LETTERS

Subsidised access to TNFα inhibitors: is the rationale for exclusion of rheumatoid-factor-negative patients defensible?

457 Christine Y Lu, Kenneth M Williams, Lyn March, James V Bertouch, Richard O Day

457 Lloyd N Sansom

The medical profession and the pharmaceutical industry: when will we open our eyes?

458 Tim Woodruff

458 Linda V Graudins

459 Scott Masters

459 Rosanna Capolingua

Multicentre research: negotiating the ethics approval obstacle course

459 Hugh G Dickson

460 Kerry J Breen

460 David J Maxwell, Karen I Kaye

460 Martin B Van Der Weyden

Management of obesity

461 Gordon R W Davies

461 Ray C McHenry, Richard W Gilhome, Chris Hensman

461 Huy A Tran

462 Joseph Proietto, Louise A Baur

Thyroid testing 10 years on

462 Richard X Davey

463 Jan R Stockigt

Preventing intrathecal administration of vincristine

464 Peter J Gilbar, Christine V Carrington

Subsidised access to TNFα inhibitors: is the rationale for exclusion of rheumatoid-factor-negative patients defensible?

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To the Editor: The tumour necrosis factor (TNFα) inhibitors etanercept, infliximab and adalimumab are new treatments for rheumatoid arthritis (RA) subsidised by the Pharmaceutical Benefits Scheme (PBS) under strict criteria. These are based on data supplied by the sponsors and protracted discussions between the stakeholders: the Pharmaceutical Benefits Advisory Committee (PBAC), the sponsors, rheumatologists and consumer representatives.[1] One eligibility criterion is that adult patients must be or have been rheumatoid-factor positive. This requirement raises particular concerns.

Rheumatoid factor is not exclusively associated with RA. It is found in a number of other autoimmune and infectious diseases, and has been detected in healthy people. Rheumatoid factor is a serological criterion in the American College of Rheumatology classification for RA. However, its presence is not definitive for a clinical diagnosis of RA, with rheumatoid factor being absent in about 30% of patients with RA. Studies suggest that patients who test positive for rheumatoid factor at baseline are more susceptible to relatively severe expression of RA, with development of erosions and functional disability.[2] As the PBS already limits access to TNFα inhibitors to patients with severe active RA, the predictive value of rheumatoid factor for severity is redundant.

We systematically reviewed 23 clinical trials of TNFα inhibitors available in the public domain (references available on request). The review showed that only the Early Rheumatoid Arthritis trial restricted recruitment to patients who tested positive for rheumatoid factor.[3] The aim of this study was to examine the effect of etanercept on the rate of development of erosions in patients with early RA, not whether rheumatoid-factor status affected response.

We conclude that the evidence for an association between rheumatoid-factor status and response to TNFα inhibitors in patients with severe RA is inadequate to justify rheumatoid-factor status as a criterion for PBS subsidisation. Similarly, no evidence for an association between rheumatoid factor and response to disease-modifying anti-rheumatic drugs has been reported.[4] Nevertheless, potential predictors of response to TNFα inhibitors and such drugs are emerging (eg, polymorphisms of HLA-DRB1, TNFα, and interleukin-10).[5] Further analysis of the unpublished individual patient data held by the sponsors is needed to shed light on this question. Clinical studies specifically designed to evaluate the influence of rheumatoid-factor status on response would be helpful.

The PBAC may have been provided with these data, but patients and clinicians operating in the public domain have not. This gives rise to an ethical dilemma whereby prescribers cannot provide a plausible explanation for why rheumatoid-factor status is an access criterion. For example, if rheumatoid-factor-positive status was selected to exclude patients with rheumatoid-factor-negative psoriatic arthritis, then the rationale would not appear to be ethically sound. Greater transparency with respect to the rationale and the evidence for the criteria selected for targeting subsidised access to important high-cost pharmaceuticals will enhance confidence in the PBS process.

Competing interests: Richard Day is a member of the Advisory Board to sponsors of adalimumab and infliximab, but all payments are received into an audited trust account for research. Ken Williams is a member of the Advisory Board and has been an advisor to the sponsor of adalimumab (Abbott), but has not received recompense. Lyn March is chairperson of the Australian Rheumatology Association Database Steering Committee and, in this capacity, has negotiated with sponsors of etanercept, adalimumab, infliximab, anakinra and leflunomide for educational grants that have been placed in audited trust funds in the Australian Rheumatology Association and the University of Sydney. James Bertouch has been an advisor to sponsors of adalimumab, infliximab, etanercept, anakinra and leflunomide. Recompense received for clinical trials has been placed in audited hospital trust funds for use in the research activities of the Rheumatology Unit, Prince of Wales Hospital, Sydney.

1 Lu CY, Williams K, Day R, et al. Access to high cost drugs in Australia [editorial]. *BMJ* 2004; 329: 415-416.
2 Kim JM, Weisman MH. When does rheumatoid arthritis begin and why do we need to know? *Arthritis Rheum* 2000; 43: 473-484.
3 Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000; 343: 1586-1593.
4 Anderson JJ, Wells G, Verhoeven AC, Felson DT. Factors predicting response to treatment in rheumatoid arthritis — the importance of disease duration. *Arthritis Rheum* 2000; 43: 22-29.
5 Padyukov L, Lampa J, Heimburger M, et al. Genetic markers for the efficacy of tumour necrosis factor blocking therapy in rheumatoid arthritis. *Ann Rheum Dis* 2003; 62: 526-529. ❑

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Comment: I am grateful for the opportunity to put the perspective of the Pharmaceutical Benefits Advisory Committee (PBAC) on this important issue for patients and prescribers using TNFα inhibitors for rheumatoid arthritis.

I can confirm that the PBAC based its recommendation to exclude patients who test rheumatoid-factor negative on a meta-analysis of the data presented to it in the sponsor's reports of two published randomised trials.[1,2] The sponsor of etanercept requested a restriction that limited use to patients with rheumatoid-factor-positive status — a proposition that was queried by the PBAC in its evaluation. The sponsor indicated in its response that rheumatoid-factor status was a treatment-effect modifier. As anticipated by Lu and colleagues, the reason for the recommendation was neither to confirm the diagnosis of rheumatoid arthritis nor an attempt to identify patients with more severe disease. The main reason is that there was some statistical support for the contention that, in patients with rheumatoid arthritis, being rheumatoid-factor positive is associated with a better response to treatment with these drugs. Unfortunately, my request to the sponsor to be able to release in this letter the information on which the decision was based was refused.

The statistical analysis relied on by the PBAC was based on individual patient data, stratifying trial participants into two groups (rheumatoid-factor positive and rheumatoid-factor negative), and then formally applying a test for interaction against the reported treatment effect compared with placebo. Although a post-hoc analysis, this approach has the advantage of relying on the entire trial dataset rather than increasing the likelihood of detecting spurious differences by conducting a series of post-hoc subgroup analyses. It also differs from the systematic review reported by Lu and colleagues, which sought to examine the question based on the reported eligibility criteria of the trials, and therefore could only

be conducted at the level of the overall trial, not the level of the individual patient in the trials. The interpretation of the data available to the PBAC at the time was supported by rheumatologists advising the PBAC about actual restrictions for the subsidy of these expensive agents.

It is perhaps noteworthy that many decisions that guide treatment are made purely on the basis of biological plausibility. On this occasion, there was some statistical support, albeit from a post-hoc analysis, to support any biological arguments. There is inevitably an element of judgement about these decisions, as is clear in the letter from Lu et al, who describe "accumulating evidence" in relation to whether gene polymorphisms "may be predictive of clinical responsiveness".

The current situation, as exemplified in this letter, in which the PBAC is unable to give detailed reasons for its decisions, clearly demonstrates the urgent and critical need for greater transparency of the PBAC processes, and underscores the fundamental right of Australian consumers and prescribers to information relevant to decisions about the subsidy of medicines in this country. The PBAC is willing to examine any new evidence relating to the influence of rheumatoid-factor status on health outcomes and the cost-effectiveness of these agents. If there is additional evidence supporting a review of the current listing, the PBAC would encourage the sponsors of these drugs to prepare appropriate submissions to enable us to evaluate these data. As Chair of the PBAC, I intend to continue to work towards the goal of greater transparency, whereby the outcome of any such new evaluation, and its basis, could be made available to Australian consumers and prescribers.

1 Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumour necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999; 340: 253-259.

2 Moreland, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized controlled trial. *Ann Intern Med* 1999; 130: 478-486. ❑

The medical profession and the pharmaceutical industry: when will we open our eyes?

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To the Editor: It is encouraging to see the Journal continuing its tradition of taking on contentious issues in publishing articles about the negative influence of the pharmaceutical industry.[1] With respect to the practical suggestions to address this issue, I suggest that reliance on our profession to substantially improve the situation, although laudable and appropriate, is too optimistic given the gross denial by our colleagues that there is an issue. Our professional bodies simply do not have the support to enforce codes of conduct. The Royal Australasian College of Physicians (RACP) has published guidelines on this issue,[2] but I doubt most of its members have read them.

I fully support Breen's comments relating to funding of educational activities, but I suggest that the pharmaceutical pseudo-educational dollar be bypassed by a major expansion in government funding.[3] The provision of regularly updated, easily accessible treatment guidelines integrated into prescribing software (which most general practitioners use daily) would go a long way to decreasing our reliance on the drug dollar for information on appropriate treatment. This requires government investment and professional college cooperation, but would lead to recurrent savings to the Pharmaceutical Benefits Scheme and better treatment.

Currently, the federal government spends $21 million on drug information to doctors,[4] while the drug industry spends $1 billion on marketing.[5] To partially redress this imbalance would, however, require both political will and pressure from the profession.

1 Breen KJ. The medical profession and the pharmaceutical industry: when will we open our eyes? *Med J Aust* 2004; 180: 409-410.

2 Royal Australasian College of Physicians. Ethical guidelines in the relationship between physicians and the pharmaceutical industry. Available at: www.racp.edu.au/public/Ethical_guide_pharm.pdf (accessed Jul 2004).

3 Woodruff TG. Pharmaceutical marketing, the PBS, and patient care. *New Doctor* 2004; 81: 21-22 (in press).

4 National Prescribing Service Limited. Annual report 2002–03, p. 32. Available at: www.nps.org.au/resources/content/nps_annual_report_02-03.pdf (accessed Jul 2004).

5 Spending on drug promotion. Available at: www.healthyskepticism.org/promotion/spending.htm (accessed Jul 2004). ❑

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To the Editor: Thank you for publishing the Viewpoint by Breen regarding pharmaceutical industry relationships with the medical profession[1] — but please do not coin the word "pharmaproof". This word unintentionally casts aspersions on fellow clinicians — pharmacists — who share the dilemma of aggressive pharmaceutical marketing influencing professional decisions.

The relationship between the industry and pharmacists is actually more complicated, as we are not only advocates for patients and advisers to doctors on the safe and evidence-based use of medicines, but also the buyers of the pharmaceutical products. This last function means that most pharmacists cannot be removed from the business side of medicine supply and must work with the manufacturers to obtain supplies in a timely fashion and at the best price.

In my work as a hospital pharmacist, the pharmaceutical industry helps in planning financial aspects of medicine supply, sponsoring various activities that the public health system and universities are unable to, and providing specific product information — be it for marketed, unregistered or trial medicines.

Most pharmacists cannot choose to *not* see industry representatives. The formation of such relationships can indeed insidiously affect our clinical decision-making, as outlined by Breen. Unfortunately, the issue of

Correspondents

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There should be no more than 5 references. The reference list should not include anything that has not been published or accepted for publication. Reference details must be complete, including: names and initials for up to 4 authors, or 3 authors et al if there are more than 4 (see mja.com.au/public/information/uniform.html#refs for how to cite references other than journal articles).

industry's influence on pharmacists' decision-making has only rarely been discussed in the pharmacy literature.[2-4]

Both medical and pharmacy clinicians must be aware of this influence and act accordingly. Peter Mansfield's Healthy Skepticism (www.healthyskepticism.org) is a good starting point to increase this awareness. However, the movement must include physicians and pharmacists on the same side. I have often been told that we must have the latest new drug on the hospital's formulary because . . . and have been given a hefty manufacturer-prepared dossier as the sole reason for the request.

I urge physicians to work with pharmacists and be "pharma(cist)friendly", yet also "industryaware".

1 Breen KJ. The medical profession and the pharmaceutical industry: when will we open our eyes? *Med J Aust* 2004; 180: 409-410.
2 Forse RW. Confessions of a fly-fisherman and sometime drug company courtesan. *Pharmacotherapy* 2002; 22: 269-270.
3 Peddicord TE, Baker M, Oki J, et al. A casting call from industry: reel in and retain appropriate information, release the rest. *Pharmacotherapy* 2002; 22: 934-938.
4 Graudins L. Concerns about commercialism [letter]. *Aust J Pharmacy* 2003; 84: 255. ❑

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TO THE EDITOR: The Journal recently published three interesting articles on the relationship between the medical profession and the pharmaceutical industry.[1-3] With Medicines Australia (the pharmaceutical manufacturers' association) setting up a strict code of conduct (tighter than for any other industry I know), a better balance seems to be on the horizon. Breen reminded us of our responsibilities to protect ourselves and our patients from slick marketing by pharmaceutical companies.[1]

One technique our surgery has found useful is to have a personal code of conduct. Our surgery has a guide for pharmaceutical reps (copies available from the author). It advises reps that we are not interested in seeing their promotional material, especially those useless coloured graphs. However, we are very happy to look at published trials regarding their product and associated diseases. Personally, I have found the resources available from many reps useful and timesaving.

Breen is concerned about our professional leaders being in denial about the influence of the pharmaceutical industry on doctors' prescribing habits. If this is so, then the same leaders have complete amnesia and catatonia about another influence that potentially threatens to engulf us.

The sale of supplements and complementary medicines in Australia is a billion-dollar business now. Every month I receive more requests to use supplements for conditions varying from heart disease, cancer and fatigue to non-specific therapies such as detoxification, immune support, metabolic enhancer and anti-ageing. I can sell all these products directly to consumers (patients) at a mark-up I consider reasonable. Alternatively, I can recruit patients to become sellers in a multilevel marketing scheme (similar to pyramid selling). One doctor who practises nutritional medicine full-time has told me he buys $10 000 worth of vitamin E at the start of the year and manages to sell it over the ensuing 12 months for $100 000. I imagine most of that doctor's patients are recommended vitamin E for their health complaints or health maintenance. This is entirely legal, although there are major ethical concerns about conflict of interest.

To date, there has been little debate among our leaders regarding proper guidelines and regulation of this behaviour. With the enormous potential of the complementary industry to be a useful partner in health management, this needs to be sorted out sooner rather than later.

1 Breen KJ. The medical profession and the pharmaceutical industry: when will we open our eyes? *Med J Aust* 2004; 180: 409-410.
2 Rogers WA, Mansfield PR, Braunack-Meyer AJ, Jureidini JN. The ethics of pharmaceutical industry relationships with medical students. *Med J Aust* 2004; 180: 411-414.
3 Hutchinson M. Pharmaceutical companies and medical students: a student's view. *Med J Aust* 2004; 180: 414. ❑

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COMMENT: I commend Masters on his personal code of conduct in dealing with the pharmaceutical industry. I also share his concerns about the ethical minefield that lurks in the interface between complementary and conventional medicine. Some of the issues involved have recently been explored in the Journal's series on Complementary and Alternative Medicine.[1]

However, his scenario of a doctor selling vitamin E to patients raises specific concerns, and the Australian Medical Association's Code of Ethics[2] provides some ethical principles in this regard. Specifically, it states that a doctor should:

- "make sure that you do not exploit your patient for any reason";
- "exercise caution in publicly endorsing any particular commercial product or service not covered by the Therapeutic Goods Advertising Code";[3] and
- "when referring your patient to institutions or services in which you have a direct financial interest, provide full disclosure of such interests".

Translating these principles into daily professional conduct means the practitioner must at all times declare pecuniary interest in the sale of products and be aware of the evidence base of the commercial recommendation so as to not mislead the patient. This involves clear communication of potential benefit, adverse effects, and possible drug–drug interactions of whatever product is promoted.

But, above all, the whole thrust of the AMA Code of Ethics is to ensure that perverse incentives remain foreign to the patient–doctor relationship. Ultimately, it is an individual doctor's choice.

1 Kerridge IH, McPhee JR. Ethical and legal issues at the interface of complementary and conventional medicine. *Med J Aust* 2004; 181: 164-167.
2 Australian Medical Association. Code of ethics. Canberra: AMA, 2004. Available at: www.ama.com.au/web.nsf/doc/WEEN-5WW598 (accessed Sep 2004).
3 Therapeutic Goods Administration. Therapeutic goods advertising code. Available at: www.tga.gov.au/advert/index.htm (accessed Jul 2004). ❑

Multicentre research: negotiating the ethics approval obstacle course

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TO THE EDITOR: Roberts et al[1] state that the National Health and Medical Research Council's *National statement on ethical conduct in research involving humans*[2] clearly outlines that, once approval has been gained from one human research ethics committee (HREC), other sites should accept that approval. Nowhere does the national statement state this.

What Roberts et al appear not to appreciate is that research projects may consume resources within a health service. The HREC might also have the responsibility of ensuring that the tasks required for successful completion of research can be performed without compromising the standard of care of the health facilities in which the research is to be performed. The project in question required the extraction of medical records — someone has to do this and be paid for the task. While centralisation of human research ethics approval might make the task of approval of research faster, each administrative unit has to be able to decide whether to allow participation in a project given its current level of service demand. Approval for multicentre research will therefore still take time whether or not central ethics approval is obtained, and researchers will not find an easy solution to this.

1 Roberts LM, Bowyer L, Homer CS, Brown MA. Multicentre research: negotiating the ethics approval obstacle course [letter]. *Med J Aust* 2004; 180: 139.
2 NHMRC. National statement on ethical conduct in research involving humans. Canberra: NHMRC; 1999. Available at: www.nhmrc.gov.au/publications/synopses/e35syn.htm (accessed Sep 2004). ❑

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COMMENT: It is correct that the National Health and Medical Research Council's *National statement on ethical conduct in research involving humans*[1] (paragraph 3.4) does *not* say that other sites should accept ethics review of a research proposal from another human research ethics committee (HREC). However, the national statement is written to permit and encourage this, but not to enforce it.

Dickson's letter also raises the issue of the terms of reference of HRECs. He alludes to an additional role — as gatekeeper of an institution's resources — which some may feel is beyond the domain of HRECs. The national statement provides the framework for the composition and role of HRECs in their work of ethical review, but does not prevent an institution from asking its committee to also be the steward of access to resources regularly used (eg, medical records, pathology laboratories). The national statement requires an institution to set out the terms of reference for its HREC, "including the scope of its responsibilities" (paragraph 2.2). The prime function of HRECs is to make recommendations about whether a research proposal is ethical, but the final approval about whether the research can proceed rests with each individual institution.

Thus, there is more to getting approval for a research proposal than just the ethical review.

1 NHMRC. National statement on ethical conduct in research involving humans. Canberra: NHMRC; 1999. Available at: www.nhmrc.gov.au/publications/synopses/e35syn.htm (accessed Sep 2004). ❑

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TO THE EDITOR: We are currently coordinating the New South Wales arm of a national quality assurance (QA) project to improve the management of community-acquired pneumonia in Australian hospital emergency departments (CAPTION project: Community-Acquired Pneumonia: Towards Improving Outcomes Nationally, funded by the National Prescribing Service). In the project drug usage evaluation methods are used, and it involves an audit (retrospective review of patient medical records) as well as feedback and targeted education of healthcare professionals about national management guidelines for community-acquired pneumonia.[1] There is no direct patient contact at any stage.

Because this is a QA project, we did not request that participating NSW hospitals seek human research ethics committee (HREC) review. However, we did request that the project proposal be supported by HRECs as a QA activity. Further endorsement from the Chief Executive Officer, Director of Emergency, Director of Pharmacy and other key people and groups was also required.

According to the National Health and Medical Research Council (NHMRC),[2] an appropriately planned QA activity can proceed without HREC review and patient consent if:

- there is consistency with National Privacy Principle 2.1(a); and
- all people involved in the activity are unlikely to suffer burden or harm.

To assist hospitals reviewing this QA project proposal, we developed a number of tools that explicitly outlined the nature of the project and provided answers to the questions in the NHMRC document.[2] These tools were provided to emphasise that this QA project was consistent with NHMRC requirements.

The NHMRC further describes the establishment of hospital policies to allow efficient review of QA proposals that involve minimal risk, burden, alteration of care or invasion of privacy. It is recommended that a member of the HREC be appointed to review such proposals.

Despite the NHMRC recommendations and the provision of tools as described above, full HREC submissions have still been required by four out of eight hospitals to date (recruitment still ongoing). After receipt of an initial expression of interest, completing the HREC submission and obtaining approval in three of these hospitals has taken an average of 5 months. The HREC review has not yet been completed in the fourth hospital. As the project is only funded for a 2-year period, this has resulted in a significant delay in the progress of the project.

We do not challenge the vital role of HRECs, and we value the importance of ensuring the safety and privacy of all involved in human research. If QA coordinators and HRECs work together within the NHMRC recommendations, valuable time and resources could be saved, for both parties. In doing so, the Australian Research Ethics Committees' belief that "quality assurance activities are an essential and integral part of health care delivery that should be encouraged and facilitated" would be one step closer to becoming a reality.

1 Writing Group. Therapeutic guidelines: antibiotic. 12th ed. Melbourne: Therapeutic Guidelines Limited, 2003.
2 National Health and Medical Research Council. When does quality assurance in health care require independent ethical review? Canberra: NHMRC, 2003. Available at: www.health.gov.au/nhm (accessed Aug 2004). ❑

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COMMENT: The distress conveyed by Maxwell and Kaye is the latest in a litany of concerns and complaints to the Journal over recent years about the workings of ethics committees.[1]

At the centre of the protests is the perceived tardiness and inefficiency of human research ethics committees (HRECs) in Australia.[2,3]

But the past decade has also seen reform. The National Health and Medical Research Council (NHMRC) has clarified the relation-

ship between research and quality assurance and when quality assurance proposals require ethical scrutiny.[4] Furthermore, the NHMRC's *National statement on ethical conduct in research involving humans* is clear in its advice that HRECs must establish working procedures that include "timely consideration and review of research protocols", and it also outlines procedures for expediting review of minimal-risk research.[5]

On multicentre research, the statement is also clear, stressing the need to minimise unnecessary duplication in review of such research, and calling for "prompt and efficient consideration of multi-centre research protocols" and adoption of "other administrative procedures to accelerate timely consideration and avoid unnecessary duplication".[5]

With such clear enunciations, what could go wrong? But, as Maxwell and Kaye attest, things *do* go wrong. It seems that either the NHMRC recommendations have yet to be translated into reality or the "silo" mentality of HRECs is deeply ingrained. The time may well have arrived to consider performance indicators for HRECs, or even an accreditation process.

After all, clinical research and quality assurance should not be at the mercy of inefficient HRECs.

1 Jamrozik K. Ethics committees: is the tail wagging the dog? *Med J Aust* 1992; 157: 636-637.
2 Lowenthal RM. Outdated ethical review system impedes important research [letter]. *Med J Aust* 1999; 171: 51.
3 Roberts LM, Bowyer L, Homer CS, Brown MA. Multicentre research: negotiating the ethics approval obstacle course [letter]. *Med J Aust* 2004; 180: 139.
4 National Health and Medical Research Council. When does quality assurance in healthcare require independent ethical review? Canberra: NHMRC, 2003. Available at: www.nhmrc.gov.au/publications/pdf/e46.pdf (accessed Sep 2004).
5 National Health and Medical Research Council. National statement on ethical conduct in research involving humans. 1999. Available at: www.nhmrc.gov.au/publications/pdf/e35.pdf (accessed Aug 2004). ❑

Management of obesity

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To the Editor: The recent article on obesity by Proietto and Baur in the Journal[1] coincided with another by Campos in *New Scientist*,[2] in which he criticised the conventional view of the risks of obesity and the norms usually accepted. Campos quoted evidence suggesting that, in fact, the group in the overweight range (body mass index [BMI], 25–30 kg/m^2) are healthier than those with a BMI below 25 kg/m^2. He also noted that between 1990 and 2002, despite a further increase in the prevalence of obesity in the United States, the incidence of type 2 diabetes hardly changed, while cardiovascular death rates fell. According to Campos, similar claims about the risks of obesity have been repeated over the past 50 years and relate more to cultural and political factors than to reliable scientific evidence.

Clearly, this view is inconsistent with that articulated by Proietto and Baur. While Campos' view obviously does not apply to the grossly obese, there is a strong suggestion that the overall evidence base is inconsistent. This may be because the assumption of a linear relationship between excess weight and illness is false. It is further likely that there is confounding of variables, with weight a proxy for lack of exercise. As Campos points out, large-scale observational studies are inevitably poorly controlled.

If this is so, then it may well be more useful for the medical profession to emphasise exercise and lifestyle rather than weight loss. It may be much easier to obtain and reinforce behavioural change in these areas, and avoid the common feeling of hopelessness ("why bother") expressed by people who find it hard to diet and to lose weight.

1 Proietto J, Baur A. Management of obesity. *Med J Aust* 2004; 180: 474-480.
2 Campos P. Why our fears about fat are misplaced. *New Sci* 2004; 1 May: 20-21. ❑

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To the Editor: We take issue with the recommendations on treatment of morbid obesity in the otherwise excellent article on obesity management by Proietto and Baur.[1]

Like most non-surgical clinicians involved in the management of obesity, they fail to differentiate between the treatment of obesity (body mass index [BMI], 30–35 kg/m^2) and morbid obesity (BMI > 35 kg/m^2). The literature is crystal clear — non-surgical treatments are unsuccessful in achieving and maintaining weight loss in morbid obesity.[2,3] We are unaware of any branch of medicine, other than morbid obesity management, where respected clinicians routinely recommend treatments (drugs, diet and lifestyle modification) which have been *proven* not to be effective.

We challenge all clinicians to accept what the evidence clearly shows, that:

- the only known effective treatment for morbid obesity is surgery;[2,3] and
- laparoscopic adjustable gastric banding is much safer than bypass/diversion surgery[4] and just as effective; it is the treatment of choice for morbid obesity.

1 Proietto J, Baur AL. Management of obesity. *Med J Aust* 2004; 180: 474-480.
2 Perri MG, Fuller PR. Success and failure in the treatment of obesity: where do we go from here? *Med Exerc Nutr Health* 1995; 4: 255-272.
3 National Task Force on the Prevention and Treatment of Obesity, National Institutes of Health. Very low-calorie diets. *JAMA* 1993; 270: 967-974.
4 Chapman A, Game P, O'Brien P, et al. Systematic review of laparoscopic adjustable gastric banding for the treatment of obesity: update and re-appraisal. Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S) report no. 31. 2nd ed. Adelaide: ASERNIP-S, The Royal Australasian College of Surgeons, 2002. Available at: www.surgeons.org/asernip-s/systematic_review/LAGBreviewUp0602.pdf (accessed Aug 2004). ❑

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To the Editor: I read with interest the recent article on obesity in Australia by Proietto and Baur[1] and would like to comment on the issue of proteinuria and measurement of insulin level in obese patients.

Proteinuria in obesity, commonly referred to as obesity-related glomerulopathy, is a clinical syndrome with an estimated incidence of about 2% in obese subjects.[2] With a fifth of the population being obese,[1] the sheer number suspected to have this condition will create an enormous management and cost burden. Furthermore, the incidence of this condition appears to have increased disproportionately to the incidence of obesity.[2]

The syndrome of obesity-related glomerulopathy comprises the triad of morbid obesity, marked proteinuria *without* oedema, and *normal* serum albumin concentration. It can occur in any degree of obesity but is more common in the morbidly obese group (body mass index > 40 kg/m^2; Class III obesity). It often presents as proteinuria on urinary dipstick testing, with marked proteinuria seen on confirmatory testing (up to 32 g/day).[2] Other features of the nephrotic syndrome do not occur, and the cholesterol level is often lower than that in patients with nephrotic syndrome. However, glomerular filtration rate is raised, and glomerulosclerosis is seen on biopsy. The pathogenesis is unknown.

Obesity-related glomerulopathy is a diagnosis of exclusion: secondary causes of proteinuria should be fully eliminated, including hypertensive renal disease and undetected type 2 diabetic renal disease. More often than not, biopsy will be required to guide management, with cost implications.

Although the condition is said to be benign, in a small proportion of patients it progresses to end-stage renal failure requiring replacement therapy, further adding to the cost of management. Fortunately, the condition is readily reversible with weight loss, which is an important emphasis in management.[3]

My second comment relates to the case of the overweight adolescent described by Proietto and Baur. In this patient, measurement of insulin level is not indicated.[4] There is no standardised insulin immunoassay, the sample has to be collected and processed correctly to produce a valid result, and the result would not add to or alter the management of the condition. It is doubtful if normative data exist for adolescents, but the clinical picture suggests the insulin resistance syndrome. As the primary goal would be to detect disordered glucose metabolism, appropriate testing of glucose level is all that is required.

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2 Kambham N, Markowitz GS, Valeri AM, et al. Obesity-related glomerulopathy: an emerging epidemic. *Kidney Int* 2001; 59: 1498-1509.
3 Chagnac A, Weinstein T, Herman M, et al. The effects of weight loss on renal function in patients with severe obesity. *J Am Soc Nephrol* 2003; 14: 1480-1486.
4 American College of Endocrinology. Position statement on the insulin resistance syndrome. *Endocr Pract* 2003; 9: 236-252. ❑

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In reply: We agree with McHenry and colleagues that, until very recently, surgery was the only effective treatment for morbid obesity. However, the development of effective pharmacotherapy that targets the underlying cause — increased hunger — may well change this situation, as evidenced by the effect of leptin treatment in leptin-deficient children.[1] In the not-too-distant future, a medical alternative may be possible.

The issue of the relative merits of surgery to insert a foreign body (gastric band) or permanently alter the anatomy of the gastrointestinal tract versus lifelong pharmacotherapy will need to be considered. However, economic as well as health issues may be important, and, as McHenry and colleagues suggest, may still favour surgery as the preferred therapy.

We thank Davies for bringing to our attention Campos' book *The obesity myth*, in which he claims that overweight individuals are in fact healthier than those of normal weight.[2] While many of the book's other claims can be challenged (such as the statements that the prevalence of type 2 diabetes is not rising in the United States, and that bald men have higher testosterone levels), the fact that there is no simple linear relationship between body mass index (BMI) and illness is correct. Sex, race and fat distribution can all influence the relationship. Moderately overweight women with gynoid (hip and thigh) fat are not at increased risk of illness.[3] In contrast, South Asian people have an increased risk of developing diabetes at lower BMI values than people of European background. We agree with Davies that maintaining fitness through regular exercise is very important in minimising the health consequences of obesity.

Tran raises the issue of whether it is useful to measure insulin levels in children. It is not unreasonable to assume that insulin levels are raised in most obese children, but this is not always the case. The National Health and Medical Research Council clinical practice guidelines for management of overweight and obesity in children and adolescents state that: "Fasting insulin and glucose should be considered in obese children or adolescents, particularly those with a family history of type 2 diabetes, those with acanthosis nigricans and those from certain ethnic backgrounds".[4] In the presence of insulin resistance, serum glucose level remains normal because of high insulin levels. Thus, glycaemia cannot be used to monitor improvement in insulin sensitivity.

1 Farooqi IS, Jebb SA, Langmack G, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N Engl J Med* 1999; 341: 879-884.
2 Campos P. The obesity myth. Viking, 2004.
3 Lean ME, Han TS, Seidell JC. Impairment of health and quality of life in people with large waist circumference. *Lancet* 1998; 351: 853-856.
4 National Health and Medical Research Council. Clinical practice guidelines for the management of overweight and obesity in children. Canberra: NHMRC, 2003. Available at: www.obesityguidelines.gov.au (accessed Mar 2004). ❑

Thyroid testing 10 years on

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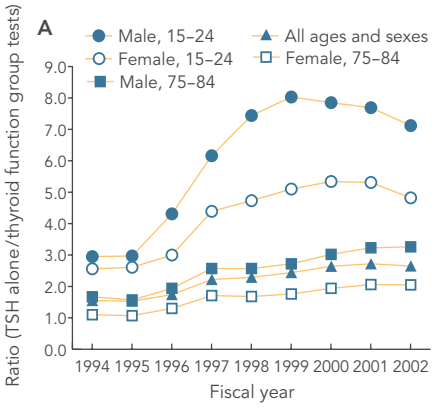
To the Editor: In 1996, the journal published my assessment of the scientific validity of a 1994 decision by the Australian Health Insurance Commission (HIC) to limit the Medicare rebate payment for assessment of thyroid function to thyroid-stimulating hormone level (TSH), except in certain more complex clinical conditions.[1] For these, levels of TSH and of other indicators of thyroid function, such as thyroxine, are tested simultaneously and a rebate given for the group of tests. Although discussion concerning this diagnostic strategy persists,[2] nearly a decade later it is appropriate to assess the outcome of this initiative.

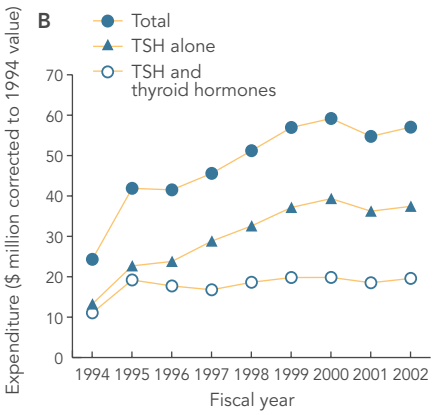
Publicly accessible HIC data[3] on privately ordered, then publicly refunded, thyroid function tests in Australia for the fiscal years 1994–2002 were retrieved and are presented graphically (Box).

Figure A shows the change in thyroid function test ordering sought by the HIC occurring in 1997 through to 2000 and probably now consolidating. Overall, before the initiative, there were 1.55 TSH tests ordered for each thyroid function group test, and in 2002 this increased to 2.65. The outcome in the elderly is similar, but the change is even more noticeable for thyroid testing in young women and men (with

Effect of changes to the Health Insurance Commission rebate for thyroid function testing



A: Ratio of the number of single tests ordered (thyroid-stimulating hormone [TSH]) to the number of thyroid function group tests ordered (TSH and thyroid hormones). Data are tests per 100 000 persons per annum.



B: Annual expenditure on thyroid function testing in Australia.

ratios of about 5 to 1 and 7 to 1, respectively).

Clinicians have presumably come to accept the high negative predictive value of a normal TSH result for ruling out primary thyroid disease as both necessary and sufficient to finalise thyroid diagnoses in the young. By contrast, thyroid disorders are more common among the elderly, who thus more readily satisfy the HIC requirements for thyroid function group tests.

The approximately fourfold increase in absolute terms in the number of single TSH tests performed over 9 years (from 2731 per 100 000 persons per annum in 1994 to 10 763 in 2002) can also be seen as vindicating the HIC's decision to run with a "TSH first" testing protocol. The same pattern is seen in the age and sex groups illustrated (15–24 years and 75–84 years). The present speed, ease and relative economy of obtaining a TSH test, and the reliability, particularly at low TSH levels, of using this measure for thyroid disease case finding, make ordering a TSH test no longer an indulgence,[4] but a clinical necessity.

The national cost-of-living index for 30 June of each fiscal year[5] was used to standardise the annual expenditure on thyroid function tests to 1994 dollar values, thus allowing comparison across the decade (Figure B). From 1995 to 2002, the HIC has contained annual expenditure to under $20 million for thyroid function group testing. This is both desirable and appropriate. That this has been sustained for 7 years in the face of increasing numbers of first-line TSH tests is both astonishing and commendable.

Most of the increase in costs of TSH testing is probably explained by the acceptance of its use as a first-line test. Between the 1996 and 2001 censuses, the population grew from 17.9 to 18.8 million, and the proportion over 65 years also increased (from 12% to 12.5%). Both these trends are continuing,[5] and both also explain some of the increase in ordering of TSH tests. It is unclear if any of this change is also due to testing moving from the totally public, hospital sector, not funded by the HIC, to the HIC-funded sector.

1 Davey RX, Clarke MI, Webster AR. Thyroid function testing based on assay of thyroid stimulating hormone: assessing an algorithm's reliability. *Med J Aust* 1996; 164: 329-332.
2 Beckett GJ, Toft AD. First-line thyroid function tests — TSH alone is not enough [commentary]. *Clin Endocrinol* 2003; 58: 20-21.
3 Health Insurance Commission. Medicare Benefits Schedule (MBS) Item Statistics Reports. Available at: www.hic.gov.au/statistics/dyn_mbs/forms/mbs_tab4.shtml (accessed Nov 2003).
4 White GH, Walmsley RN. Can the initial clinical assessment of thyroid function be improved? *Lancet* 1978; 2: 933-935.
5 Australian Bureau of Statistics. 6401.0 Consumer Price Index, Australia; 2001 Census Basic Community Profile; and 1996 Census of Population: Basic Community Profile. Available at: www.abs.gov.au (accessed Nov 2003). ❑

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COMMENT: In his timely review of changing patterns of thyroid function testing, Davey suggests that Australian Health Insurance Commission (HIC) policy is responsible for the increased emphasis on a "TSH-first" strategy, with consequent containment of costs for other thyroid function tests. While this may in part be true, the trend towards initial TSH testing has been advocated worldwide[1] following the development of TSH assays sufficiently sensitive to distinguish the typical suppressed TSH levels of thyrotoxicosis from normal levels. The developments documented by Davey are a consequence of technological development, perhaps enhanced by selective rebating as a result of HIC policy.

It is unfortunate that current HIC policy is sometimes described as *prohibiting* more complete thyroid function testing, unless TSH level is abnormal. Rebate policy does not prohibit any line of testing and it is because the "TSH-first" approach has some serious, well-documented deficiencies.[2] Measurement of levels of thyroid hormone in addition to TSH is clearly sanctioned in HIC regulations when TSH level alone can be misleading, for example in suspected pituitary dysfunction, or in monitoring the treatment of thyroid dysfunction. The adverse consequences, both human and financial, of relying on TSH measurement alone in such situations can be serious and may outweigh the savings achieved by restrictive testing. It must be noted again that a normal concentration of immunoreactive TSH has no predictive value in ruling out potentially life-threatening hypopituitarism,[3] which may present with prominent hypothyroid features.

The effective integration of clinical and laboratory investigation of potential thyroid dysfunction requires an active laboratory–clinical interface. There are over a dozen patterns of thyroid function — some trivial or inconvenient, some quite serious — that can be misdiagnosed or incorrectly managed if communication across this interface is inadequate.[4] Effective communication requires relevant information from the clinician and a response to this information within the laboratory. It is a reality that current patterns of investigation in Australia frequently fall short of this ideal. If, as a result of automation and effective competition, the unit cost of assays can eventually be reduced in relation to the total cost of medical care, it may become appropriate to revert to a more complete panel of initial testing that integrates tropic hormone and target gland secretion, a strategy that remains the cornerstone of definitive endocrine investigation.

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2 Beckett GJ, Toft AD. First line thyroid function tests – TSH alone is not enough. *Clin Endocrinol (Oxf)* 2003: 58; 20-21.
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reduced biological activity of immunoreactive thyrotropin. *J Clin Endocrinol Metab* 1979; 48: 989-998.
4 Stockigt JR. The laboratory-clinical interface. In: Clinical strategies of thyroid function testing. Thyroid disease manager, Chapter 6B. Available at: www.thyroidmanager.org/ (accessed Sep 2004). ❑

Preventing intrathecal administration of vincristine

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TO THE EDITOR: The national media recently highlighted the tragic consequences of the inadvertent spinal administration of the antineoplastic drug vincristine. The *7.30 Report* (ABC Television) detailed the case of a young man erroneously administered vincristine intrathecally instead of, as intended, intravenously, resulting in progressive neurotoxicity, paralysis and death.[1]

Since the first report in 1968 of unintentional intrathecal administration of vincristine,[2] many, invariably fatal, cases have been described. These have involved a combination of human and system errors affecting the medical, nursing and pharmacy professions.

On behalf of the Society of Hospital Pharmacists of Australia, we recommend the following strategies to reduce the opportunity for error:

- Only specifically trained and designated oncology staff should prepare, dispense and administer cytotoxic medication.
- Intrathecal chemotherapy should only be administered during normal working hours, and in an area where no other cytotoxic drugs are given or stored.
- Medical staff must use a formal checking procedure, involving an oncology-trained nurse, to ensure the right drug is given at the right dose, by the right route, to the right patient.
- Intrathecal drugs must be packaged separately and clearly labelled both on the syringe and outer container "For intrathecal use".
- Specifically designated containers should be used for transportation of intrathecal drugs from the pharmacy and for storage on the ward.
- Intrathecal doses should be delivered separately and preferably administered after drugs to be given by other routes have been supplied to the ward and administered.
- Vincristine should be prepared in a small-volume intravenous bag rather than a syringe.[3] For adults, prepare vincristine in an intravenous bag in 50 mL of sodium chloride 0.9% and administer it as a short intravenous bolus over 5–10 minutes. Smaller volumes and a slower administration rate are suggested for children. While this method has been criticised as potentially increasing the risk of extravasation injury, this has not been reported as a problem.
- Vincristine should be clearly labelled both on the intravenous bag and outer container "For intravenous use only — fatal if given by other routes". Negative labels, such as "Not for intrathecal use", must *never* be used.

Many hospitals currently use syringes for vincristine and increase the diluent volume in the syringe as a deterrent to intrathecal administration; however, fatalities have occurred after the administration of vincristine supplied in 10 mL[4] and 20 mL[5] syringes. The safest method of eliminating the potential for spinal instillation of vincristine remains the abolition of the syringe as a means of administration.

1 ABC Television. The 7.30 Report. 2004; 5 May. Hospital mistakes. Available at: www.abc.net.au/7.30/content/2004/s1102214.htm (accessed Sep 2004).
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