed at both physicians and patients to utilise better the available and effective therapies. Since guidelines can contribute to improved care only if they succeed in moving actual practice closer to the recommended norm, an expanded asthma management programme that provides feedback to physicians on their compliance with asthma guidelines and its impact on asthma control may help improve implementation of the guidelines and better asthma control.

Management of Interstitial Lung Disease (ILD)

Prof. Athol Wells

Royal Brompton Hospital, London, UK. Email: a.walls@imperial.ac.uk

The primary conceptual problem in the management of ILD is the fact that there is a multiplicity of individual disorders, but only a handful of management strategies. The art of managing ILD is to classify patient presentations to fit with available treatment approaches. Therefore, ILD needs to be classed broadly as: a) self-limited inflammation; b) major inflammation with progression to fibrosis; c) stable fibrotic disease; d) insidiously progressive fibrosis (with stabilisation a realistic goal); and e) inexorably progressive fibrosis. This pragmatic classification can be achieved with knowledge of: 1) likely cause, if any; 2) CT/biopsy findings; 3) quantification of disease

severity, and 4) evaluation of disease behaviour with time. Based on this classification, management distinctions can be made between: a) observation; b) high dose therapy to reverse inflammation, followed by longer term low dose therapy to preserve gains; c) long-term low dose therapy from the outset with the realistic hope of preventing progression; d) long-term low dose therapy in the hope of slowing progression, and e) best palliative care in end-stage disease. The aim of this presentation is to demonstrate that with a minimum of readily obtainable information, it is possible to move from diagnostic uncertainty to confident pragmatic management in ILD, using terminology that is immediately understood by the patient, family and referring physician.

Primary and Secondary Prevention of Cardiovascular Disease

Prof. David Wood

National Heart and Lung Institute, Imperial College, London, UK. Email: d.wood@imperial.ac.uk

The WHO and Joint European Societies guidance on prevention of cardiovascular disease (CVD) in clinical practice recommends a common approach to lifestyle and risk factor intervention for patients with established atherosclerotic CVD and high risk persons in the population. This is based on the concept of total risk assessment and management first advocated in the Joint European recommendations on coronary prevention in 1994. The most recent report by the Joint European Societies, published in 2007, now addresses cardiovascular disease as a whole. The clinical priorities are: 1) patients with established atherosclerotic disease; 2) asymptomatic individuals who are at high risk of developing atherosclerotic disease because of a) multiple risk factors resulting in a ten year risk of >5% now or, if extrapolated to age 60, for developing a fatal CVD event; b) markedly raised levels of single risk factors; c) diabetes mellitus, and 3) close relatives of patients with early onset atherosclerotic disease and asymptomatic individuals at particularly high risk. A new model for total risk estimation called SCORE (Systematic Coronary Risk Estimation), based on European populations, is recommended and can be adapted to correspond with national CVD mortality in any European country. The risk threshold for more intensive lifestyle intervention and, where appropriate, the use of drug therapies, is now defined as ≥5% fatal CVD risk over 10 years. Lifestyle, risk factor and therapeutic goals have been set for all priority patient groups. The most recent results from EUROASPIRE III show a continuing large gap between the professional standards set by guidelines and everyday clinical practice for both coronary patients and individuals at high risk of developing the disease in primary care. The EUROACTION demonstration project in preventive cardiology has stepped up to this professional challenge through a nurse coordinated multidisciplinary prevention programme which has set a new standard of preventive care for Europe.

Secondary Hypertension: Investigation and Management

Prof. Nicholas JY Woodhouse

Department of Medicine, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman. Email: nickwood2@doctors.org.uk

Primary or essential hypertension (HTN) affects approximately 25% of the adult population worldwide and is a leading cause of mortality and morbidity. Frequently, two or more medications are required to achieve good blood pressure (BP) control and the financial costs to government are huge. Secondary hypertension, on the other hand, is potentially curable often without the need for lifelong medications. Patients should therefore be carefully screened to exclude treatable causes. In the literature, secondary disease is quoted as being 5% of the total hypertensive population, but the worldwide massive increase in obesity, together with more accurate data on the prevalence of primary hyperaldosteronism (PA) indicates that the total percentage is likely to be closer to 20%. The obesity epidemic has result in progressively more cases of the metabolic syndrome with its attendant dyslipidemia insulin resistance, type 2 diabetes (T2DM), obstructive sleep apnoea (OSA) and systemic HTN. This effect is compound by a parallel increase in alcohol consumption which on its own can produce persistent disease. In Oman, end stage renal disease (ESRD) requiring dialysis is estimated to increase by 10% annually again as a result of the increasing incidence of T2DM. At the present time, roughly 800 patients are undergoing dialysis and a similar number have had renal transplants. Endocrine causes of secondary HTN are rare, except in the case of primary aldosteronism which is found in 14% of the general UK hypertensive population and two-thirds of all hypertensive Omanis who have a positive family history of the disease. A careful family history and physical examination will give clues to the diagnosis in many patients. The remainder will require electrolyte, bone profile, hormonal studies and renal vascular imaging studies. In this brief review, we will illustrate these points with clinical examples and touch on new treatment options.

REFERENCES

1. Hood S, Cannon J, Foo R and Brown M. Prevalence of primary hyperaldosteronism assessed by aldosterone renin ratio and spironolactone testing. Clin Med 2005; 5:55–60.
2. Woodhouse NJY, El-Shafie OT, Ben Abid F, Doi S. Familial mineralocorticoid induced hypertension in the Sultanate of Oman. SQU Med J 2008; 8:165–9.
3. Aditga BS, Wilding JPH. Modern management of obesity. Clin Med 2009; 9:617–21.

Management of Stroke

Peter Langhorne

Prof. of Stroke Care, University of Glasgow, Scotland, UK. Email: P.Langhorne@clinmed.gla.ac.uk

The last decade has seen dramatic changes in our understanding of the management of stroke. This presentation will encompass recent developments in acute assessment and diagnosis, acute medical management, general (stroke unit) management, rehabilitation and secondary prevention. *Acute assessment and diagnosis*: One of the key changes in the public perception of stroke is the increased recognition of stroke as a medical emergency. This has encompassed developments to enhance the early recognition and diagnosis of acute stroke and transient ischaemic attack (TIA) patients together with the rapid triage for appropriate management. *Acute medical*

management: The main recent development has been the increased use of thrombolytic therapy in the form of recombinant tPA. Recent trials have supported an expansion of the time window and the challenge now is to make this available to all eligible patients. *General (Stroke Unit) Management*: Although the concept of stroke unit care is well established, many countries have recently made efforts to ensure that all stroke patients can access such care. The potential health gains from patients accessing appropriate stroke unit care are substantial. *Rehabilitation:* Substantial developments are taking place in our understanding of rehabilitation although research lags behind some other aspects of stroke management. Alternative models of rehabilitation (such as early supported discharge) are now becoming well established. *Secondary prevention:* This area of stroke management has been marked by two key themes: first, the recognition of the high risk of early recurrence after TIA or minor stroke; second, the establishment of a wide battery of effective secondary prevention measures including dual antiplatelet therapy, anticoagulation, early carotid endartorectomy, statin therapy and active blood pressure management. The presentation will include an assessment of the potential impact of the different strategies for managing strokes and the potential value at a public health level.

Management Issues for Women with Epilepsy

Dr Abdullah Al-Asmi

Department of Medicine, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman. Email: aalasmi@gmail.com

Epilepsy is a chronic neurological disorder which presents with various syndromes and different aetiologies. It is estimated that more than one million women and girls in the USA are suffering from seizure disorders. There are a number of management issues related to epilepsy and women, especially in the childbearing age group. The menstrual cycle with its hormonal changes may affect seizure frequency. Catamenial epilepsy is defined as increased seizure related to the menstrual cycle, likely due to hormonal changes. Hormonal manipulation may significantly reduce such seizures. Oral contraceptive pills (OCP) may interfere with antiepileptic drugs (AEDs) and vice versa. Selection of the appropriate OCP for these women is essential. In addition, women should be counselled about a slight increase in the potential risk of unplanned pregnancy even though taking OCP. Certain AEDs, e.g. valproate, may cause irregular periods, weight gain and can lead to polycystic ovarian syndrome. Pregnancy can lead to increase in seizure frequency in women with epilepsy. This is due to multiple factors including hormonal factors, changes in the level of AEDs, etc. Planning of pregnancy becomes very important with the aim to use minimum AEDs and as low a dosage as possible. The pregnant woman should be counselled about the potential teratogenic effects of the AEDs even though this is small. Over 90% of babies delivered by women with seizure disorders are healthy and normal. It is noted that many general physicians may advise the patient to stop AEDs during pregnancy fearing the teratogenic effect. This, unfortunately, may lead to increased seizure frequency during pregnancy and unwanted consequences for the mother and the foetus. Almost all AEDs have potential teratogenic side effects. Congenital anomalies are variable and include neural tube defect, and congenital heart diseases. These patients ideally should be followed as high risk pregnancy cases where regular obstetric ultrasounds and blood tests are done. The long term side effects of AEDs on the babies of these women is not well established, therefore it is important to develop and maintain a pregnancy registry at national and international levels. Delivery is a stressful and exhausting event which may precipitate seizures. The postnatal period may lead to increased seizure frequency due also to many factors including poor sleep, and hormonal changes. Also concerns will arise regarding lactation and potential side effects of AEDs on the neonate. In general, lactation is considered safe with special precaution among mothers who are taking benzodiazepines and phenobarbitol or primidone. There are many management issues physicians face when dealing with women who have epilepsy requiring the treating doctors to be well informed about this disease.

Viral Encephalitis

Dr Nick Beeching

Senior Lecturer (Clinical) in Infectious Diseases, Liverpool School of Tropical Medicine, Liverpool, UK. Email: nbeeching@blueyonder.co.uk

Encephalitis, or inflammation of the brain, has many causes and there is an overlap of clinical presentation with bacterial and viral meningitis and a wide variety of encephalopathies caused by metabolic and degenerative conditions, other infections, drugs and alcohol. Infectious causes include the herpes group of viruses, especially herpes simplex virus (HSV) and varicella zoster virus, enteroviruses, bacteria (especially *Listeria*), tuberculosis, and a wide range of geographically based viruses such as rabies, tick-borne encephalitis, Japanese encephalitis virus, Ross River virus and emerging problems such as Nipah virus and the spread of West Nile virus. Non-infectious causes include immune mediated conditions, particularly acute disseminated encephalomyelitis (ADEM), paraneoplastic syndromes and voltage gated potassium channel limbic encephalitis. There is a rising incidence of encephalitis in immunosuppressed individuals, including viral causes e.g. cytomegalovirus (CMV), human herpes virus 6 (HHV6), Eppstein-Barr (EBV) virus infection, subacute encephalitis due to polyoma viruses JC/BK, and parasitic causes e.g. *Toxoplasma gondii*. The medical history should enquire about details of travel, animal exposure and occupation and leisure activities. Incidence rates are typically quoted as 5–10/100,000 per year, and are higher in the young and the elderly. In the UK, there are thought to be about 1.5 hospitalisations per 100,000 per year due to HSV encephalitis. The classical clinical description of a flu-like illness prodrome leading to confusion, headache, fever, seizures and focal neurological signs may be more subtle, and easily confused with neuropsychiatric problems. Common diagnostic and management errors include: attributing fever and confusion to urinary tract or respiratory infection; ignoring subtle mental changes described by relatives; missing a fluctuating fever if temperature is normal at presentation; failure to investigate and manage seizures, and failure to perform adequate neuroimaging and/or lumbar puncture. All patients require neuroimaging, often CT initially for features of raised intracranial pressure followed by MR scans which show more subtle changes, but both may be normal at presentation and require repeating. Lumbar puncture (LB) should be performed unless there are specific contraindications, although the cerebrospinal fluid (CSF) findings overlap with viral and bacterial meningitis and there may be a predominance of CSF neutrophils early in viral encephalitis. Increasingly sensitive polymerase chain reaction (PCR) techniques have largely replaced brain biopsy and antibody detection in viral diagnosis, especially for HSV, varicella zoster virus (VZV), CMV and enteroviruses. HIV testing should be part of the routine workup.

EEG is particularly useful for detection of recurrent subtle seizure activity. Management includes review and control of any underlying predisposing condition, aggressive management of seizures, detection and control of raised intracranial pressure and specific antiviral medication. Empirical antiviral therapy (aciclovir) should be started early, often with antibacterial agents, if there are uncertainties about diagnosis and there are diagnostic delays while waiting for imaging or for opportunity for safe LP. Aciclovir reduces mortality from HSV encephalitis from about 70% to about 20%, but the optimum duration remains unknown (most physicians give 14–21 days). There is reasonable evidence that it should be started within 48 hours. Steroids are frequently used but their role remains unproven, particularly in less severe disease. The use of other immunomodulatory agents, particularly interferons, in most forms of encephalitis remains anecdotal or unproven. Encephalitis has a poor outcome, and two thirds of survivors have neuropsychiatric sequelae and up to 25% have epilepsy. Patients and their families require prolonged support, and the need for chronic care and changes in family dynamics represent a substantial long term burden on them and health services. Patient support groups have an important role in assisting this process. US guidelines have recently been published (Tunkel, *et al.* Clin Inf Dis 2008; 47:303) and should be read together with informal UK guidance (Solomon *et al.* Pract Neurol 2007; 7:288–305). Joint BIS/BAN guidelines are being finalised for consultation in the UK. Performance indicators for clinical audit include adequate use of neuroimaging (or documentation of reasons for omitting it), use of empirical aciclovir and /or antibacterial agents, and targeted use of specific antimicrobials for identified aetiologies. Optimum "door to needle" times for best treatment need to be defined, as does the proportion of patients that should be investigated with CSF PCR.

Diagnosis and Management of Neuroendocrine Tumours (NETs)

Dr. Omayma Elshafie

Department of Medicine, College of Medicine & Health Sciences, Sultan Qaboos Universtiy, Muscat, Oman. Email: omayma0@hotmail.com

Neuoroendocrine (NE) cells are enterchromaffin cells (EC) occupying the epithelial lining of the digestive and respiratory tract and were discovered by Prof. Kulchitsky. The term amine precursor uptake and decarboxylation (APUD) was first coined by Prof. Anthony Pearse to describe their histochemical features. Normally, they are widely distributed in the gut, giving rise to the term the diffuse endocrine system of the gut. Their function includes modulation of peristaltic reflexes and water, electrolyte, mucous and hormone secretion (e.g. 5HT). Octreotide is a somatostatin analogue, which binds mainly to receptor 2 in the cell membrane of the EC. This result is inhibition of hormone production and cell proliferation. As a result labelled octreotide may be used to locate and treat NET. NETs of the gastrointestinal tract were thought to be rare and usually present with symptoms related to the actions of the peptide they secrete. 70% of these carcinoid tumours are present in the digestive system while 30% are in the lung. The carcinoid syndrome only occurs when vasoactive hormones reach the systemic circulation. This invariably means that the tumour has metastasised to the liver. Hormones secreted by the primary tumour into the portal vein are metabolised by the liver and do not cause flushing. Tumours of the pancreas are only 3% of the total. Of these, 50% are insulinomas, 25% gastrinomas, 20% non-functional and 5% PPomas, VIPomas, glucagonomas and somatostatinomas. Pancreatic tumours may form part of the multiple endocrine neoplasia type 1 (MEN 1) syndrome and sometimes secrete a number of other hormones including ACTH, GHRH and PTHrP. Their diagnosis is often delayed and most present with metastatic disease. Earlier diagnosis can be improved by taking good history and confirmed by serum chromogranin A measurements, octreotide scanning and immunohistochemistry. Advances in the treatment of NETS with metastatic disease includes the use of: 1) Sandostatin long acting octreotide (LAR); 2) Octreotide + RAD 001 (mTOR) Inhibitor); 3) Somatostatin receptor targeted radiotherapy. The incidence of NETs appears to be increasing. Early diagnosis is critical to improve survival, but the prognosis of patients with metatastatic disease has improved considerably with new treatment strategies.

REFERENCES

1. Treatment of carcinoid tumors and the carcinoid syndrome. From www.uptodate.com. Accessed Oct 2009.
2. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors. From www.jco.ascopubs.org. Accessed Oct 2009.
3. Ezziddin S, Attassi M, Guhlke S, Ezziddin K, Palmedo H, Reichmann K, et al. Targeted radiotherapy of neuroendocrine tumors using Lu-177-DOTA octreotate with prolonged intervals. J Nucl Med 2007; 48:394.

Chronic Viral Hepatitis B and C Infection

Prof. Humphrey Hodgson, Sheila Sherlock

Chair of Medicine and Director, Centre for Hepatology, Royal Free Hospital; Senior Censor & Vice-President Education & Training, Royal College of Physicians of London, UK. Email: h.hodgson@madsch.ucl.ac.uk

Overview: Chronic viral Hepatitis B and C infections constitute a world health problem numerically far in excess of HIV disease. Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) both predispose to cirrhosis, liver failure and liver cancer, but the rate of progression (infection to cirrhosis), though variable, is slow, and generally at least 10–20 years. Prevalence rates vary geographically depending on both genetic and more importantly environmental (e.g. transmission mode) factors. Current UK figures for each virus are ~0.5% of unselected populations so not dissimilar to published Omani results. However there are at-risk populations, which are different for each virus in the UK, for HBV: origin from high prevalence areas, intravenous drug abuse and promiscuity; for HCV: drug abuse, transfusions prior to 1990s. Importantly, HBV and its complications are preventable by immunisation, pursued as a policy in well over 100 nations. An HCV vaccine is not yet available. *Natural history and treatment of HBV*: The response to HBV infection varies with age and immune status. Most infants become chronic carriers. Most adults have an episode of acute self-limited infection (which is often asymptomatic) but a small proportion (~5%) also becomes chronic carriers. Amongst the childhood-infected, there may be many years of 'tolerance' to the virus with high levels of viral DNA in the blood, but no liver damage. This is then typically followed by an immune attack on viral-infected liver cells (sero-conversion) associated with a change in immune markers in the blood (e-ag+ve to e-ab+ve) during which fibrosis and eventually cirrhosis may result. Treatment strategies vary. Paradoxically, the high viral DNA level (no

liver damage immunotolerant stage) is generally not treated until there is evidence of liver damage with elevated transaminase levels. Treatment options then include either immune activation (interferon therapy for 6–12 months), or direct antiviral drugs probably long term. First generation antiviral drugs lead to high levels of viral resistance (i.e. lamivudine resistance in 40–60% of patients after 4 years); newer generation drugs after 3 years are showing much less resistance (0–2%). With later stage disease, (after seroconversion), if there is active inflammation and high viral DNA levels, the antiviral drugs are the appropriate approach. In general, these strategies do not cure the disease but suppress the virus. The costs of long term therapy are high. *Natural history and treatment of HCV*: Most (>60%) of patients who contract HCV infection become long-term carriers. Anti-HCV antibodies persist in all who are infected, so chronic carriers need to be identified by detecting HCV-RNA in the blood by polymerase chain reaction (PCR) testing. Unlike HBV, successful treatment can cure the patient with chronic HCV, i.e. a sustained viral response (SVR). Treatment involves 6–12 months of pegylated interferon injections (weekly) in combination with daily ribavirin. Different HCV subtypes (genotypes) respond differently. Genotype 1 responds relatively poorly (40% SVR with 48 weeks therapy) whilst Genotype 3 does well (80% after 24 weeks or even shorter periods). Genotype 4 is intermediate. Fatigue, anaemia, depression, thrombocytopaenia and leucopaenia may all limit therapy. General measures in chronic viral liver disease: Liver decompensation requires treatment as it occurs, including consideration for liver transplantation. However in patients who are well with compensated cirrhosis, surveillance for hepatocellular cancer is worthwhile as, if detected early, surgical approaches or local ablation can enhance survival.

Bone as an Endocrine Organ

Prof. Graham Russell

The Botnar Research Centre, Oxford University Institute of Musculoskeletal Sciences, Oxford, UK. Email: graham.russell@ndos.ox.ac.uk

There have been remarkable recent advances in knowledge about skeletal biology and the changes that take place in disease. These are largely the result of discoveries in genetics and cell biology. Skeletal development is programmed by the sequential activation of specific genetic pathways, that culminate in the production of the adult skeleton which is light but strong. Systemic hormones, including the parathyroid hormone (PTH), vitamin D metabolites, and calcitonin, regulate blood calcium levels and contribute to the overall calcium economy of the body. Many other hormones have subtle but important effects on skeletal behaviour and its modelling and remodelling activity. In addition to understanding how osteoblasts form bone, and osteoclasts resorb bone, the important role of osteocytes as mechanosensors is receiving increasing attention. A novel and emerging concept is the notion that bone may itself function as an endocrine organ, not only locally but also systemically. At a local level, the integration of cellular differentiation and function within the microenvironment of bone is under the influence of a large number of cytokines and growth factors. There are several important recently discovered pathways that are involved in osteoblast regulation and osteoblast/osteoclast interactions and some of these are suitable for pharmacological intervention, including the wnt/LRP5 pathway, the ephrin system, and particularly the receptor activator of nuclear kappa beta (RANK) Ligand/RANK/osteoprotegerin (OPG) system. At a systemic level, there is evidence that products of bone cells may have distant endocrine effects. Indeed, osteocytes have their own repetoire of regulatory molecules, including FGF23, which is involved in phosphate metabolism, and sclerostin which is a powerful negative regulator of bone formation. Furthermore there is evidence that osteocalcin, secreted by osteoblasts, may act as a systemic metabolic regulator by controlling insulin secretion, and insulin sensitivity. There are also potential regulatory links between the hypothalamus, the gut, and adipose tissue involving leptins, serotonin, and adipokines. This new knowledge is offering novel opportunities for therapeutic interventions.

REFERENCES

1. Clifford Rosen. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 7th Ed. Washington DC: ASBMR (The American Society for Bone and Mineral Research), 2008.
2. Baron R, Rawadi G. Targeting the Wnt/beta-catenin pathway to regulate bone formation in the adult skeleton. Review. Endocrinology 2007; 148:2635–43.
3. Boyden LM, et al. High bone density due to a mutation in LDL-receptor-related protein N Engl J Med 2002; 346:1513–21.
4. Matsuo K, Irie N. Osteoclast-osteoblast communication. Review. Arch Biochem Biophys 2008; 473:201–9. Epub 2008 Mar 29.
5. Piters E, Boudin E, Van Hul W. Wnt signaling: a win for bone. Review. Arch Biochem Biophys 2008; 473:112–6.
6. Hinoi E, Gao N, Jung DY, Yadav V, Yoshizawa T, Kajimura D, et al. An osteoblast-dependent mechanism contributes to the leptin regulation of insulin secretion. Ann N Y Acad Sci 2009; 1173:E20–30.
7. Yadav VK, Oury F, Suda N, Liu ZW, Gao XB, Confavreux C, et al. A serotonin-dependent mechanism explains the leptin regulation of bone mass, appetite, and energy expenditure. Cell 2009; 138:976–89.
8. Yoshizawa T, Hinoi E, Jung DY, Kajimura D, Ferron M, Seo J, et al. The transcription factor ATF4 regulates glucose metabolism in mice through its expression in osteoblasts. J Clin Invest 2009; 119:2807–17.
9. Ferron M, Karsenty G. The gutsy side of bone. Cell Metab. 2009; 10:7–8.
10. Karsenty G, Kronenberg HM, Settembre C. Genetic control of bone formation. Review. Ann Rev Cell Dev Biol 2009; 25:629–48.

Management of Chronic Kidney Disease

Dr. Dawood Al Riyami

Department of Medicine, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman. Email: alriyamidawood@yahoo.com

All patients with renal disease (whether acute or chronic) should undergo an assessment of renal function by estimating the glomerular filtration rate (GFR). This measurement is used clinically to evaluate the degree of renal impairment. The kidney is able to adapt to damage by increasing the filtration rate in the remaining normal nephrons, a process called adaptive hyperfiltration. As a result, the patient with mild renal insufficiency often has a normal or near-normal serum creatinine concentration. The K/DOQI working group defined chronic kidney disease in adults as: evidence of structural or functional kidney abnormalities (abnormal urinalysis, imaging studies, or histology) that persist for at least three months, with or without a decreased GFR (as defined by a GFR of less than 60 mL/

min per 1.73 m2). Chronic kidney disease (CKD) alone is an independent risk factor for cardiovascular disease. Among patients with CKD, the risk of death, particularly due to cardiovascular disease, is much higher than the risk of eventually requiring dialysis. The presentation covers the general management of CKD which involves: treatment of reversible causes of renal dysfunction; 2) preventing or slowing the progression of renal disease; 3) treatment of the complications of renal dysfunction, and 4) identification and adequate preparation of the patient in whom renal replacement therapy will be required.

Adult Stem Cell Transplantation in Autoimmune Disease

Prof. Alan Tyndall
on behalf of EULAR and EBMT. Email: alan.tyndall@fps-basel.ch

During 1995, informal discussions between members of the scientific committee of the European League Against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT) concerning the potential of haematopoietic stem cell transplantation (HSCT) for the treatment of severe autoimmune disease (AD) resulted in a consensus statement and the commencement of a small phase I/II trial. The mission statement of the working group was and remains "to show through prospective, randomised controlled trials (RCT) the place, if any, of HSCT in the treatment of severe AD." A secondary aim is to increase the understanding of AD onset and persistence through mechanistic scientific side-studies. Twelve years later, over 1,000 patients in Europe have received an HSCT (mostly autologous) for treatment of a severe AD, with around one third having improved significantly. In some, a durable clinical and serological remission has been observed, including normalisation of tissue changes in scleroderma and loss of autoimmune memory in SLE. In others, the treatment resulted in death, treatment related mortality (TRM) overall being 11% in 2005. A recent analysis indicates a reduction in the TRM. Currently three EBMT sponsored RCTs are in progress or completed in Europe (scleroderma, multiple sclerosis and Crohn's disease), the scleroderma trial (ASTIS) being part financially supported by EULAR. EULAR has also recently launched a stromal cell working group to develop recommendations for the use of mesenchymal stem cells (MSC) as therapeutic agents in rheumatic disorders exploiting their anti-inflammatory, immunomodulatory, tissue protective properties and apparent minimal acute toxicity. It is hoped that the preliminary positive results in acute graft versus host disease will translate to positive benefits for autoimmune diseases such as Crohn's disease, lupus nephritis and vasculitis.

Genetic Basis of Common Diseases

Prof. Riad Bayoumi
Department of Biochemistry, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman. Email: bayoumi@squ.edu.om

The recent advances in genomics and microarray technology at manageable cost, has enabled research groups, worldwide, to conduct successful genome-wide association studies (GWA) unravelling some aspects of the genetics of complex traits and common diseases, such as Type 2 diabetes, obesity, myocardial infarction, stroke, asthma, schizophrenia, bipolar disorders, Alzheimer's disease, Crohn's disease, autoimmune diseases and some cancers. The newly discovered genetic architecture of these diseases is helping in the understanding of pathophysiology and the development of novel approaches to prevention and therapeutic applications. However, most of the GWA studies have been designed to detect potential susceptibility loci and genes attributable to common simple nucleotide polymorphism (SNPs) which are limited by the very design of microarrays. In almost all diseases tested up to date, the variants discovered could only explain 10–15% of the inherited predisposition (heritability). The next big move to identify the probable source of missing heritability is in examination of low frequency rare variants and copy number variants that awaits the design of novel microarrays and low cost high-throughput sequencing.

Epidemiology of Viral Pandemics

Dr. Nick Beeching
Senior Lecturer (Clinical) in Infectious Diseases, Liverpool School of Tropical Medicine, Liverpool, UK. Email: nbeeching@blueyonder.co.uk

Historically, the epidemic and pandemic spread of infections such as measles, plague, cholera, smallpox and syphilis have had devastating effects in Europe and elsewhere. Endemic infections that have been controlled worldwide by public health interventions have the potential to re-emerge rapidly if such measures are relaxed or thwarted, a recent example being the international dissemination of polio after disruption of immunisation programmes. Many factors influence the development progress of a pandemic, including crowding, travel, close proximity to host animals or livestock, infectivity to contacts, and the availability, feasibility and effectiveness of control measures. This presentation contrasts recent international experience with severe acute respiratory syndrome (SARS), avian influenza and "swine-flu", focusing on the effects on political and economic planning and outcomes, and the reality for public health practitioners and clinicians at a local level. Lessons learnt from these events need to be disseminated to inform policy for dealing with future pandemics, which are inevitable.

Sickle cell disease (SCD) - The Road Towards Prevention and Cure

Dr Salam Alkindi, Department of Haematology, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman.
Email: sskindi@yahoo.com

Sickle cell disease is prevalent in Oman with 5.7% of Omani people carrying the gene and about 0.2% affected; therefore, it is estimated that 120–150 babies born in Oman every year will become patients with SCD. Although SCD is traditionally regarded as a predominantly red cell disease, it is a complex disease demonstrating a model for red cell interactions with white cells and the endothelial cell lining. Recent work from our laboratory on acute chest syndrome (which is one of the major causes of death in this disease) and vaso-occlusive

crisis (VOC), the most frequent presentation of this disease, just demonstrated this. An alteration in the level of nitric oxide as well as a shift in lymphocytes and monocytes activations plays a role in both conditions. Similarly, the altered red cells (sickled cells) leading to perturbed platelets and haemostatic functions plays an important role in stroke development, added to the hereditary component of thrombophilia in this syndrome. These changes are promising an important opening for studies in the various therapeutic interventions that are available for this disease such as hydroxyurea, and more recently low molecular weight heparin, nicosan, and other agents that are undergoing testing. Also light is seen at the end of the tunnel with good progress made in reduced intensity conditioning (RIC) bone marrow transplant for patients with SCD. This was seen in the recent experience in our Centre, allowing the sickled and normal cells to co-exist together, and the use of stem cells to help patients with avascular necrosis of the hips (AVN), a crippling complication seen in some of our patients. Thus SCD is a unique disease requiring a multi-faceted approach.

Lymphoma is Different Here

Dr. Ikram A Burney

Sultan Qaboos University Hospital, Muscat, Oman. Email:ikramburney@hotmail.com

Lymphoma is a heterogeneous group of neoplastic disorders. Knowledge about different types, sub-types, and aetiology is evolving continuously, and the incidence is on the rise. With the advent of immunophenotype and molecular markers, it has become apparent that there is a significant heterogeneity in disease presentation and clinical course in different parts of the world. Amongst non-Hodgkin's lymphoma (NHL) cases, T-cell immunotype is much more frequent in the Far East than in developed countries in the West. Indolent lymphoma of B-cell immunophenotype constitute around 20% of all cases, compared to around 40% in the West. Diffuse large B-cell Lymphoma (DLBCL) constitutes 60% of NHL in developing countries, compared to up to 30% in developed countries. Whereas 38% of patients with aggressive NHL present with high or high-intermediate risk features in the International Prognostic Index (IPI) in developed countries, around 60% present with such features in developing countries. Around 50% compared to 25% present with primary extra-nodal disease. Between 7% and 30% of the patients present with concomitant hepatitis B virus (HBV) infection in developing countries, compared to <5% in the developed countries, while the incidence of hepatitis C virus (HCV) co-infection is 5–15 fold higher in the developing countries. A significantly higher proportion of patients present with aberrations of bcl-2 gene, mutant type of p53 protein, and a higher Ki-67 index. There are reports to suggest that patients with an aggressive type of NHL from developing countries are more likely to be immunosuppressed, and have concomitant co-morbidities, such as diabetes mellitus, which has an impact not only on the aetiogenesis, but also on long-term outcomes. Furthermore, there are important differences in the gene polymorphisms in various ethnic groups, resulting in differences in susceptibilities to develop lymphoma. Taken together, these observations suggest that there is hitherto an unmet need to study NHL in developing countries as a distinct entity.

Medical Education

Prof. Nigel Bax

University of Sheffield, UK. Email: n.d.s.bax@sheffield.ac.uk

Hippocrates recognised the need for experiential learning in medicine, Osler highlighted the personal qualities needed to become a good doctor, as well as the role of medical schools, and over 4,000 years ago Hammurabi made laws to enhance patient safety. The requirement of a scientific foundation to medical practice was emphasised by Flexner in 1910 and has resulted in a style of medical education that remains evident today. However, since these principles were espoused, the stakeholders in medical education have changed considerably. Patients, employers, regulatory bodies, governments and students themselves are understandably now central to educational matters and the autonomy of medical schools and of clinicians who teach both students and doctors has waned. Changing models of care have altered learning opportunities and large teaching hospitals in many parts of the world are becoming less ideal places for learning about general medicine than previously. Increased financial and time pressures on doctors to deliver care do not always integrate with plans to produce the next generation of high quality medical practitioners. The learning of medical sciences by students and doctors has decreased, possibly consequent to their curricula becoming occupied by other topics. The role of doctors has been challenged, both in terms of their clinical skills and from a financial viewpoint, with cheaper alternatives now available. The distinctiveness and value of a doctor is being increasingly questioned. Thus, what are the defining qualities of a doctor, not just at present but what would we wish them to be in 20 years time? How should these qualities and abilities be acquired and assessed? The principles determined by our forbears, namely clinical experience, appropriate personal and inter-personal qualities and the understanding and support of society, with all activities underpinned by scientific knowledge, remain central to medical education. We should still heed these tenets and help ensure that all stakeholders, as well as those learning and teaching in medicine, are responsive to them.

Treating Osteoarthritic Pain: What are the Options?

Dr. Ali S M Jawad

Rheumatology Department, Barts and the London NHS Trust, Whitechapel, London E1 1BB, UK. Email: ali.jawad@bartsandthelondon.nhs.uk.

Over the last 10 years, several guidelines have been published for the treatment of osteoarthritis (OA). In 2000, the American College of Rheumatology published its management guidelines for the management of patients with OA of the hips and the knees. The European guidelines (EULAR) followed and more recently the National Institute for Clinical Excellence (NICE) in the UK and the Osteoarthritis Research Society International (OARSI) guidelines were published in 2008. Based on a published systematic search of clinical guidelines and systematic reviews, twenty six interventions recommended for the treatment of knee pain in older adults in primary care have been identified. For example, the NICE guideline lists five interventions regarded as "core treatments" for osteoarthritis of the knee: paracetamol, patient education and information, exercises, weight loss (if the patient is overweight), and topical non-steroidal anti-

inflammatory drugs (NSAIDs). The guideline lists another 14 interventions, ranging from those that are safe (such as alterations to footwear or local heat and cold), to those that also are potentially harmful (such as oral NSAIDs, opioids, and surgery). Evidence exists that interventions recommended as core treatment for knee pain in older adults are underused, in particular, exercise, weight loss and the provision of written information. There appeared to be early reliance on pharmacological treatments with underuse of nonpharmacological interventions in early treatment choices.

Pregnancy and Rheumatic Diseases

Dr. Samar Elemadi
Department of Medicine, Sultan Qaboos University Hospital, Muscat, Oman. Email:ali.jawood@bartsandthelondon.nhs.uk

Systemic lupus erythematosus (SLE) occurs frequently in women of childbearing age. Although patients with SLE are as fertile as women in the general population, their pregnancies may be associated with complications. The prognosis for both mother and child is best when SLE has been quiescent for at least six months prior to the pregnancy, and the patient's underlying renal function is stable and normal or near normal. Thus, family planning is important. Maternal health and fetal development should be monitored frequently during pregnancy. If possible, delivery should occur in a controlled setting. In addition, women with SLE should be followed by an obstetrician knowledgeable in high-risk pregnancies.

Childhood Primary Angiitis of the Central Nervous System

Dr. Reem Abdawani
Department of Child Health, Sultan Qaboos University Hospital, Muscat, Oman. Email: reemabd@hotmail.com

Childhood primary angiitis of the central nervous system (cPACNS) is a rare and potentially devastating condition. It poses the clinician with significant diagnostic and therapeutic challenges. An overview of cPACNS will be discussed with special considerations pertinent to children.

Vascular Aspect of Behcet's disease

Dr. Juma Al-Kaabi
Department of Medicine, Sultan Qaboos University Hospital, Muscat, Oman. Email:kaabi@squ.edu.om

Behcet's disease (BD) is a chronic multisystem inflammatory disease characterised by recurrent mouth and genital ulcerations, uveitis, skin lesions along with musculoskeletal, central nervous system, gastrointestinal and other systems manifestations. The disease is associated with morbidity, mainly due to the eye and central nervous system manifestations. Furthermore, the mortality rate of BD has been reported to be higher than the general population with an estimated rate of 4-10%. Most of this mortality is related to vascular thrombosis, which accounts for about 40% of overall causes of mortality in BD. The vascular involvement varies from 7.7 to 43% depending on the ethnicity. Pulmonary artery aneurysms are the one of most series complications of BD, as these may rupture with fatal consequences. The presentation highlights the spectrum of the vascular manifestations of BD (vasculo-Behcet), with reference to Omani populations.

Fit for Purpose and Fit to Practise - Revalidation and Recertification in the UK

Dr. Ian Starke
Medical Director, Revalidation, Royal College of Physicians, London, UK. Email: Ian.Starke@uhl.nhs.uk

The maintenance and continuing development of the professional competence of trained doctors are key elements in ensuring that patients receive the highest standards of care. In the UK, these processes began to be formalised in the 1990s with the introduction of Continuing Medical Education and later Continuing Professional Development as formal processes, built largely on the recording of what most doctors were already doing. The General Medical Council (GMC) consulted on revalidation in 2000 and produced guidance for licensing and revalidation in 2003. Annual medical appraisal was first introduced in 2001 to support formal revalidation, which would start in 2005. This process was halted by a series of high profile criminal and medical negligence cases, in particular the activities of Dr Harold Shipman. An extended public inquiry, chaired by Justice Dame Janet Smith, led to a series of reports, the last of which appeared in 2005. In her reports, Dame Janet criticised many aspects of the regulation of doctors, and in particular stated that the current processes of appraisal were "patchy and not fit for purpose". The Chief Medical Officer (CMO) for England, Sir Liam Donaldson, chaired a further inquiry, which led to the publication of a Report in 2006 (Good Doctors, Safer Patients) and to the government White Paper, "Trust, Assurance and Safety" in 2007. This proposed processes for the formal revalidation of all health professionals, and included: 1) A change from the criminal to the civil standard of proof in medical fitness to practise cases; 2) The development by the GMC of a new framework for appraisal based on "Good Medical Practice"; 3) The separation of revalidation into the two elements of relicensure (for all doctors) and specialist recertification (for doctors on the Specialist and General Practice registers held by the GMC); 4) The creation of GMC Affiliates who would represent the GMC at Regional or Strategic Health Authority level; 5) The creation of the role of Responsible Officer (RO) in every organisation that employs doctors – responsible for making a positive recommendation on revalidation to the GMC; 6) A clear statement of the role of the Medical Royal Colleges and Faculties and their specialist associations in making a positive recommendation on specialist recertification; 7) An expectation that the Colleges and Faculties, co-ordinated by the Academy of Medical Royal Colleges, would develop standards of specialist practice, and means of assessing specialists against those standards. In July 2008, a further report from a working party chaired by the CMO emphasised the importance of relicensure and specialist recertification forming "intertwined strands of a single process", and the need to maintain the "predominantly formative"

nature of appraisal. The New Framework for Appraisal and Assessment developed by the GMC was to become a "core module" within every appraisal encounter. Although medical revalidation is mainly a Department of Health (DH) (England) initiative, there is a clear understanding that the processes in the devolved nations will be closely aligned with that in England, and national Revalidation Delivery Boards have been established in Scotland and Wales, working closely with the UK Revalidation Programme Board. Revalidation has three aims: 1) to confirm that licensed doctors practise in accordance with the GMC's generic standards (relicensure); 2) for doctors on the GP register and specialist register to confirm that they meet the standards appropriate to their speciality or general practice (recertification); 3) To identify, for further investigation and remediation, poor practice where local practice is not robust enough to do this or does not exist. The Royal College of Physicians (RCP) position on revalidation is that the primary objective should be to ensure continuing high standards of professional practice and the continuing improvement of those standards over time. A model of how the various processes will fit together has been developed by the GMC and the Academy. The GMC's Revised Framework divides the professional performance of doctors into four Domains, each of which has three Attributes. The actions, behaviours and skills expected of a well-performing doctor are stated as a total of some 67 "standards". In common with others, the RCP has developed a Specialist Framework setting out the supporting information required to demonstrate that a physician is practising according to the 12 Attributes. A number of tools have been, and continue to be, developed by the RCP to support physicians in obtaining and recording relevant supporting information. These include multi-source feedback, a patient survey, an enhanced CPD system, personal "point-of-care" learning and quality improvement tools and a bedside teaching assessment. High standards for appraisers and for their training and support have also been developed. The Responsible Officer (RO) role has been defined by the DH; the ways and circumstances in which ROs will link with the College and its Regional representatives are to be defined. The College will have a key role in the quality assurance of the appraisal and revalidation processes taking place within NHS organisations. All those working with patients will require a licence to practice, and thus a Responsible Officer and regular annual appraisal. The next steps in the process include: 1) Ten "Pathfinder" or "Whole-system" pilots in 2010-11; 2) The introduction of "Early Adopter" pilots in 2011–12, the start of revalidation for those involved; 3) The development of appropriate electronic support tools and consideration of data protection and inter-operability between systems; 4) The development of appropriate training for appraisers and ROs; 5) Development of supportive remediation methodology; 6) Development of quality assurance mechanisms, and 7) Consideration of so-called "orphan" groups of doctors.

REFERENCES

1. The Shipman inquiry. From www.the-shipman-inquiry.org.uk/home.asp. Accessed Nov 2009.
2. Good doctors, safer patients: Proposals to strengthen the system to assure and improve the performance of doctors and to protect the safety of patients. Department of Health, 2006. From www. dh.gov.uk/prod>consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4137276.pdf. Accessed Nov 2009.
3. Trust, Assurance and Safety – The Regulation of Health Professionals in the 21st Century. From www.official-documents.gov.uk/document/cm70/7013/7013.pdf. London. HM StationaryOffice, 2007. Accessed Nov 2009.
4. Good Medical Practice. General Medical Council, 2006. From www.gmc-uk.org/static/documents/content/GMC_0911.pdf. Accessed Nov 2009.
5. Medical Revalidation – Principles and Next Steps – The Report of the Chief Medical Officer for England's Working Group. From www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/en/documents/digitalasset/dh_086431.pdf. Accessed Nov 2009.
6. General Medical Council. A Revised Framework for Appraisal and Assessment, 2008. From www.gmc-uk.org/Framework_4_3.pdf_snapshot.pdf. Accessed Nov 2009.
7. Assuring the Quality of Medical Appraisal for Revalidation. Shelley M, Judkins K. Revalidation Support Team, May 2009. From www.rcpsg.ac.uk/Education/Revalidation_CPD?Documents/Revalidation%20Papers%2009/Steering%20Group%20Meeting%20-%20June%2009/Papers%203.pdf. Accessed Nov 2009.
8. The Role of Responsible Officer. Responsible Officer Guidance – Closing the Gap in Medical Regulation. From www. dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_104594.pdf. Accessed Nov 2009.