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Fatal paramethoxyamphetamine (PMA) poisoning in the Australian Capital Territory

Paul G Lamberth, Geoff K A Ding and Liisa A Nurmi

TO THE EDITOR: Recently, we treated a patient with fatal paramethoxyamphetamine (PMA) poisoning. We believe this is the first PMA poisoning to be reported in the Australian Capital Territory.

PMA (street name, "death") was first reported in the early 1970s during the emergence of recreational use of 3,4-methylenedioxyamphetamine (MDMA ["ecstasy"]).^{1,2} Hyperthermia, coma and seizures are features of MDMA and PMA poisoning, but they are more severe with PMA ingestion; features of hypoglycaemia, hyperkalaemia and QRS interval prolongation are suggestive of PMA poisoning.³

Our patient was a 20-year-old man who was conveyed to the emergency department by ambulance after presumed MDMA ingestion. On presentation, he was unconscious (Glasgow Coma Score, 4/15) and had the following signs: temperature, 42.8°C; heart rate, 90 beats/min; QRS interval, 160 ms (reference range [RR], < 100 ms); blood pressure, 171/148 mmHg; oxygen saturation, 76% (RR, 95%–100%); and respiratory rate, 40 breaths/min.

After intubation, external cardiac compressions and multiple DC shocks were required to restore circulation. The initial serum potassium level was 8.9 mmol/L (RR, 3.2–5.0 mmol/L). Hypoxaemia per-

sisted, and a chest x-ray showed extensive bilateral airspace consolidation.

The patient's associates alleged that he habitually used equine clenbuterol and ovine androgen preparations in addition to ecstasy.

The subsequent days were notable for resistant shock, rhabdomyolysis, cardiomyolysis and severe coagulopathy refractory to therapy. Oliguric renal failure necessitated extracorporeal blood purification. Hepatic failure and hypoglycaemia were pronounced. The most extreme biochemical derangements recorded in this case are listed in the Box.

Five days after admission, the patient's pupils were sluggishly reactive. Oculocephalic and oculocaloric reflexes were present but abnormal, while gag and cough reflexes were absent. A cerebral computed tomography scan showed extensive cerebral oedema.

By Day 8, the patient had fixed pupils and worsening haemodynamic instability. He died 10 days after ingestion of PMA.

The patient's antemortem blood concentration of PMA was 2.3 mg/L — 2.0 mg/L above the typical fatal threshold of 0.3 mg/L previously reported.²⁻⁴ MDMA, methylenedioxyamphetamine (MDA) and methylecgonine were also detected at low levels.

Since 2005, the Pharmacy Guild of Australia has instituted its "Pseudo Watch" program to reduce diversion of pseudoephedrine to illicit methamphetamine manufacture by a combination of retail restrictions and recording details of purchasers judged genuine. Supporting legislation varies by state.⁵ However, PMA is made from the readily available and unmonitored precursor, anethole. Further, PMA has a slower onset of action than MDMA, leading to the possibility of additional doses being ingested while awaiting effects.

We believe medical practitioners should consider PMA poisoning in cases of severe reactions to ecstasy, especially those in which hypoglycaemia and hyperkalaemia are present. A "market" shift in drug use towards the more lethal PMA because of reduced availability of pseudoephedrine would be a cause for concern.

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Ready, SET, go for academic surgery?

Timothy J Smith, Carly M Fox and Michael A Bonning

TO THE EDITOR: The recent editorial by Waxman¹ implies that early streaming of students during medical school training is to become the norm for admission to the Royal Australasian College of Surgeons' Surgical Education and Training (SET) program. We would like to draw attention to the disturbing nature of this development for medical students and junior doctors alike.

Waxman described the imperative for students to now decide upon a career in surgery "usually as undergraduate medical students".¹ He stated that some universities have proposed early streaming of students into specific surgical modules in later years of their medical programs. While early streaming may appear to be the answer to the growing conflict between the time constraints of undergraduate medical programs and the expanding body of medical knowledge, there are a number of significant pitfalls to this approach that are yet to be explored.

First, early streaming may jeopardise the quality of the generalist education offered at medical schools. International experience from McGill University in Canada, which implemented an early-streaming program in the late 1970s, supports this notion.² The cohorts from McGill's early-streaming program had poorer overall performance than their predecessors in the non-streamed program on the Medical Council of Canada's national licensing examination, which was attributed in part to their reduced opportunity for generalist training.

Laboratory markers of multisystem organ dysfunction in a case of PMA poisoning

Biochemical marker	Extreme value (peak or nadir)	Reference range
Creatine kinase (U/L)	58 358	20–200
Troponin I (U/L)	85.83	<0.06
Bilirubin (µmol/L)	412	2–20
ALT (U/L)	3961	<55
Ammonia (µmol/L)	219	10–50
Platelet count (x 10 ⁹ /L)	18	150–400

ALT = alanine aminotransferase.
PMA = paramethoxyamphetamine. ◆

Second, the notion that well resourced university surgical departments could provide an early-streaming package for undergraduate students that “[gives] their students an advantage and an almost guaranteed pathway into SET”¹ creates gross inequity in access to surgical training. This system would disproportionately disadvantage students from both graduate-entry programs, which have a shorter course duration, and newer universities, which lack the resources to provide advanced surgical training modules.

Third, the program disadvantages students who have not formed firm career intentions by the later years of their medical program. With data from the United Kingdom showing that more than a quarter of junior doctors change their career intentions in the 3 years after graduation,^{3,4} a significant proportion of medical graduates will gain no appreciable benefit from early streaming, and may in fact be disadvantaged by it.

We strongly discourage the introduction of early-streaming programs in medical schools. All schools should graduate “pluripotent” undifferentiated doctors with a strong generalist background.

Competing interests: We are final-year medical students at the University of Queensland and members of the Australian Medical Students’ Association national executive.

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1 Waxman BP. Ready, SET, go for academic surgery [editorial]? *Med J Aust* 2008; 188: 67-68.

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4 Edwards C, Lambert TW, Goldacre MJ, Parkhouse J. Early medical career choices and eventual careers. *Med Educ* 1997; 31: 237-242. □

John P Collins and Ian D Civil

TO THE EDITOR: The editorial by Waxman¹ on the Royal Australasian College of Surgeons’ new Surgical Education and Training (SET) program contains some factual errors that have led to anxiety among potential applicants. We wish to give the formal position of the College and to correct any misunderstandings. The SET program² is evolutionary, builds on the strengths of

the previously available program, and is based on an educationally sound framework and group of principles.

Registering an interest in training with the College does not in itself confer an advantage but will enable those registered to receive up-to-date information and College publications. The College website also provides up-to-date, relevant information for potential applicants. Completion of the Australian and New Zealand Surgical Skills Education and Training (ASSET) course is not compulsory before selection into SET, but it must be completed by the end of the first 2 years of the SET program.

The College and the specialist surgical associations and societies involved in the delivery of the SET program will rely on robust workplace-based assessment to monitor trainees’ progress and provide career advice. New in-training assessment tools are necessary to achieve this, and their implementation requires support, including courses for surgeons who undertake this vital work.

Those contemplating a career in surgery will not have to decide on their career choices at an earlier stage than previously. In the previous program, graduates could apply during their internship but now must wait until their second year after graduation. The College is committed to a broad-based period of preparation for surgical training but does not wish to deny the opportunity to those in their second year after graduation who are certain of their career aspirations. Applications will also be accepted from those who delay their career decisions for whatever reason.

Streaming medical students for vocational careers is an attractive educational philosophy, provided it does not interfere with the generalist experience required for all graduates. Furthermore, streaming is predicated on the medical colleges recognising this prior learning in their programs. Until this is resolved, the question of its implementation remains some way off. The current practice of undertaking electives in an area of interest is strongly supported.

The College is committed to working with the universities for a more integrated approach across the continuum of learning and seeks to build on the meaningful and collaborative partnerships already established. The key interface is the practising surgeon in an academic position who understands the requirements of the College and the university, as well as the needs of the community.

Selection into surgical training is through a national merit-based process. The curriculum vitae (CV) and its components of academic achievement, other accomplishments and clinical experience will each be scored and given appropriate weighting. The lower percentage overall for CVs (15%–25%) takes into account that many candidates will apply very early in their careers.² While we laud the suggestion of university surgery departments providing a package for potential trainees, “giving their students an advantage and an almost guaranteed pathway into SET”¹ does not necessarily follow, given the competitive nature of selection.

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Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations

William R Adam

TO THE EDITOR: The revised recommendations of the Australasian Creatinine Consensus Working Group¹ are improved with the recognition of an age-related reduction in glomerular filtration rate (GFR), but don’t deal with a number of other significant problems associated with an estimated GFR (eGFR).

When a plasma creatinine measurement is requested, an eGFR is commonly provided, increasing the sensitivity but reducing the specificity of diagnosis of kidney disease. The eGFR remains a substantially flawed estimate of GFR. It is associated with significant predictive error (up to 30% of individual eGFRs differ by more than 30% from the measured GFR at 60–90 mL/min)² and with substantial false positive and false negative outcomes.

The flaws in the eGFR are, firstly, the limitations of creatinine clearance rate as a measure of GFR, and secondly (and more importantly), the use of age, sex and race as surrogates for muscle mass (the determining factor in creatinine production and, together with creatinine clearance, plasma creatinine level).

Age, sex and race are imperfect predictors of muscle mass, and this leads to underestimation of GFR in people who are fit and well muscled and overestimation in those who are wasted and disabled. While reporting eGFR values represents a worthwhile advance on using plasma creatinine levels to detect kidney disease, it could be considered, at best, the “least bad” readily available measure of GFR.

When no better test is readily available, how should we handle a suboptimal measure of GFR? Educating the medical profession about the limitations of eGFR is important, but, based on personal experience and anecdotal evidence, I believe that using conventional methods of informing doctors has not been uniformly effective. Providing “just in time” information support is likely to assist this process.

Thus, I support the recommendation that laboratories routinely report eGFRs, but suggest that, when they do so, they add a product warning along the following lines:

The eGFR is calculated assuming a normal muscle mass for age, sex and race. It will underestimate GFR in well muscled individuals and overestimate GFR in patients with muscle wasting. A creatinine clearance test or formal GFR measurement may be helpful in patients whose muscle mass differs from the average for their age and sex. Proteinuria and haematuria are other useful indicators of kidney disease.

In patients over 70 years of age, an additional product warning, consistent with the Australasian Creatinine Consensus Working Group's revised recommendations,¹ could be as follows:

GFR declines with age, and, in patients over 70 years of age, an eGFR of 45–59 mL/min/1.73m², if stable over time and unaccompanied by proteinuria or haematuria, is unlikely to have specific renal prognostic or therapeutic implications.

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1 Mathew TH, Johnson DW, Jones GRD, on behalf of the Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations. *Med J Aust* 2007; 187: 459-463.

2 Poggio ED, Wang X, Greene T, et al. Performance of the Modification of Diet in Renal Disease and Cockcroft–Gault equations in the estimation of GFR in health and in chronic kidney disease. *J Am Soc Nephrol* 2005; 16: 459-466. □

Andrew J McLachlan, on behalf of the
Editorial Advisory Board, *Australian
medicines handbook*

TO THE EDITOR: The revised recommendations for the use of the estimated glomerular filtration rate (eGFR) in the clinical setting use the Modification of Diet in Renal Disease (MDRD) formula to adjust drug dosing in people with renal impairment (Recommendation 6).¹ Although the utility of the MDRD-based eGFR as a screening tool to identify people with chronic kidney disease represents an important clinical opportunity, we, and others,^{2,3} remain concerned about this recommendation.

Certainly, adjusting the dose of renally excreted medicines based on a patient's serum creatinine concentration alone is not appropriate. Accordingly, many drug monographs provide explicit dosing recommendations based on the estimated creatinine clearance (calculated using the Cockcroft–Gault formula) as a rational basis for dose adjustment using sound pharmacological principles. This assumes a significant correlation between the estimated creatinine clearance and the actual clearance of a drug (or metabolite). But such a correlation has not been established for the MDRD formula.

Indeed, an empirical study comparing the use of the Cockcroft–Gault formula to the MDRD formula in 1067 elderly patients found that the MDRD formula significantly overestimated renal function and would, if used, lead to significantly higher doses of two drugs in question (enoxaparin and gentamicin) being administered.² This highlights the need for further research to rigorously characterise the relationship between MDRD estimates of renal function and drug clearance before this formula can be recommended to guide dose adjustment in the clinical setting.

Recommendation 6, that the MDRD-based eGFR should be used for dosing after considering body size,¹ requires further clinical information about the patient — the same information needed to use the Cockcroft–Gault formula. Even limiting Recommendation 6 to drugs that are not “critical-dose drugs”¹ is confusing. Many drugs would be considered critical-dose drugs when used in frail older people with some degree of renal impairment.

We reaffirm the statement, from the 2008 *Australian medicines handbook*, that “there is no evidence that [automatically reported eGFR] is suitable for adjusting drug doses in people with renal impairment”.⁴

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Timothy H Mathew, David W Johnson and Graham RD Jones, on behalf of the Australasian Creatinine Consensus Working Group

IN REPLY: We agree with Adam's points that:

- The estimated glomerular filtration rate (eGFR) represents a worthwhile advance on the plasma creatinine level for detecting kidney disease, and is currently the best readily available measure of GFR;
- Educating the medical profession on the limitations of eGFR is important; and
- Further refinements of eGFR accuracy are highly desirable.

Since the advent of automated laboratory reporting of eGFR, there has been a concerted effort by the Kidney Check Australia Taskforce to educate medical professionals and other clinicians about the strengths and limitations of eGFR and about how best to approach the patient with a significantly reduced eGFR. Education has been via printed office materials, accredited workshops, medical journal articles, online education, and decision-support systems embedded in medical software. Adding statements to laboratory reports has also been considered by the Australasian Creatinine Consensus Working Group, and some laboratories do provide explanatory eGFR statements. However, many have not embarked on this because of the difficulty of providing adequately informative explanatory remarks in very limited space.

Individual laboratories balance the need for such supporting information against the space requirements on reports and the diminishing effect of excessive repetition. Given that routine reports are already complex, often containing over 20 result items,

and that many millions of reports with serum creatinine results are produced annually in Australia, the value of any repetitive comment needs careful consideration.

The response of clinicians to the introduction of automatic reporting of eGFR together with the linked educational campaign has been strongly positive, with outcomes that have included easier identification of chronic kidney disease, better decision making for affected patients, and more appropriate referral patterns, both in Australia and overseas. Nevertheless, we agree with Adam that eGFR is only an approximation of actual GFR and is subject to error. There are ongoing attempts to further improve the accuracy and clinical utility of eGFR through such ventures as the universal standardisation of creatinine calibration (which has already taken place in Australia and New Zealand) and the Chronic Kidney Disease Epidemiology Collaboration.¹

McLachlan, on behalf of the Editorial Advisory Board of the *Australian medicines handbook*, reaffirms the Board's position that eGFR is not appropriate for use in dosage calculations. However, for the reasons stated in the consensus document,² we remain convinced that eGFR is a useful tool for most drug dosing decisions.

We note with interest the recent change in the position taken by the British National Formulary (BNF 54) to one of support for the Modification of Diet in Renal Disease (MDRD)-based eGFR¹ being used in place of creatinine clearance rate "for most drugs and for most patients of average build and height"³ — a stance similar to ours. In particular, we re-emphasise that eGFR, because of its ready availability, increases the rate of identification of renal failure.

We agree with McLachlan that prescribers should continue to follow specific published recommendations for drugs such as enoxaparin and gentamicin (these are good examples of "critical-dose drugs" in the hospital setting). We note additionally that there is increasing acceptance of the eGFR in the drug literature. In the case of enoxaparin, the MDRD equation for eGFR has been used to assess the effect of renal function on bleeding in elderly patients⁴ and has been found to provide the best relationship with enoxaparin clearance in this setting.⁵

The eGFR is now an established feature of pathology reports in Australia, and we believe it is important to integrate this information into routine practice for drug dosing decisions. We therefore offer to work with the authors of the *Australian medicines hand-*

book and other interested parties to develop guidelines for drug dosing decisions using all available information.

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5 Berges A, Laporte S, Epinat M, et al. Anti-factor Xa activity of enoxaparin administered at prophylactic dosage to patients over 75 years old. *Br J Clin Pharmacol* 2007; 64: 428-438. □

Successful lung transplantation for adolescents at a hospital for adults

Monica C Robotin

TO THE EDITOR: I read with interest the article by Morton et al, summarising their impressive results of lung transplantation in adolescents treated in an adult hospital.¹ The authors state they “do not have an exclusion policy for patients suitable for LTx [lung transplantation] based on age or size criteria alone”, and refer small or very young children to overseas units. The accompanying editorial by Snell et al comments that a paediatric transplant unit would have too low a caseload (four to eight transplants per year) to ensure they deliver good results.² I agree that large-volume units are desirable, yet of the 158 centres reporting adult lung transplantation to the International Society for Heart and Lung Transplantation, 59%

averaged fewer than 10 lung transplants a year.³

While a Surgical Fellow at St Louis Children's Hospital, Mo, USA (1996–97), I was part of the surgical team undertaking a transplantation operation on a 13-month-old ventilator-dependent infant referred from Sydney. He had an uncomplicated postoperative course, leading to early hospital discharge and early return to Australia. Over the ensuing 5 years, while I was in touch with the family, they travelled regularly to St Louis for follow-up, as local expertise in managing young lung transplant recipients was lacking. Referring families to overseas units may be a good, albeit extremely expensive, short-term solution, yet developing local expertise in the follow-up of these patients has to be part of this package, to ensure optimal management, referrals and dialogue with overseas transplantation centres.

Such local expertise could provide the backbone of a future paediatric lung transplantation unit, preventing unnecessary deaths in this population. Although paediatric lung transplantation is challenging, results for isolated operations in children are similar to those in older age groups,³ so the “perception that the risk of undertaking LTx in children and adolescents does not warrant the reward”² needs to be challenged. From 1990 to 2002, 190 children received transplants at St Louis Children's Hospital (45% of them younger than 10 years), 30 of whom underwent living-related lung transplantation (generally reserved for patients too ill to wait for cadaveric lung transplants); although they were a higher-risk group, their survival statistics exceeded those of adult lung transplant patients.⁴

After all, a low case workload does not stop any of the four paediatric cardiac surgery units in this country from offering arterial switch operations. A local paediatric lung transplant follow-up service, perhaps attached to an adult unit, would be instrumental in optimising paediatric lung transplantation outcomes and could inform the debate on the pros and cons of setting up local paediatric lung transplantation services.

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1 Morton JM, Malouf MA, Plit ML, et al. Successful lung transplantation for adolescents at a hospital for adults. *Med J Aust* 2007; 187: 278-282.

2 Snell GI, Westall GP, Williams TJ. Lung transplantation: does age make a difference [editorial]? *Med J Aust* 2007; 187: 260-261.

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4 Huddleston CB. Pediatric lung transplantation. *Semin Pediatr Surg* 2006; 15: 199-207. □

Judith M Morton and Allan R Glanville

IN REPLY: We were interested to read about Robotin's insights gained from her experience at St Louis Children's Hospital, which has one of the largest and most successful paediatric lung transplantation units in the world. We agree that development of local expertise in paediatric lung transplantation would be a cost-efficient means of offering optimum care to young Australians. Because the experience in lung transplants at St Vincent's Hospital, Sydney, has grown, we would like to provide this service for younger recipients, but our centre lacks specific expertise and facilities for ongoing paediatric care.¹

A dedicated paediatric ward with experienced nursing staff in a family-friendly environment is essential to meet world's best practice in this area. There are many complications of the underlying conditions that might benefit from paediatric specialty expertise.

Our experience emphasises that a close working relationship with the patient and his or her family is crucial, and that distance from the location of care delivery and ease of access to the primary treating team are important factors. Given the tyranny of distance, a single Australian centre would be inefficient. However, analysis of outcomes in adult centres shows superior results with increasing transplantation volume, so the concept of small stand-alone centres is not supported by evidence.²

Logistics dictate that linking paediatric services to existing adult services in Australia should improve long-term outcomes. Our data show that performing adolescent lung transplantation in a centre with proven expertise in adult procedures produces excellent results.

We advocate provision of adequate funding and resources in all Australian transplantation centres to achieve optimum service delivery in paediatric lung transplantation.

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1 Morton JM, Malouf MA, Plit ML, et al. Successful lung transplantation for adolescents at a hospital for adults. *Med J Aust* 2007; 187: 278-282.

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Gregory I Snell, Glen P Westall and Trevor J Williams

IN REPLY: We thank Robotin for her positive comments. We agree that the current successful lung transplantation outcomes for adolescents in Australia should be able to be extended to the whole paediatric population in due course.^{1,2} The appropriate timing of the operation and peritransplantation management of young children with advanced lung diseases requires further consideration and debate.³ This should involve the existing lung transplantation services and specific committed paediatric institutions.

However, we disagree that a very low caseload, with procedures performed in a number of institutions, is acceptable. On the basis of cost, training, staffing and political support, it is appropriate to concentrate the expertise. A solid case can be made for a national approach, supported by the Australian Government, with Nationally Funded Centre status. In time, this would provide solid paediatric expertise and access to lung transplantation, either in Australia, or even overseas, as appropriate, during the early evolution of such a program. The objective would be improved survival in children with severe lung disease while minimising the disruption and cost associated with young Australians and their families travelling internationally for lung transplantation care.

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1 Morton JM, Malouf MA, Plit ML, et al. Successful lung transplantation for adolescents at a hospital for adults. *Med J Aust* 2007; 187: 278-282.

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Informing prospective medical students

James M Hillis and Robert D Mitchell

TO THE EDITOR: Applying for medical school in Australia is not an easy process. Prospective applicants must choose from 19 medical schools and multiple course options, navigate admissions processes and tests, and develop some understanding of the pathway towards full registration and vocational training.

Despite this complexity, there is a paucity of information that provides a bird's eye view of the Australian medical school admissions process. There is no single source of information that comprehensively maps the options available to those wishing to embark on a career in medicine. Existing references are often outdated¹ or do not accurately identify all medical courses.²

To fill this information gap, the Australian Medical Students' Association (AMSA) launched its inaugural Medical School Guide in 2007. The guide paves the way for informing prospective medical students about the challenges of studying medicine and the diversity of medical courses on offer in Australia.

The guide contains two sections: "Essential Information" includes details about the categories of entry, admissions tests, support schemes and vocational training pathways; and "The Medical Schools" contains information about individual universities,

including location, entry requirements and procedures, and contact details.

AMSA produced the guide in conjunction with Medical Deans Australia New Zealand (MDANZ) and the Australian Medical Association. Information on individual courses was supplied by the universities, via MDANZ, to ensure accuracy. All but one medical school submitted enrolment information for publishing.

The Medical School Guide was launched on the AMSA website (at <http://www.amsa.org.au/medschoolguide.pdf>), and promotional letters were sent to relevant stakeholder groups. In the 110 days immediately after its release, there were 37 555 hits on the webpage, with more than 3500 downloads of the guide.

In 2008, AMSA hopes to attract the financial and in-kind support required to publish and distribute a hardcopy version of the Medical School Guide. AMSA also hopes to further develop the guide to include information for prospective international students about visa requirements and opportunities to enter the Australian health workforce.

In a dynamic environment where numbers of medical students and schools are on the rise, there is a convincing case for a comprehensive, user-friendly guide to medical school admissions. The AMSA Medical School Guide aims to do this, and its effectiveness will require rigorous evaluation in years to come.

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1 MacKerras P. *Medicine: a guide for prospective students*. Canberra: AGPS, 1996.

2 Australian Government Department of Education, Employment and Workplace Relations. *Course finder [website]*. <http://www.goingtouni.gov.au/CourseFinderSearch.htm> (accessed Dec 2007). □