Short cuts

What's new in the other general journals

Cognitive performance is rock bottom just after waking

Sleep deprivation is bad for performance, but being woken up is worse. In a laboratory experiment, adult volunteers performing a series of random adding tests scored lower in the three minutes after waking than they did at any time over the next 24 hours. One minute after waking, their scores were only 65% of their best, significantly worse than all other test scores during the experiment, including the test done after a whole night without sleep ($P \leq 0.01$). After 20-60 minutes awake, the volunteers had bounced back to over 80% of their peak performance.

The experiment was small but carefully done. The nine healthy volunteers had no caffeine, alcohol, nicotine, or drugs (recreational or medicinal) for three weeks before the study. For the same period they logged a regular eight hours' sleep every night.

The results suggest that cognitive performance is worst just after waking, which has obvious implications for on-call doctors, truck drivers, soldiers, and others who are woken from sleep to do complex tasks more or less immediately.

JAMA 2006;295:163-4

Simple strategy for diagnosing pulmonary embolism looks safe

Diagnosing pulmonary embolism can be a complicated, multistage process. In an attempt to simplify it, Dutch doctors developed a new more straightforward approach. Firstly, decide whether pulmonary embolism is likely or unlikely using a simplified version of the Well's rule. If pulmonary embolism is unlikely, do a D-dimer test. If that's negative, withhold anticoagulants. For everyone else, go

straight for computed tomography and rely on the results to make a treatment decision.

It seems to work. In a large trial of 3306 patients with suspected pulmonary embolism, treatment was withheld from 1028 who were classed as "unlikely" to have embolism and had a negative D-dimer test result. Over the next three months, only five of them (0.5%, 95% CI 0.2% to 1.1%) developed venous thromboembolism. Treatment was also withheld from 1436 patients who had a negative tomogram. Eighteen of these patients had a thromboembolic event within three months (1.3%, 0.7% to 2.0%), a rate comparable to the rate seen after a negative pulmonary angiogram.

A key advantage of this diagnostic strategy is that about a third of patients with suspected pulmonary embolus can be managed with little interference (history taking, examination, and a blood test) and no radiation. A linked editorial (pp 213-5) describes it as "practical and safe."

JAMA. 2006;295:172-179.

Routine iron and folic acid supplements harm preschool children in Zanzibar

Children in Pemba, Zanzibar, are bitten about 400 times each year by mosquitoes carrying malaria. The children are poor, and most are anaemic. But in a large randomised trial, routine iron and folic acid supplements were positively harmful, increasing the risk of severe illness or death among preschool children. In a sister trial from southern Nepal (pp 144-52), where incomes are also low but malaria is insignificant, iron and folic acid supplements with or without zinc had no measurable effect on risk of death among preschool children. Why the difference?

In Pemba, first line treatment for malaria is the antifolate combination sulfadoxine and pyrimethamine. Folic acid supplements could have reduced the effectiveness of treatment and increased the risk of severe illness or death from malaria, according to a linked editorial (pp 90-1). Others have also suggested that iron deficiency protects against malaria and that iron supplements increase parasitaemia.

The findings of the Pemba trial were convincing enough to stop recruitment early. Even so, more than 24 000 children contributed to the analysis, making it the biggest and best trial by far to look at this

issue. The authors conclude that international guidelines recommending universal supplementation with iron and folic acid should be overturned in areas where malaria is endemic.

Lancet 2006;367:133-43

Clear pattern emerges from surveillance of imported tropical diseases

A study of sick travellers returning to Western countries from developing ones found that fever was the commonest problem for those returning from sub-Saharan Africa or South East Asia, diarrhoea was the commonest problem for those returning from south central Asia, and travellers from the Caribbean and Central or South America tended to have skin disease (usually insect bites or cutaneous larva migrans). In most regions, parasitic diarrhoea (giardiasis, amoebiasis) was more common than bacterial diarrhoea. Malaria and dengue fever were the predominant causes of fever.

This pattern emerged from an international surveillance programme of 30 tropical medicine clinics. Most of the 17 353 travellers in this study presented to clinics in Europe (49%) or North America (33%).

The findings tell us nothing about the absolute risks of travel to various developing world destinations, but they do give region-specific information about what is common and what is not (Ebola virus disease, rabies, tetanus, yellow fever) among returning travellers sick enough to visit a specialised travel medicine clinic. They also serve as a reminder to ask anyone with fever, perplexing diarrhoea, or an unusual rash where they have been in the past six

months. Over a third of the travellers in this study presented a month or more after they got back.

N Engl J Med 2006;354:119-30

Don't wait for the classic features of meningitis

In the minds of parents, teachers, and many doctors, childhood meningitis is associated with a non-blanching rash, a stiff neck, and drowsiness. Researchers from Oxford warn this classic picture should be sidelined because it appears much too late to be useful. They suggest that doctors and parents should focus instead on a new trio of signs—leg pain, cold hands and feet, and pale or mottled skin—since these were the first specific features to appear in a cohort of 448 children admitted to hospital with meningococcal disease. All indicate septicaemia.

In most children, the first few hours of illness were dominated by fever, nausea and vomiting, irritability, and sometimes a runny nose and sore throat—the common currency of general practice. But this early stage lasted only about four hours in young children and about eight hours in adolescents. Leg pain (37%), cold peripheries (43%), and mottled or pale skin (19%) appeared within 7-12 hours, while most children were still at home and before they first saw a doctor. The classic features of rash, impaired consciousness, and stiff neck appeared after a mean of 13-22 hours, by which time many children were in hospital and some were close to death.

Lancet 2006 doi 10.1016/S0140-6736(06)67932-4

Wanted: clinical trials in lung transplantation

The specialty of lung transplantation is in urgent need of some decent multicentre trials, writes a cardiothoracic surgeon from Boston. There is, he says, no consensus on any important aspect of this complex operation, and without clinical trials the lung transplant community is “doomed to re-create a series of anecdotal experiences.” One team at least has made a start. In their small randomised trial (pp 141-50), extra immunosuppression with inhaled ciclosporin did not prevent acute rejection but did seem to delay chronic rejection and improve survival over two years. Despite serious problems with recruitment (they enrolled only 58 patients over three years), compliance, and baseline differences between the groups, the researchers were pleasantly surprised by their mixed results. Other transplant teams should get together to reproduce their efforts. Only bigger and better.

N Engl J Med 2006;354:191-3

Obesity is an independent risk factor for cardiovascular disease

Obesity causes cardiovascular disease because it causes hypertension, dyslipidaemia, and diabetes. But if you had no other risk factors, is obesity dangerous on its own? In the latest of several attempts to answer this question, US researchers analysed data from an old cohort recruited more than 30 years ago. They divided the 17 643 men and women from Chicago into five cardiovascular risk groups using baseline measurements of blood pressure, serum concentration of total cholesterol, and smoking recorded between the ages of 31 and 64. The researchers then looked for a link between obesity in middle age and later cardiovascular disease within each risk group, using data from Medicare claims and national death records. Participants, who had no coronary heart disease or diabetes at baseline, were followed up for a mean of 32 years.

The results were fairly clear. Regardless of other risk factors, being obese in middle age increased the risk of cardiovascular disease in later life. For example, among non-smokers with normal blood pressure and low serum cholesterol concentration at baseline, the odds ratio for being hospitalised with heart disease after the age of 65 was 4.25 (95% CI 1.57 to 11.5) for obese people compared with those of normal weight. Only 6.7% of this cohort were in the low risk category at recruitment.

JAMA 2006;295:190-8

Stem cells for myocardial infarction: we're not there yet

Stem cells from a patient's own bone marrow could be a useful tool for repairing myocardium damaged by infarction. The difficulty seems to be getting the right cells to the right place at the right time. The

latest trial tested an infusion of stem cells harvested 24 hours after coronary angioplasty and infused soon afterwards into the affected coronary artery. The 33 patients who had stem cell transfer did no better clinically over the next four months than the 34 patients who had a placebo infusion instead. However, they did end up with slightly smaller infarcts (11 g decrease in size v 7 g decrease, $P=0.036$).

The authors are not sure why the stem cells didn't improve patients' left ventricular function. They suspect it has something to do with microvascular obstruction, which adversely affected outcome in over the half the patients in both groups. The disappointing results could also be related to the timing of the infusion, the phenotype of the cells infused, or even the patients. All the patients in this double blind trial had moderate left ventricular dysfunction, and a percutaneous coronary intervention (with stenting) a median of only five hours after their symptoms began.

Lancet 2006;367:113-21

Benazepril may slow the progress of advanced renal failure

Angiotensin converting enzyme (ACE) inhibitors can slow the progress of mild or moderate renal failure, but it's still unclear whether they are safe or effective for patients with advanced disease. In a small randomised trial from China, generous doses of benazepril worked well in non-diabetic patients with serum creatinine concentrations of 274-442 $\mu\text{mol/L}$. Compared with a placebo, benazepril reduced the risk of the combined end point (death, end stage renal failure, or a doubling of baseline serum creatinine concentration) from 60% (65/107) to 41% (44/108). The benefits, reported after a follow-up of more than three years, were independent of any effect on blood pressure. Hyperkalaemia was not a serious problem.

One US physician is unconvinced, however. In a linked editorial (pp 189-91) he writes that the dose used in this study (20 mg benazepril daily) was surprisingly high and the risk of hyperkalaemia surprisingly low. It's possible that patients prone to hyperkalaemia were weeded out during the pretrial run-in period. It's also possible that the Chinese people in this trial ate less dietary potassium than people generally eat in the West. Or perhaps it was the diuretics they took.

Whatever the reason, he cautions against wide generalisation from these results. If you do want to give an ACE inhibitor to someone with advanced renal failure, start with a low dose, and test their intake of dietary potassium first.

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