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### SEMINAR

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WORLD REPORTS

Mauritius has much to celebrate as it marks its 40th year of independence. Life expectancy has increased and infant mortality has fallen since the late 1960s. But drug addiction and chronic disease continue to challenge the island’s health system. Sharmila Devi reports from Port Louis. When Mauritius emerged independent of British rule 40 years ago, the island in the Indian Ocean appeared to have few prospects, dependent as it was on sugar cane and workers’ remittances. Two Nobel-prize winners gave the country little chance of pulling out of poverty. James Meade, a Cambridge economics don, said in the 1960s that it would be a “great achievement” if Mauritius ever found employment for its increased population. Author V S Naipaul, meanwhile, labelled Mauritius the “overcrowded barracoon”, saying the island’s “problems defy solution”. But Mauritius has defied the naysayers, regularly topping regional African groupings in terms of growth, progress, and competitiveness, as well as human factors such as education, media freedom, and health.

Mental health is coming out from under the shadows in the Czech Republic, with more people now seeking professional help. But, despite this positive step, psychiatric care in the country is largely lagging in the past, with too much emphasis on hospitalisation. Katka Krosnar reports. More Czechs are seeking psychiatric help now than in the 1990s—a phenomenon which many observers have said means that the negative attitudes towards mental-health problems in communist times are being overcome. Recently released figures from the Czech Institute of Health Statistics show that about a third more Czechs sought psychiatric help in 2006 than in 2000. The figures indicate that in 2006, 17000 Czechs were admitted to hospital due to mental-health problems, while 458000 people sought psychiatric help. Experts say that mental health issues were either neglected or misused by the former communist regime, which was in power from 1948 to 1989. During that time society looked very negatively on anyone who admitted to having mental-health problems. But now attitudes in society are changing, said Rostislav Kotrc, executive director for the Czech Association for Mental Health—an umbrella organisation for groups who work in the field and support patients and their families.

A series of recent drug scandals and regulatory lapses in the USA are setting the stage for major reform of the US Food and Drug Administration. Experts say the agency needs more human and financial resources to ensure that the country’s drug supply is safe. Samuel Loewenberg reports. A series of aggressive investigations by the US Congress into malfeasance by the pharmaceutical industry and lack of regulatory oversight is setting the stage for what could be a major reform of the Food and Drug Administration. The spate of drug recalls over the past few years, from Vioxx to the blood thinner heparin, has brought so much negative publicity to industry that even drug makers are backing off from their usual anti-government stance and have joined the call to give the agency more resources. Exactly how those new resources will be spent, however, remains hotly contested.

Last year, researchers reported that Alice Springs had the highest known incidence of stab injuries in the world and that these attacks were only the tip of the iceberg of the violence in Aboriginal communities. Stephen Pincock visited the small town in central Australia to investigate. Alice Springs is as close as you are likely to get, in geographical terms at least, to the heart of the Australian continent. Roughly equidistant from the cities of Adelaide on the south coast and Darwin in the far north, the isolated town of 27000 people sits beside the normally dry Todd River, a wide ribbon of sandy soil lined with eucalyptus. Around the town, the landscape is reddish and rocky, with small boulder-strewn hills running into the nearby MacDonnell Ranges, a dramatic line of bluffs, crags and ridges that are rich with sites of spiritual importance to the local Aboriginal people. On a Friday afternoon in early April, on the main pedestrian shopping strip, Todd Mall, tourists sipped lattes and contemplated expensive Indigenous art. 5 minutes’ walk away in the local hospital, however, the scene was fundamentally different. There, the beds of the second-floor surgical ward were largely occupied by Aboriginal patients, many of them women, most the victims of trauma and interpersonal violence.

John McCain entered typical Democratic turf last month by announcing plans to reform health care in the USA if he is elected as the country’s next president. His blueprint is one that may prove popular with employers, but will it impress voters? Todd Zwillich reports from Washington, DC. John McCain—the Republicans’ presumptive nominee for next US president—last month unveiled the most details to date of his health-care plan, saying he would give consumers more control over their own care. At the heart of the plan is a move to de-emphasise employer-sponsored health coverage—from which more than 70% of Americans get their medical insurance now. Relentlessly rising health-care costs have sent employers clamouring for a way to control spending. For some,
that has meant a search for new ways to get out of the business of providing health care. McCain’s plan would eliminate current tax exemptions for employee health benefits. Instead, it would shift much of the money to tax credits, entitling individuals to US$2500 and families to $5000 to be put toward purchasing medical insurance. In a speech in Tampa, Florida, last month, McCain said “millions of Americans would be making their own health care choices again”, because consumers could take their tax credits and shop for insurance anywhere.

ARTICLES


Severe graft-versus-host disease (GVHD) is a life-threatening complication after allogeneic transplantation with haemopoietic stem cells. Mesenchymal stem cells modulate immune responses in vitro and in vivo. We aimed to assess whether mesenchymal stem cells could ameliorate GVHD after haemopoietic-stem-cell transplantation. Patients with steroid-resistant, severe, acute GVHD were treated with mesenchymal stem cells, derived with the European Group for Blood and Marrow Transplantation ex-vivo expansion procedure, in a multicentre, phase II experimental study. We recorded response, transplantation-related deaths, and other adverse events for up to 60 months’ follow-up from infusion of the cells. Between October, 2001, and January, 2007, 55 patients were treated. The median dose of bone-marrow derived mesenchymal stem cells was 1.4×10⁶ (min–max range 0.4–9×10⁶) cells per kg bodyweight. 27 patients received one dose, 22 received two doses, and six three to five doses of cells obtained from HLA-identical sibling donors (n=5), haploidentical donors (n=18), and third-party HLA-mismatched donors (n=69). 30 patients had a complete response and nine showed improvement. No patients had side-effects during or immediately after infusions of mesenchymal stem cells. Response rate was not related to donor HLA-match. Three patients had recurrent malignant disease and one developed de-novo acute myeloid leukaemia of recipient origin. Complete responders had lower transplantation-related mortality 1 year after infusion than did patients with partial or no response (11 [37%] of 30 vs 18 [72%] of 25; p=0.002) and higher overall survival 2 years after haemopoietic-stem-cell transplantation (16 [53%] of 30 vs four [16%] of 25; p=0.018). Infusion of mesenchymal stem cells expanded in vitro, irrespective of the donor, might be an effective therapy for patients with . . .


Although carotid bruits are deemed to be markers of generalised atherosclerosis, they are poor predictors of cerebrovascular events. We investigated whether a carotid bruit predicts myocardial infarction and cardiovascular death. In this meta-analysis, we searched Medline (1966 to August, 2007) and Embase (1974 to August, 2007) with the terms “carotid” and “bruit”. Bibliographies of all the retrieved articles were also searched. Articles were included if they reported the incidence of myocardial infarction or cardiovascular death in adults. Outcome variables were extracted in duplicate and included the rate of myocardial infarction and cardiovascular mortality. Quality of the articles was independently assessed with the Hayden rating scheme. Data were pooled with a random effects model. Of the 22 articles included, 20 (91%) used prospective cohorts. Our analysis included 17295 patients with 62413·5 patient-years of follow-up, with a median sample size of 273 patients (range 38–4736) followed up for 4 years (2–7). The rate of myocardial infarction in patients with carotid bruits was 3·69 (95% CI 2·97–5·40) per 100 patient-years (eight studies) compared with 1·86 (0·24–3·48) per 100 patient-years in those without bruits (two studies). Yearly rates of cardiovascular death were also higher in patients with bruits (16 studies) than in those without (four studies) [2·85 [2·16–3·54] per 100 patient-years vs 1·11 [0·45–1·76] per 100 patient-years). In the four trials in which direct comparisons of patients with and without bruits were possible, the odds ratio for myocardial infarction was 2·15 (1·67–2·78) and for cardiovascular death 2·27 (1·49–3·49). Auscultation for carotid bruits in patients at risk for heart disease could help select those who might benefit the most from an aggressive modification strategy for cardiovascular risk.


Schools in many countries undertake programmes for smoking prevention, but systematic reviews have shown mixed evidence of their effectiveness. Most peer-led approaches have been classroom-based, and rigorous assessments are scarce. We assessed the effectiveness of a peer-led intervention that aimed to prevent smoking uptake in secondary schools. We undertook a cluster randomised controlled trial of 10730 students aged 12–13 years in 59 schools in England and Wales. 29 schools (5372 students) were randomly assigned by stratified block randomisation to the control group to continue their usual smoking education and 30 (5358 students) to the intervention group. The in-
the clinic that provided antiretroviral therapy opened, 65.1% were attributed to AIDS. 8 months after
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utilisation-level effect of HIV on adult mortality
and early evidence of reversal after introduc-
tion of antiretroviral therapy in Malawi. Lan
cet, 371 (9624), 1603-1611.
Malawi, which has about 800000 deaths from AIDS
every year, made free antiretroviral therapy available
to more than 80'000 patients between 2004 and 2006.
We aimed to investigate mortality in a population be-
fore and after the introduction of free antiretroviral
therapy, and therefore to assess the effects of such
programmes on survival at the population level. We
used a demographic surveillance system to measure
mortality in a population of 32'000 in northern Malawi,
from August, 2002, when free antiretroviral therapy
was not available in the study district, until February,
2006. 8 months after a clinic opened. Causes of death
were established through verbal autopsies (retrospec-
tive interviews). Patients who registered for
antiretroviral therapy at the clinic were identified and
linked to the population under surveillance. Trends in
mortality were analysed by age, sex, cause of death,
and zone of residence. Before antiretroviral therapy
became available in June, 2005, mortality in adults
(aged 15–59 years) was 9.8 deaths for 1000 person-years
of observation (95% CI 8.9–10.9). The probability of dy-
ing between the ages of 15 and 60 years was 43% (39–
49) for men and 43% (38–47) for women: 229 of 352
deaths (65.1%) were attributed to AIDS. 8 months after
the clinic that provided antiretroviral therapy opened,
Leonardi, C.L., Alexa B Kimball, Kim A Papp, Newman
Yeilding, Cynthia Guzzo, Yuhua Wang, Shu
human interleukin-12/23 monoclonal anti-
body, in patients with psoriasis: 76-week re-
sults from a randomised, double-blind, pla-
cebo-controlled trial (PHOENIX 1). Lancet,
371 (9625), 1665-1674.
Interleukins 12 and 23 have important roles in the
pathophysiology of psoriasis. We assessed ustekinumab, a human monoclonal antibody directed
against these cytokines, for the treatment of psoria-
sis. In this phase III, parallel, double-blind, placebo-
controlled study, 766 patients with moderate-to-severe
psoriasis were randomly assigned to receive
ustekinumab 45 mg (n=255) or 90 mg (n=256) at weeks
0 and 4 and then every 12 weeks; or placebo (n=255) at
weeks 0 and 4, with subsequent crossover to
ustekinumab at week 12. Patients who were initially
randomised to receive ustekinumab at week 0 who
achieved long-term response (at least 75% improve-
ment in psoriasis area and severity index [PASI 75] at
weeks 28 and 40) were re-randomised at week 40 to
maintenance ustekinumab or withdrawal from treat-
ment until loss of response. Both randomisations were
done with a minimisation method via a centralised
interactive voice response system. The primary end-
point was the proportion of patients achieving PASI 75
at week 12. Analyses were by intention to treat. This
study is registered with ClinicalTrials.gov, number
NCT00267969. All randomised patients were included
in the efficacy analysis. 171 (67.1%) patients receiv-
ing ustekinumab 45 mg, 170 (66.4%) receiving
ustekinumab 90 mg, and eight (3.1%) receiving pla-
cebo achieved PASI 75 at week 12 (difference in re-
sponse rate vs placebo 63.9%, 95% CI 57.8–70.1, p<0.0001 for 45 mg and 63.3%, 57.1–69.4, p<0.0001 for
90 mg). At week 40, long-term response had been
achieved by 150 patients in the 45 mg group and 172
patients in the 90 mg group. Of these, 162 patients
were randomly assigned to maintenance ustekinumab
and 160 to withdrawal. PASI 75 response was better maintained to at least 1 year in those receiving maintenance ustekinumab than in those withdrawn from treatment at week 40 (p<0.0001 by log-rank test). During the placebo-controlled phase, adverse events occurred in 278 (54.5%) of the 510 patients receiving ustekinumab and 123 (48.2%) of the 255 receiving placebo. Serious adverse events occurred in six (1.2%) of 510 patients receiving ustekinumab and in two (0.8%) of 255 receiving placebo in this phase. The pattern of adverse events was much the same in the placebo crossover and randomised withdrawal phases as it was in the placebo-controlled phase. Ustekinumab seems to be efficacious for the treatment of moderate-to-severe psoriasis; dosing every 12 weeks maintains efficacy for at least a year in most patients.


Ustekinumab, a human monoclonal antibody against interleukins 12 and 23, has shown therapeutic potential for psoriasis. This study assessed the efficacy and safety of ustekinumab in psoriasis patients and assessed dosing intensification in partial responders. In this multicentre, phase III, double-blind, placebo-controlled study, 1230 patients with moderate-to-severe psoriasis (defined by a psoriasis area and severity index [PASI] score ≥12, and at least 10% total body surface area involvement) were randomly assigned to receive ustekinumab 45 mg (n=409) or 90 mg (n=411) at weeks 0 and 4, then every 12 weeks, or placebo (n=410). Partial responders (ie, patients achieving ≥50% but <75% improvement from baseline in PASI) were re-randomised at week 28 to continue dosing every 12 weeks or escalate to dosing every 8 weeks. Both randomisations were done with a minimisation method via a centralised interactive voice response. The primary endpoint was the proportion of patients achieving at least 75% improvement in PASI (PASI 75) at week 12. Analyses were by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00307437. All randomised patients were included in the efficacy analysis. 273 (66.7%) patients receiving ustekinumab 45 mg, 311 (75.7%) receiving ustekinumab 90 mg, and 15 (3.7%) receiving placebo achieved the primary endpoint (difference in response rate 63.1%, 95% CI 58.2–68.0, p<0.0001 for the 45 mg group vs placebo and 72.0%, 67.5–76.5, p<0.0001 for the 90 mg group vs placebo). More partial responders at week 28 who received ustekinumab 90 mg every 8 weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks (22 [68.8%] vs 11 [33.3%]; difference in response rate 35.4%, 95% CI 12.7–58.1, p=0.004). There was no such response to changes in dosing intensity in partial responders treated with ustekinumab 45 mg. During the placebo-controlled phase, 217 (53.1%) patients in the 45 mg group, 197 (47.9%) in the 90 mg group, and 204 (49.8%) in the placebo group experienced adverse events; serious adverse events were seen in eight (2.0%) patients in the 45 mg group, five (1.2%) in the 90 mg group, and eight (2.0%) in the placebo group.

Malignant pleural mesothelioma is almost always fatal, and few treatment options are available. Although active symptom control (ASC) has been recommended for the management of this disease, no consensus exists for the role of chemotherapy. We investigated whether the addition of chemotherapy to ASC improved survival and quality of life. 409 patients with malignant pleural mesothelioma, from 76 centres in the UK and two in Australia, were randomly assigned to ASC alone (treatment could include steroids, analgesics, drugs, bronchodilators, palliative radiotherapy [n=136]); to ASC plus MVP (four cycles of mitomycin 6 mg/m2, vinblastine 6 mg/m2, and cisplatin 50 mg/m2 every 3 weeks [n=137]); or to ASC plus vinorelbine (one injection of vinorelbine 30 mg/m2 every 2 weeks for 12 weeks [n=136]). Randomisation was done by minimisation, with stratification for WHO performance status, histology, and centre. Follow-up was every 3 weeks to 21 weeks after randomisation, and every 8 weeks thereafter. Because of slow accrual, the two chemotherapy groups were combined and compared with ASC alone for the primary outcome of overall survival. Analysis was by intention to treat. At the time of analysis, 393 (96%) patients had died (ASC 132 [97%], ASC plus MVP 132 [96%], ASC plus vinorelbine 129 [95%]). Compared with ASC alone, we noted a small, non-significant survival benefit for ASC plus chemotherapy (hazard ratio [HR] 0.89 [95% CI 0.72–1.10]; p=0.29). Median survival was 7·6 months in the ASC alone group and 8·5 months in the ASC plus chemotherapy group. Exploratory analyses suggested a survival advantage for ASC plus vinorelbine compared with ASC alone (HR 0·80 [0·63–1·02]; p=0·08), with a median survival of 9·5 months. There was no evidence of a survival benefit with ASC plus MVP (HR 0·99 [0·78–1·27]; p=0·95). We observed no between-group differences in four predefined quality-of-life subscales (physical functioning, pain, dyspnoea, and global health status) at any of the assessments in the first 6 months. The addition of chemotherapy to
ASC offers no significant benefits in terms of overall survival or quality of life. However, exploratory analyses suggested that vinorelbine merits further investigation.

SEMINAR


Most head and neck cancers are squamous cell carcinomas that develop in the upper aerodigestive epithelium after exposure to carcinogens such as tobacco and alcohol. Human papillomavirus has also been strongly implicated as a causative agent in a subset of these cancers. The complex anatomy and vital physiological role of the tumour-involved structures dictate that the goals of treatment are not only to improve survival outcomes but also to preserve organ function. Major improvements have been accomplished in surgical techniques and radiotherapy delivery. Moreover, systemic therapy including chemotherapy and molecularly targeted agents—namely, the epidermal growth factor receptor inhibitors—has been successfully integrated into potentially curative treatment of locally advanced squamous-cell carcinoma of the head and neck. In deciding which treatment strategy would be suitable for an individual patient, important considerations include expected functional outcomes, ability to tolerate treatment, and comorbid illnesses. The collaboration of many specialties is the key for optimum assessment and decision making.


Stroke is the second most common cause of death and major cause of disability worldwide. Because of the ageing population, the burden will increase greatly during the next 20 years, especially in developing countries. Advances have occurred in the prevention and treatment of stroke during the past decade. For patients with acute stroke, management in a stroke care unit, intravenous tissue plasminogen activator within 3 h or aspirin within 48 h of stroke onset, and decompressive surgery for supratentorial malignant hemispheric cerebral infarction are interventions of proven benefit; several other interventions are being assessed. Proven secondary prevention strategies are warfarin for patients with atrial fibrillation, endarterectomy for symptomatic carotid stenosis, antiplatelet agents, and cholesterol reduction. The most important intervention is the management of patients in stroke care units because these provide a framework within which further study might be undertaken. These advances have exposed a worldwide shortage of stroke health-care workers, especially in developing countries.