LETTERS

Pancreatitis following human papillomavirus vaccination

Amitabha Das, David Chang, Andrew V Biankin and Neil D Merrett

To the Editor: A 26-year-old woman presented with 24 hours of severe constant epigastric pain and vomiting. She had no history of similar pains, alcohol consumption or gallstones. Four days before presentation she had received her first dose of human papillomavirus (HPV) vaccine. Two days after vaccination she developed a fever and self-limiting rash of 3 days' duration.

Examination revealed marked epigastric tenderness and temperature of 40° C. Other physical parameters were within normal limits. Biochemical investigations showed normal liver function, moderate leukocytosis, a serum amylase level of 1900 U/L (reference range [RR], 23–85 U/L) and lipase level of 3400 U/L (RR, 0–160 U/L).

An upper abdominal ultrasonography showed a non-dilated biliary tree and no evidence of gallstones. Computed tomography showed an oedematous pancreas with peripancreatic fat stranding and arterial enhancement of the pancreatic parenchyma, consistent with pancreatitis without necrosis (Box). Other investigations showed normal serum levels of calcium, triglycerides and parathyroid hormone. Serological tests were negative for acute infection with coxsackie A9, coxsackie B1–6, echo, mumps, herpes simplex, hepatitis and varicella zoster viruses.

The patient was diagnosed with pancreatitis and treated conservatively with intravenous fluids and analgesia. Pain, symptoms and biochemical abnormalities settled after 10 days. She was discharged and remains well. Magnetic resonance cholangiopancreatography performed after discharge showed no pancreatic parenchymal or ductal abnormality.

Acute pancreatitis is common, with an incidence of 5.4–80 per 100 000.[1] Gallstones and alcohol use account for 70%–85% of cases; other causes include drugs, viral infections, tumours, hyperlipidaemia, hypercalcaemia, trauma, iatrogenic injury and pancreatic ductal anomalies. The cause is unidentified in up to 10% of cases.[1,2]

Viral pancreatitis is well recognised, with cytomegalovirus and mumps, coxsackie, hepatitis, herpes simplex, and varicella viruses all known causes.[3] Vaccines have been implicated, with pancreatitis associated with measles–mumps–rubella and hepatitis A and B vaccines.[4,5] To date, there has been no report linking HPV vaccination with pancreatitis.

The pathophysiology linking vaccination with pancreatitis is unclear. It has been postulated that viral replication in immunodeficient hosts receiving live attenuated viral vaccines can cause pancreatitis. Alternatively, "molecular mimicry" could stimulate production of auto-antibodies, which react with host antigens and cause autoimmunity.[5] The HPV vaccine is a quadrivalent, recombinant, non-infectious formulation, eliminating viral replication as a mechanism of pancreatitis. Therefore, an autoimmune mechanism is possible.

Extensive clinical testing has demonstrated the safety of HPV vaccine in the general population. In our patient, intensive history taking and investigation failed to identify another cause for pancreatitis, and the close temporal relation of the HPV vaccination, the development of a prodromal illness, and fever without evidence of sepsis led us to postulate that pancreatitis was secondary to vaccination. A coincidental illness causing pancreatitis cannot be ruled out, but neither can HPV vaccination be excluded as a potential cause. We therefore suggest that pancreatitis be considered in cases of abdominal pain following HPV vaccination and if proven, notified to the Adverse Drug Reactions Advisory Committee.

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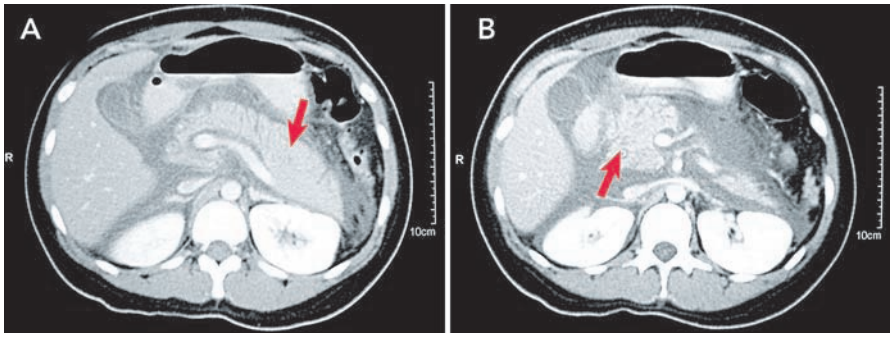
Computed tomography scan of the abdomen in a patient with pancreatitis



Portal venous computed tomography images showing oedematous enlargement of the pancreas, with surrounding fat stranding and ascites. The pancreas (arrows) appears fully enhanced with contrast, suggesting there was no necrosis. ***A:*** *Pancreatic head.* ***B:*** *Pancreatic body and tail.* ◆

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Feeding choice for children with immediate allergic reactions to cows milk protein

Sam S Mehr and Andrew S Kemp

To the Editor: Australian consensus guidelines for selecting formulas for infants with cows milk protein allergy (CMPA) have recently been published.[1] We reviewed formula choices and outcomes for 51 children with immediate allergic reactions to cows milk protein who were referred to one of us (S S M) in a tertiary specialist clinic over a 2-year period before the guidelines were published. The formula was selected by the referring specialist medical practitioner in 44 cases (and by S S M in the other seven).

Of the 51 children (mean age at initial reaction to cows milk protein, 7.8 months), 42 had skin and/or gastrointestinal features, and nine had an anaphylactic reaction with

Feeding choice for 51 children referred with cows milk protein allergy

Type of feeding selected	No. of children	Mean age at initial reaction to cows milk (months)	No. who reacted to selected feeding
Soy	29	9.5*	0
Extensively hydrolysed formula (EHF)	8	5.3	3
Amino acid-based formula (AAF)	6	4.2	0
Partially hydrolysed formula (PHF)	3	6.0	1
Breastfeeding	5	6.0	0

* $P < 0.05$ for soy versus PHF, EHF, AAF or continuing to breastfeed (*t* test). ◆

respiratory and/or cardiac features. Forty-six children had a positive skin prick test to cows milk protein, and one had a positive radioallergosorbent test. Four children with immediate (< 30 min) reactions of generalised erythema and/or angioedema (3) or vomiting (1), but a negative skin prick test, were also included.

Soy was the most common formula used, followed by extensively hydrolysed formula (EHF) (Box). Three of eight children commenced on EHF had allergic reactions, with urticaria and angioedema, and one child also had a transient (60 s) cough. Three children were given partially hydrolysed formula (PHF), with one experiencing an immediate cutaneous reaction.

These observations suggest that, in clinical practice, soy is frequently a satisfactory first choice for children with CMPA, as suggested in the guidelines.[1] Some children with CMPA will also react to EHF, providing a rationale for choosing amino acid-based formula as a first-line treatment prior to allergy evaluation in children with anaphylaxis to cows milk protein. As about 5% of infants with CMPA also react to EHF,[2] some allergists advocate the introduction of EHF under medical supervision in either all children with immediate CMPA[3] or only those who have had severe life-threatening reactions.[4]

Although PHF is tolerated by a significant proportion of children (70%) with immediate CMPA,[3] it is not recommended for the treatment of CMPA[1] due to its high content of potentially allergenic cows milk protein. The fact that three children with CMPA were given PHF suggests there is confusion in the prescribing community, and that the availability of the new guidelines may help in achieving a more appropriate choice of formula.

Competing interests: Andrew Kemp has received a speaker fee for a clinical updates meeting sponsored by Nutricia, and has participated in consensus panel conferences sponsored by Nutricia to develop a position statement on the treatment of CMPA. His department has held a clinical update meeting sponsored by Abbott.

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Recognition of USA300 isolates of community-acquired methicillin-resistant *Staphylococcus aureus* in Australia

Thomas Gottlieb, Wei-Yuen Su, John Merlino and Elaine Y-L Cheong

To the Editor: A 37-year-old man was referred to our emergency department with an acute 7 cm abscess of the buttock. The abscess was incised, and the patient was prescribed oral β-lactam antibiotics and discharged.

After 48 hours, culture of samples from the abscess showed methicillin-resistant *Staphylococcus aureus* with a community-acquired antibiotic resistance pattern (CA-MRSA). The isolate was resistant to β-lactam antibiotics, but sensitive to trimethoprim, gentamicin, and tetracycline. Unusually for an Australian CA-MRSA strain,[1] the isolate was also resistant to erythromycin and ciprofloxacin.

On reviewing the patient's history, it was noted that he was a previously well United States resident who had visited Australia and New Zealand as part of the support team for an international rock band. Further testing was undertaken, and the isolate tested positive for genes coding for the Panton–Valentine leukocidin toxin, associated with staphylococcal virulence (eg, recurrent furunculosis, abscess formation, and necrotising pneumonia).[2] Pulsed-field gel electrophoresis (performed by the Gram-Positive Bacteria Typing and Research Unit, Department of Microbiology and Infectious Diseases, Royal Perth Hospital, WA) confirmed the isolate as the ST8-MRSA-IV strain, also known as USA300.

Most CA-MRSA strains remain susceptible to a majority of non-β-lactam antibiotics, including clindamycin, trimethoprim–sulfamethoxazole, tetracyclines and fluoroquinolones. This helps distinguish CA-MRSA isolates from the typically multiresistant hospital strains, and facilitates oral outpatient therapy. USA300 is the dominant strain causing CA-MRSA infections in the US.[3] Among 422 patients with soft-tissue infections presenting to 11 US emergency departments in 2004, 59% of cases were caused by CA-MRSA, of which 99% were USA300. Recent reports indicate that multiresistance is emerging within this strain, with acquisition of resistance to erythromycin, clindamycin, mupirocin and fluoroquinolones.[4] An increasing association of USA300 infections with buttock and perineal infections is also reported, as well as potential sexual transmission, particularly among men who have sex with men.

Our case highlights the ease of international spread of microorganisms. Arguably, a "one-night stand" tour could be an ideal vehicle for microbial dissemination. CA-MRSA was not considered in the patient's initial assessment, and the patient was discharged with oral β-lactam antibiotics and no planned follow-up. Moreover, the isolate may not have been identified as the "epidemic" USA300 strain without more involved tests. A recent study documented a rising incidence of USA300 isolates in Western Australia between 2003 and 2007. Of 61 patient isolates, 35 were diagnosed in 2007 (Pearson J, Coombs G, Christiansen K, et al. USA300 MRSA identified in the Australian community [abstract PP3.2]. Abstract presented at the Australian Society for Antimicrobials 9th Annual Scientific Meeting; 2008; Feb 21–23; Sydney).

Our case suggests we should be more alert to CA-MRSA infection presenting with furunculosis and soft tissue infections, not

only in Indigenous communities and young people, but also in international travellers and patients whose infections fail to respond to usual therapy. It also reinforces the value of incision and drainage. As β-lactam susceptibility is no longer assured, such specimens should routinely undergo culture and susceptibility testing.

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Bupropion and bradycardia

Jacqueline Landau and Andrew E Ajani

To the Editor: We report significant sinus bradycardia in a patient presenting with an acute coronary syndrome shortly after beginning bupropion therapy to assist with smoking cessation.

A 53-year-old man was attended by paramedics for typical ischaemic chest pain. He had sinus bradycardia (45 beats/min) and hypotension (blood pressure, 85/60 mmHg), and was found to have a serum troponin I concentration of 1.2 μg/L, but no diagnostic electrocardiographic changes. He was admitted to our hospital with an acute coronary syndrome. He reported his medications at the time of admission as including metoprolol 50 mg twice daily (for hypertension) and paroxetine 20 mg daily (for depression).

The patient was given multiple doses of intravenous atropine (total, 1.2 mg) and adrenalin (total, 2 mg). After an adrenalin infusion was begun, he developed ventricular tachycardia (170 beats/min), but his cardiac rhythm spontaneously returned to sinus bradycardia. Two days after admission, two coronary stents were successfully deployed in a critically stenosed right coronary artery. Bradycardia (45–50 beats/min) persisted.

The following day, it was discovered that 3 weeks previously, the patient's general practitioner had prescribed bupropion 150 mg twice daily to assist with smoking cessation, which he had been taking up until the day of admission.

Bradycardia continued until hospital discharge. One month after discharge, he was in sinus rhythm (60 beats/min) and was clinically well.

Bupropion is a selective noradrenalin, dopamine and serotonin reuptake inhibitor. The mechanism by which it enhances the ability of patients to abstain from smoking is unknown.[1] Bupropion inhibits the activity of the cytochrome P450 2D6 isoenzyme, which metabolises metoprolol.[2] Concurrent use of bupropion and metoprolol can increase serum metoprolol levels, and clinically significant bradycardia has been reported.[3] Further, paroxetine, a selective serotonin reuptake inhibitor (SSRI), is a potent cytochrome P450 2D6 inhibitor, which would have further increased serum metoprolol levels.[4] Bradycardia associated with metoprolol and paroxetine dual therapy has been described.[5] Additionally, there is the potential for serotonin syndrome to develop in a patient administered multiple SSRIs. In our patient, the administration of bupropion and paroxetine could have potentially led to serotonin syndrome.[6]

Our patient's pharmacological profile was complex, with potential adverse pharmacodynamic effects. The most likely precipitant of the patient's bradycardia was his acute coronary syndrome, although bupropion may have contributed. The case highlights the potential for significant drug interactions when new drug therapies are initiated. Bupropion and metoprolol (and other drugs metabolised by the cytochrome P450 2D6 isoenzyme pathway) should be co-administered with caution. The importance of common pathways of drug metabolism should be recognised to avoid potential adverse events, particularly when multiple medications are used.

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Misleading advertising of PI-based drug information?

Lilon G Bandler

To the Editor: I challenge the assertion made by Donohoo (Managing Editor of MIMS [the Monthly Index of Medical Specialities]) that "MIMS is held ... in high regard" and that the "vast majority of MIMS subscribers recognise that the quality information provided by MIMS is essential in their daily encounters with their patients".[1]

In fact, the most common MIMS annual to be seen around hospitals, in nursing homes and in doctors' surgeries is an out-of-date one. Furthermore, as a general practitioner, when I do use MIMS, it is because it is packaged with our desktop software, rather than by choice or active decision.

I have online access to the *Australian medicines handbook* (http://www.amh.net.au/), and various other references. I have no need to refer to MIMS, and I tire of the understandable bias MIMS has always had for proprietary prescribing.

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1 Donohoo EA. Misleading advertising of PI-based drug information? [letter]. *Med J Aust* 2008; 188: 679-680. ❑

Personal carbon trading: a potential "stealth intervention" for obesity reduction?

Cathal A Smith

To the Editor: Walters recently suggested that Australia should implement population control strategies as part of an approach to reduce global warming.[1] As a father of four, I found his assertion that my decision to father more than two children is "arrogant" to be offensive.

Walters' arguments are, at best, poorly reasoned. As a "citizen of this world", he clearly rejects the rights of other citizens to live on an equal footing and follow their religious, cultural or social beliefs if those beliefs oppose contraception. I would argue this is contrary to law.[2,3] His mathematical calculations ignore all costs required to achieve his objective, such as those associated with "contraceptives, intrauterine devices, diaphragms, condoms and sterilisation procedures". Further, he fails to consider costs associated with the supporting bureaucracies required to effect his policy, including material amendments to the Australian taxation system. Rather, and in my opinion strangely, he advocates issuing carbon credits for the additional consumption of contraceptive products.

According to Walters, people should be judged by their anticipated rather than actual emissions. A logical extension would be to punish those who exceed a predetermined mean acceptable level of emissions. No doubt, meeting the medical and ancillary needs of many sick, older and disabled people often generates excess emissions. Perhaps we should adopt some of the practices used in China and India, including abandonment and neglect of disabled children and older people.[4,5] How would we deter and punish those who cannot pay?

Walters addresses the issue of overpopulation by comparing Australia to India and China. This is notwithstanding that Australia has one of the lowest population growth rates in the world[6] and, with its ageing population and labour shortages,[7,8] has significantly different population and social concerns to these countries. There are no grounds to support the comparison made.

Environmental issues are among the greatest challenges facing society. As a father, I am deeply concerned for the world my children will inherit. We must deploy our limited resources efficiently and effectively to maximise their impact. To demand social controls in the manner Walters suggests, within a society heavily burdened with laws and struggling to meet labour and health system demands, would defeat this objective.

Reading Walters' views, which I consider fundamentally flawed, in a publication such as the Journal imparts to them a validity I believe is unjustified. I do not consider that Walters' social engineering policies could benefit anyone in Australia, while his "moral" concerns are ill conceived.

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Barry N J Walters

In reply: I thank Smith for the opportunity to clarify some scientific points. The science behind climate change is undeniable and was reviewed in February this year.[1] Moreover, "there is a greater than 90 per cent probability that the warming observed since the 1950s is due to human activities".[2] Therefore, attempts to prevent environmental calamity will not succeed with boundless population growth. In this sense, the more people there are, the worse it is for our earth. In particular, no nation should encourage population growth. I do not argue for compulsory sterilisation. I do argue that we recognise the cost of every extra human being to our overburdened earth.

Smith labelled my note of caution about limitless procreation as "offensive". I believe such disparagement is founded on personal and cultural beliefs, not on science, which informs and guides medicine.

There is only one atmosphere. Australians occupy this planet with no more rights than others do. Racism is anathema to us. If others must observe population restraint, then so must we.

Contrary to Smith's assertion, I plead that all should be able to "live on an equal footing". Is this not the laudable basis of law? I share his concern for the world that his "children will inherit"; my concern embraces the children of others as well.

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Probiotics: sorting the evidence from the myths

Shimonti Chatterjee and John Fraser

To the Editor: We read Pham and colleagues' recent article[1] with interest, as evidence mounts against the use of probiotics in critically ill patients. Although a plausible and attractive theory, probiotics in the patient with acute illness now appear ineffective, if not positively harmful.

A recent randomised trial of probiotics in 298 patients with severe acute pancreatitis showed a non-significant rise in infective complications,[2] in keeping with results of previous studies of critically ill patients.[3,4] Disturbingly, mortality in the probiotic group was more than double that in the placebo group ($P < 0.01$). Bowel ischaemia was a prominent feature of deaths in the probiotic group (eight patients), but was not associated with any deaths in the placebo group ($P < 0.004$). It may be that non-occlusive mesenteric ischaemia in critical illness is exacerbated by the added bacterial load itself, or through a pro-inflammatory response by gut epithelial cells.

While probiotics may be a benign and beneficial adjunct to enteral feeding in certain clinical situations, there is persuasive evidence that probiotic therapy is associated with increased infective complications in critically ill patients and significant mortality in patients with severe acute pancreatitis. Until there is evidence to the contrary, we believe probiotics should not be administered to patients with severe acute illness.

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Sanjaya N Senanayake

To the Editor: Pham and colleagues commented on the effects of probiotics;[1] however, not much is known about the impact of probiotics on weight gain and obesity. It is known that a predominance of certain bacteria, such as *Lactobacillus*, in the bowel can promote weight gain. Many of these bacteria are found in probiotic products.

The human intestinal microbiota is predominantly colonised by the *Firmicutes* and *Bacteroidetes* phyla of bacteria.[2] *Lactobacillus* and *Bifidobacterium*, found in a number of probiotic products, belong to the *Firmicutes* phylum. A study has shown that obese people carry a higher proportion of bacteria from the *Firmicutes* phylum and that there is a statistically significant decrease in the proportion of *Firmicutes* bacteria as they lose weight.[3] A similar pattern of *Firmicutes* predominance has been found in obese mice. Furthermore, the microbiota of the obese mice were more likely than those of lean mice to break down otherwise indigestible polysaccharides from the diet.[4] In other words, a higher proportion of *Firmicutes* bacteria was associated with increased and more efficient caloric uptake from food.

These data did not necessarily imply causation, so the investigators performed another experiment. They transferred intestinal microbiota from obese and lean donor mice to germ-free mice, and found that the mice who received microbiota from the obese donors had a significant increase in body fat after 2 weeks compared with the recipients from the lean donors.[4] It is therefore likely that the bacteria often found in probiotics can cause weight gain.

Obesity in children and adults is a major health problem in developed nations. Given the increasing use of probiotic products in such countries, large studies should be performed to characterise the association between probiotics and obesity. Such studies may not find any association or may find that there is only a dose-related risk. If there is an association, probiotics may still prove useful in certain circumstances (eg, for weight gain in children failing to thrive).

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Mimi Pham, Daniel A Lemberg and Andrew S Day

In reply: The comments by Chatterjee and Fraser regarding the danger of administering probiotics to patients with acute severe illnesses are important additions to the debate on the risks and benefits of probiotic administration. We also thank Senanayake for his interesting comments on the possible role of probiotics in weight gain.

The recently published multicentre trial[1] describing unexpected adverse events associated with probiotics in acutely unwell patients with severe pancreatitis is one example of an adverse outcome following probiotic administration. The use of probiotics in patients with severe comorbidities and in those who are immunocompromised is also contraindicated. There are reported cases of *Lactobacillus* GG sepsis in premature babies with short gut syndrome,[2] and *Saccharomyces boulardii* fungaemia has been described in immunocompromised patients.[3]

It is interesting to note that two systematic reviews have assessed the efficacy of probiotics in prevention of necrotising enterocolitis in premature (< 33 weeks' gestation) and very low birthweight (< 1500 g) infants.[4,5] Both reviews concluded that probiotics may decrease the incidence of necrotising enterocolitis in preterm infants, and that severe adverse events were not associated with probiotics in these unwell and immunodeficient patients. However, there were insufficient data to comment definitively on the short-term or long-term safety of probiotics in these infants; this will require assessment in future large trials.

The increased scrutiny of probiotics resulting from the publication of the adverse outcomes in adults with severe acute pancreatitis[1] may, by necessity, slow the commencement and progression of these larger trials in infants in the neonatal intensive care setting.

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Booster seat use by children aged 4–11 years: evidence of the need to revise current Australasian standards to accommodate overweight children

Yvonne A Zurynski, Lynne Bilston and Elizabeth J Elliott

To the Editor: On 25 January 2008, the Australian Transport Council approved the National Transport Commission's seventh amendment to the Australian Road Rules.[1] This amendment provides for the mandatory use of forward-facing child restraints for children aged 6 months to 4 years, and the use of Australian Standards-approved booster seats for children aged 4–7 years and weighing up to 26 kg. It also recommends that children aged less than 7 years should not travel in the front passenger seat.

These changes are welcome. They bring Australian rules on child restraints and seating position closer to (but still not on par with) restraint laws already implemented in the United Kingdom and other countries in the European Union, where booster seats are mandatory for all children aged under 12 years or less than 145 cm tall.[2]

Implementation of the amendment poses several challenges. A small proportion of children will exceed the 26 kg weight limit for booster seats by their seventh birthday; however, there is no evidence that these seats are not safe for slightly heavier children. In addition, the Australian Standard (AS 1754) is currently being revised and is likely to move towards recommending restraint selection based on seated height rather than weight, as well as developing new standards for booster seats for older children. Height is the most important determinant of adequate seatbelt fit, and children need to be about 145 cm tall before the lap portion of an adult seatbelt sits correctly over the iliac crests rather than on the soft abdomen.

Community education campaigns will be pivotal in successfully implementing these new road rules. As misuse of restraints is high, education campaigns must emphasise correct use of recommended restraints.[2-4] Furthermore, the new recommendations may contribute to financial hardship, particularly for low-income families with several children under the age of 7 years. Subsidies or loan schemes may be required to assist such families. Fitting three restraints across the rear seat of small cars may also be difficult. Adequate enforcement will be required to maximise compliance. Research studies and injury surveillance will play an important part in maximising the effectiveness of these rule changes.

Finally, the seventh amendment to the Australian Road Rules does not constitute law, and legislative changes will need to be enacted by each state and territory before these changes become law. We hope that the state and territory governments will take swift action to enact these laws, to prevent injuries and deaths in Australian children due to motor vehicle crashes.

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Mandometer treatment of Australian patients with eating disorders

Phillip Gray

To the Editor: Court, Bergh and Södersten raise the issue of why and how some therapies with prima facie evidence for their efficacy have a significant take-up by medical practitioners, while others are allowed to languish, sometimes for decades.[1]

It is 6 years since Bergh and colleagues conducted their Swedish trial on eating disorders, with significant encouraging results.[2] Again they report — albeit this time with a non-randomised but local sample — above-average outcomes.[1] Again, the fact that their patients had had previous treatments that failed renders the results compelling. We have to ask why no one has found the time, money or inclination to attempt to reproduce their findings or examine which elements of their intervention are successful. It would be ironic if the answer is that medical researchers are afraid of the unusual.

While Australian medical research and public health ignore this mandometer treatment, some private health funds have been prepared to contribute up to $60 000 per patient for it, suggesting that they view it as better value for money than alternative therapies.

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South African medical graduates in Australia

Peter C Arnold

To the Editor: More than 2000 graduates of South African medical schools have migrated to Australia since 1948. Unlike many immigrants from Europe before and after World War II, all were fluent in English and most were able to start practising almost immediately.

In chronicling this unique migration and its contribution to Australian health care, I am trying to contact, by email, as many as possible of the 1800 South African doctors now practising here, as well as surviving spouses or children of the 100 or so who have died since arrival. As a 1961 graduate of the University of the Witwatersrand in Johannesburg, I have a particular personal interest in this migration.

Assisted by a sociologist and a statistician, I have prepared an email questionnaire. Responses will be de-identified before analysis.

I would be grateful if graduates of South African medical schools would contact me by email.

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