

Medibytes

Medibytes offer readers short, informative, synopses of important or interesting papers published in specialty and other general medical journals. They are edited by Dr J Ferguson.

LIST OF ABBREVIATIONS Angiotensin-converting-enzyme (ACE); dipeptidylpeptidase-4 inhibitors (DPP-4); Food and Drug Administration (FDA); hepatitis E virus (HEV); oligomeric procyanidin (OPC); premature termination codon (PTC)

PSYCHIATRY

Antidepressants improve post-stroke executive function

Ninety-two patients who had had a stroke up to six months previously were randomised to twelve weeks' antidepressant therapy (fluoxetine or nortriptyline) or placebo. Treatment was then discontinued and patients were evaluated by neuropsychological testing. Testing was repeated 21 months later (n=36). There were no differences at twelve weeks, but by two years the executive performance of the placebo group had deteriorated, whereas the active therapy group had significantly improved. This was not due to mood state, subsequent antidepressant treatment or overall cognitive functioning. Antidepressants may facilitate the early reorganisation of neural networks associated with prefrontal tasks following a stroke.

G Masterton

From Narushima K, Paradiso S, Moser DJ et al. Effect of antidepressant therapy on executive function after stroke. *Br J Psychiatry* 2007; **190**:260–5.

DRUG RESISTANCE

No light at the end of the tunnel: multidrug resistance transporters

Profligate use of antibiotics has led to widespread problems of antibiotic resistance and the use of chemotherapy thwarted by the induction of drug resistant pathways. Unfortunately, recent advances in our knowledge of the structure and function of the major classes of multidrug transporters have not led to effective solutions. There have been many attempts to modify drugs so that they are no longer substrates for the transporters. However, the drug binding sites are large and flexible, and a precise alignment of the ligand within the binding pocket is not required, making minor modifications compatible with retaining efficacy unlikely to succeed. The alternative approach of developing specific blockers of the transporters has proved unsatisfactory, although blockers of the human P-glycoprotein have proven useful in the laboratory. Commonly, resistance to a specific antibiotic or chemotherapeutic agent results from the induction of more than one multidrug transporter, and blockage of

even a single transporter can lead to an increase in unexpected cytotoxic effects. Thus, in spite of a detailed knowledge of the structure and function of multidrug transporters, drug resistance is here to stay.

JS Kelly

From Higgins CF. Multiple molecular mechanisms for multidrug resistance transporters. *Nature* 2007; **446**:749–57.

CHOOSING YOUR POISON

Cardioprotective red wines

Regular moderate red wine consumption is believed to reduce susceptibility to coronary artery disease. Alcohol and polyphenols are possible mediators of this effect. These authors found that OPCs are the most potent vasodilator polyphenols in red wine, and this may be important as high longevity correlated with high OPC concentrations in red wine in Nuoro in Sardinia, and Gers in southwest France. Oligomeric procyanidins are absorbed from the intestine. Grape seeds are the main source of OPCs, and the use of Tannat grapes, which are rich in polyphenols, and traditional wine-making, may account for the high OPC content of red wines in these areas.

NDC Finlayson

From Corder R, Mullen W, Khan NQ et al. 2006. Red wine procyanidins and vascular health. *Nature* 2007; **444**:566.

CANCER

Orchidopexy reduces cancer risk

Undescended testis occurs in 2–5% of boys at birth. Complications include impaired fertility and testicular cancer. Orchidopexy is now done at two years or younger to protect fertility, but does age at orchidopexy affect cancer risk?

This Swedish study followed 16,983 men undergoing orchidopexy for 12.4+/-7.4 years. Fifty-six testicular cancers were identified, giving a standardised incidence ratio of 2.75 (95% CI 2.08–3.57), a ratio of 2.23 for those operated at <13 years of age, and 5.4 for those

operated >13 years of age. A sharp increase in cancer risk occurred at age 13 years.

Increased cancer risk in undescended testicle may already be determined at birth, but puberty is also important in testicular carcinogenesis. Orchidopexy to correct undescended testicle reduces cancer risk when done <13 years of age.

NDC Finlayson

From Pettersson A *et al.* Age at surgery for undescended testis and risk of testicular cancer. *NEJM* 2007; **356**:1835–41.

VACCINES

Preventing hepatitis E

Hepatitis E virus causes sporadic and epidemic hepatitis in developing countries. Death occurs in 1–3% of clinical hepatitis E, rising to 5–25% in pregnancy. Seroprevalence estimates one in three of the world population has been infected.

This study of an HEV recombinant protein vaccine randomised 2,000 Nepalese army personnel. Eight hundred and ninety-six participants received three doses of placebo, and 898 people received three doses of vaccine. From 14 days after vaccination to the end of the study, three vaccine subjects (0.3%) and 66 placebo subjects (7.4%) developed hepatitis E ($p < 0.001$). Vaccine efficacy was 95.5%. A study of 127 subjects developing hepatitis E after two vaccine or placebo doses showed that two vaccine doses were 85.7% effective. The vaccine did not cause any serious side-effects, but the at-risk population was small. This vaccine has considerable potential for preventing hepatitis E.

NDC Finlayson

From Shrestha MP *et al.* Safety and efficacy of a recombinant hepatitis E vaccine. *NEJM* 2007; **356**:895–903.

THERAPEUTICS

Two new classes of antidiabetic agents: incretin mimetics and enhancers

Glucagon-like peptide, an incretin hormone, has been known for at least 50 years to stimulate insulin and suppress glucagon secretion, inhibit gastric emptying and reduce appetite and food intake. In a recent review, Drucker *et al.* draw together the clinical evidence to show that the incretin mimetics, exenatide and liraglutide by injection, and the orally administered incretin enhancers DPP-4 sitagliptin¹ and vildagliptin,* reduce fasting and prandial glucose concentrations and haemoglobin A1c with few lasting adverse effects and no weight gain. In a number of studies, the incretin mimetics and DPP-4 inhibitors have been shown to expand β -cell mass.

Current evidence suggests exenatide is indicated in type 2 diabetics in whom one or more oral agents have failed, and DPP-4 inhibitors can be considered for first-line therapy, or as an add-on therapy in the same patients. Exenatide and liraglutide have the added advantage that their use is often associated with weight loss. Long term data on the durability and efficacy of these agents is not available. Work suggesting improvements in myocardial function following myocardial infarction² has yet to be replicated.

* Approval of vildagliptin (Novartis Galvus) by the FDA has been delayed due to concern about safety in patients with renal impairment.

JS Kelly

From Drucker D, Easley C, Kirkpatrick P. Fresh from the pipeline – sitagliptin. *Nat Rev Drug Disc* 2007; **6**:109–10. Nikolaidis LA, Mankad S, Sokos GG *et al.* Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation* 2004; **109**:962–5.

Aliskiren, an orally active renin inhibitor

Beta-blockers lower blood pressure, in part by reducing renin release from the juxta-glomerular apparatus. Angiotensin-converting enzyme inhibitors reduce the conversion of angiotensin I to the active peptide angiotensin II. Angiotensin II blockers interfere with action of Ang II on the AT1 receptor but not the angiotensin II type 2 receptor. Renin (release) inhibitors do not block renin-like enzymes such as cathepsin D or tonins which release angiotensin I from angiotensinogen. Renin, however, has only one substrate angiotensinogen and blockade of this receptor would not interfere with other metabolic pathways. The development of the 'first in class' oral renin blocker, of aliskiren, over say 40 years is outlined in the *Lancet* by Staessen *et al.* in some detail.

Compared with ACE inhibitors, renin inhibitors have fewer side-effects and may be indicated in combination with drugs such as diuretics, ACE inhibitors and angiotensin-receptor blockers which increase plasma renin through feed back loops. Renin inhibitors are eliminated via the liver with little interaction with other drugs and may be useful in patients with concomitant renal disease. They are contraindicated in the same patients as ACE inhibitors and angiotensin-receptor blockers, i.e. pregnant women and patients with bilateral renal-artery stenosis.

JS Kelly

From Staessen JA, Li Y, Richart T. Oral renin inhibitors. *Lancet* 2006; **368**:1449–56.

BLOOD TRANSFUSION

Universal blood donation

For at least half a century, it has been known that the red blood cells from individuals with blood groups A, B and AB carry antigens that cause life-threatening reactions if transfused into people with a different blood group. It now appears possible that blood from the above groups could be converted in routine laboratories into group O-like blood suitable for universal donation by the use of novel galactosidases. The study by Henrik Clausen's group¹ identified two new prokaryotic gene families containing enzymes with optimal activity at neutral pH and highly specific for A and B substrates. Both enzymes can be removed from donor blood when the antigen stripping is complete, by routine isotonic buffered solutions used in cell washing. The GH109 α -N-acetylgalactosaminidase efficiently strip the A antigen and GH110 α -galactosidase the B antigen. Pilot studies suggest that an automated cost effective process can be developed for practical use which is very much better than earlier methods relying on coffee bean extracts.²

JS Kelly

From Liu QP *et al.* Bacterial glycosidases for the production of universal red blood cells. *Nat Biotech* 2007; **25**:454–64.
Nikolaidis LA *et al.* Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation* 2004; **109**: 962–5.

GENETICS

Cystic fibrosis, Duchenne muscular dystrophy, PTC124 and the suppression of stop codons

The antibiotic gentamycin has been known for some time to cause ribosomes to read through PTCs and rescue the full length proteins that are truncated by single nucleotide mutations in diseases such as cystic fibrosis, muscular dystrophy and a number of cancers. Unfortunately, the toxicity of systemic gentamycin has prevented its use in humans. However, a paper by Welch *et al* focuses further attention on PTC124 which has been shown in Phase II trials to potentially benefit patients with PTC-induced cystic fibrosis, and Duchenne muscular dystrophy. Welch *et al*¹ show that PTC124 suppresses the termination of 'productive' premature protein translation at PTC, leading to increased levels of functional full-length proteins. The mechanism is different from that of gentamycin which suppresses the identification of PTCs in pioneer translation leading to the stabilisation of PTC-containing mRNAs and the preservation of additional mutated proteins and mRNAs that escape nonsense mediated RNA decay. The mutated proteins could lead to unpredictable problems. Thus, in summary, this may be a better way forward for the more common genetic

diseases than gene therapy involving viral constructs. PTC124, a 1,2,4-oxadiazole linked to fluorobenzene and benzoic acid rings, is active orally.

JS Kelly

From Welch EM *et al.* PTC124 targets genetic disorders caused by nonsense mutations. *Nature* 2007; **447**:87–91.
Finkel R *et al.* Interim analysis of a phase 2 study of PTC124 for nonsense mutation suppression therapy of Duchenne muscular dystrophy (DMD). *Neurology* 2007; **68**:A404.
Schmitz A, Famulok M. Chemical biology: ignore the nonsense. *Nature* 2007; **447**:42–3.

DIETARY SUPPLEMENTS

Multivitamin and omega-3 supplementation and homocysteine

Now that the Scientific Advisory Committee on Nutrition has advised the government to make the addition of folic acid to white flour mandatory it is worth pondering one's own approach to dietary supplements. Finding supplements unadulterated with ginseng and evening primrose oil takes time and a quite modest approach costs at least £10 per month. I therefore read with some relief that a double-blind four way trial of the addition of an omega-3 preparation to a multivitamin package significantly enhances the reductions in homocysteine, triglycerides and C-reactive protein seen with a combination of folic acid with B6 and B12 vitamins.¹ Interestingly, the trial was conducted in a cohort with an average age of 53 with a rather low starting average level of homocysteine of 8.1 $\mu\text{mol/L}$.² The correction of high levels of homocysteine has been shown repeatedly to improve the morbidity of victims of stroke* and myocardial infarction and to slow cognitive decline.² The down side is finding a multivitamin preparation that contains 25 mg of Vit B6, 400 μg of folic acid and 400 μg of B12 and an omega-3 preparation containing 760 mg EPA and 440 mg DHA per 1 g (dose 2 per day) without being arrested in the pharmacy for loitering.

*In a recent comment in the Lancet,³ on a very impressive trial in China which strongly supports the benefits of folic acid in stroke prevention, Cynthia Carlsson concludes, not without cause, that it is premature to conclude 'that the benefits of continued use of previously deemed "safe" vitamin supplements outweighs the risk of other adverse cardiovascular disease outcomes.'

JS Kelly

From Earnest CP *et al.* Synergistic effects of multivitamin and omega-3 fatty acid supplementation. *FASEB J* 2007; **21**:A698–A69c.
De Bree A *et al.* Homocysteine determinants and the evidence to what extent homocysteine determines the risk of coronary heart disease. *Pharmacol Rev* 2002; **54**:599–618.
Carlsson CM. Lowering homocysteine for stroke prevention. *Lancet* 2007; **369**:1841–42.