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This Issue in the Journal

Deaths from poisoning in New Zealand: 2001–2002
R McDowell, J Fowles, D Phillips

This paper summarises deaths in New Zealand as a result of poisoning for the years 2001 and 2002. Case demographics (such as age, sex, and ethnicity) are presented, along with details on the poisoning agents involved in the fatalities. These findings are then compared with fatal poisoning trends for other countries. It is expected that the findings presented (such as the prominence of poisonings amongst males, persons aged 24–44 years, and the use of carbon monoxide from vehicle exhaust) can assist health professionals to reduce the occurrence of poisoning incidents.

Increased rates of trimethoprim resistance in uncomplicated urinary tract infection: cause for concern?
D Mangin, L Toop, S Chambers, R Ikram, B Harris

This study from the Christchurch General Practice Research Group assesses changes in antibiotic resistance rates in bacteria causing urinary tract infections presenting to Christchurch GPs. The results suggest that trimethoprim still appears to be a reasonable antibiotic for treatment of urinary tract infection in women. Put another way, there is only a 1 in 13 chance women will require a second antibiotic if initially treated with trimethoprim. However, the apparent rise in trimethoprim resistance rate over two years is of concern and a third study is needed to confirm whether this rise is sustained. This further highlights the need for regular prospective monitoring of antibiotic resistance levels in the community.

Vitamin D deficiency among patients attending a central New Zealand rheumatology outpatient clinic
G Chiu

Vitamin D deficiency has been linked to autoimmune diseases such as rheumatoid arthritis, type I diabetes, and multiple sclerosis. This study looked at vitamin D levels in an outpatient arthritis clinic population in whom vitamin D levels were found to be lower than that reported for the general New Zealand population. This suggests that maintaining high levels of vitamin D through adequate sunlight exposure may have an important role in preventing autoimmune disease, and that all existing patients should be screened for vitamin D deficiency.
Older patients in the nephrology clinic—should they be referred?
S Lynn, R Sainsbury, M Searle

Kidney disease in the elderly is an increasingly common problem. A review of older patients seen at a nephrology clinic has shown that most of these patients have chronic disease and do not require intensive investigation. The majority of these patients can be managed by their family doctor with preventive strategies to delay the progression of disease. A proportion of patients do require specialist review and a set of referral guidelines has been proposed to aid in appropriate and timely referral.

The Christchurch Tissue Bank to support cancer research
H Morrin, S Gunningham, M Currie, G Dachs, S Fox, B Robinson

Advances in the management of cancer depend on research using samples of tissue from patients, with careful and detailed study of features of the cancers, including genetics changes and of the results of treatment. All research needs consent of the patient and approval by the appropriate ethics committees. The Christchurch Tissue Bank (CTB), begun in 1996, provides a common pathway for collecting samples and now has tissues from over 2000 donors. The consent form has evolved to meet changing requirements, and now includes consent for access to medical records, sending tissues overseas, and use by commercial collaborators—all of which were acceptable to more than 97% of donors. Sample disposal with a karakia blessing was requested by 36% of the donors. The CTB, now supported by the Cancer Society, Canterbury-West Coast division, offers a successful model that could be applied in other New Zealand centres.
Deaths from poisoning in New Zealand—new study helps identify and justify priorities for prevention

Michael Beasley, David Reith

The paper by McDowell et al in this issue of the Journal presents interesting data on poisoning fatality rates in New Zealand over 2001 to 2002. While the estimated annual rate is similar to those recently reported from several other industrial nations, this provides no grounds for complacency.

This type of study has been facilitated by the recent establishment of a national chemical injuries surveillance system (CISS), intended to develop improvements in the availability of poisoning data. This system incorporates data on fatal cases obtained from the Coronial Services Office (CSO)—including demographics, names (not concentrations) of drug(s) involved (usually extracted from the toxicology reports), as well as coroner verdicts on circumstances, cause, and ‘intent’ of the deceased. These developments increase the capacity to deduce the underlying causes of death, and the specific agent(s) involved, compared to earlier studies based on national mortality and hospital discharge databases that utilised ICD Codes combined with E Codes, which only classified or ‘drilled down’ to the level of broad classes of agents.

However while such developments should be applauded, some biases and uncertainties may remain as the authors acknowledge. The system relies on coroner verdicts, and there can be variation between coroners in their distinction between unintentional and intentional deaths, with under-reporting of suicide, including from poisoning.

Drug concentrations, toxicology and pathology reports, as well as police and other statements, are held only in the CSO files. Furthermore, only the ‘primary’ substance adjudged responsible for the fatality is usually discussed (although data on other drugs taken by the deceased is available), which can over simplify the situation.

Drugs can also play a significant but unrecorded role in some motor vehicle or other ‘accidental’ deaths. Comparison between studies can also be limited by different inclusion criteria. These and other factors can adversely affect the ability to make firm conclusions, and to date there is insufficient New Zealand data to examine trends.

Having said that, the author’s data is probably sufficiently ‘robust’ to consider the implications. Two-thirds of all deaths were adjudged intentional, with a substantially higher suicide rate for males. Young adults are a significant risk group but are not those at greatest risk. The observed differences with respect to geographical area and ethnicity are intriguing, though the time period surveyed may be insufficient to ‘iron out’ random fluctuations.

Less debatable is the strong correlation with low socioeconomic status, which is consistently reported. The overall pattern has similarities to other research indicating that people dying from drug-related causes are most likely to be male, unemployed (or earning a low income), single, and middle-aged.
Carbon monoxide (CO) features prominently in poisoning statistics, and the greatest specific reduction could indeed come from successful interventions in this area. Practical measures include reducing motor vehicle emissions via catalytic converters, and there is some evidence this has resulted in fewer CO deaths, both suicidal and accidental. Therefore their recommendations regarding CO detectors to enable shutting down of vehicles, and systems limiting engine idling to short periods also have merit. However as noted, earlier interventions regarding CO have not been consistently associated with reduced overall suicide deaths, due to increased utilisation of other methods.

Only four CO deaths were deemed unintentional, representing a lower rate than that reported in the United States, where this is a recurring concern (albeit declining, possibly due in part to increased safety of home appliances and use of CO alarms). Unintentional fire-related deaths included two in young children due to cooking oil fires. Educational programmes in this area are well justified, given some evidence suggesting community-wide efforts to provide free smoke detectors can be beneficial.

The most frequently involved pharmacological agents were opiates—particularly methadone, morphine, and heroin. Of significance, unintentional deaths were substantially more common than intentional deaths, particularly with methadone. Its toll likely relates to the illicit supply or diversion to persons for whom it is not prescribed, and/or the provision of multiple doses or ‘takeaways’ that may be consumed as a single dose. Naive users are particularly vulnerable, though periods of abstinence in serious users presents danger through significant loss of tolerance. This ‘takeaway’ phenomenon has been noted elsewhere, and recommendations to review this practice are justified. It appears the number of methadone deaths reflect more the conditions under which it is dispensed, rather than its frequency of prescribing.

Also featuring prominently were dextropropoxyphene/paracetamol preparations, both in terms of intentional and unintentional deaths. Reith et al presented data highlighting risks from dextropropoxyphene (long of concern in the United Kingdom, and now more recognised internationally). Deaths from overdose can be rapid, and in such cases cardiac factors can be more significant than respiratory depression. This compound also carries an unexpectedly high rate of accidental death, so restriction of its availability is well justified.

The second most commonly implicated drugs were the tricyclic antidepressants; amitriptyline most often, followed by dothiepin, doxepin, and nortriptyline. These have featured quite prominently in studies examining not only numbers of antidepressant deaths but also fatality ‘rates’, as determined by adjustments for the number of prescriptions and/or their “defined daily doses” (DDD).

The latter study, employing similar methods to this current one, found a particularly high and statistically significant rate for dothiepin and doxepin. The authors acknowledge potential for certain biases given no individual data were provided to allow statistical correction for possible confounders. However there is some experimental evidence to suggest the above tricyclics are among those of greatest risk, as assessed either by toxicity (lethality) studies in animals or by markers of effects on cardiac sodium (or other ion) channels, which can be a significant factor in their arrhythmogenic potential and ability to cause seizures in overdose.
In such situations of broad reproducibility of epidemiological findings plus some supportive experimental data, recommendations to restrict availability of adjudgedly more toxic drugs within a class can be supported. Limitations on the availability of medications with greater toxicity may result in an overall mortality reduction. Furthermore, limitation of pack sizes has contributed to a reduction in ingested doses in self-poisoning, and hence risk per episode. Such efforts to identify high-risk pharmaceuticals and provide less toxic alternatives and/or safer prescribing practices appear beneficial in reducing the toll from those agents specifically. Similarly, practical means of minimising exposures to high-risk ‘environmental’ chemicals have shown benefit.

Analysis of poisoning fatality data is useful in identifying changes in the characteristics of chemical- and drug-related deaths, and to determine what can be changed in terms of exposure sources, drug availability, and prescribing patterns. However non-fatal poisonings also can result in significant morbidity (sometimes long term) with considerable associated costs, and knowledge of their epidemiology is important.

Other data, including from hospitals and the National Poisons Centre, can play a valuable role in identifying causative agents and circumstances of exposure, so facilitating strategies for prevention. Another major source of ‘poisoning’ is adverse effects arising from medicines during therapeutic use, and the N.Z. Pharmacovigilance Centre plays an important role by assisting to identify and document such effects.

Lastly, the maintenance of all of these mechanisms is important for the future reduction in injury from medicinal and chemical exposures. Follow-up studies of various kinds will enable assessment of the effectiveness (or otherwise) of specific interventions, and will identify new threats and overall trends.

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Independent nurse prescribing in New Zealand

Peter Moller, Evan Begg

The New Zealand Government is about to legislate to allow independent nurse prescribing. Within nominated areas of expertise, suitably re-trained Nurse Practitioners would have equivalent prescribing rights to that of a Medical Practitioner. The introduction, educational requirements, scope of practice, and the monitoring of outcomes and standards would be the responsibility of the Nursing Council of New Zealand.

We propose that this is a threat to the standard of healthcare in New Zealand for three main reasons:

- Appropriate prescribing depends on accurate diagnosis. This is the fundamental purpose of a medical education. Nursing training, on the other hand, has been more about appropriate caring.
- The knowledge base for good prescribing is the medical curriculum, the subsequent training of junior doctors, and continuing medical education. Prescribing is probably the most dangerous activity that the medical degree confers on doctors.
- Good medical care depends on teamwork. Teamwork is effective when each member of the team recognises their own role and the superior capabilities of other members of the team in their roles. Duplicating activities and roles undermines this principle, and thus independent nurse prescribing will damage teamwork.

The need for change

The Ministry of Health’s July 2005 consultation document Implementing nurse practitioner prescribing\(^1\) gives several justifications for the proposed change:

- Midwives are able to prescribe.
- There is international evidence on the safety, effectiveness, and cost-effectiveness of nurse prescribing.
- “Collaboration (will be) enhanced when it is between team members who have equivalent access to power, status, and information and who share mutual goals.”
- The Nursing Council could find no research to support the contention that the nursing master’s degree is insufficient for independent prescribing.

The example of midwives

It is claimed that the administration of areas of practice of nurse practitioners by the Nursing Council is a model “similar to that which has been successful in ensuring safety for midwifery prescribing.” This contention lacks supporting evidence.
In the past, the National Women’s Hospital kept a close watch on obstetric and perinatal morbidity and mortality. But with the loss of medical involvement in primary obstetric care, this monitoring lapsed. Thus we do not know whether midwife prescribing has been as safe as it should be.

Safety and competence

It is stated in the consultation document that “the nurse practitioner must demonstrate that her/his knowledge and skills are directly applicable to the selected area. This significantly minimises any risks to public safety, as it allows the boundaries of the area of practice to be defined precisely.”

This is a naïve view of prescribing. When doctors prescribe, they must take into account all other conditions and medications. It is not possible to practice safely by prescribing with blinkers determined by a supposed limited area of practice. For example, medications for arthritis affect the control of hypertension and congestive heart failure. They may destabilise diabetes. There can be problems in those with impaired renal function. Indeed, there are many potential organ-system side-effects. We are thus dealing with a complexity of interactions with other disorders, other drugs, and side effects on various systems, which are wider than a nominated area of practice. Thus the knowledge base required is thorough and comprehensive.

How can someone with less training in physiology, pathophysiology, pathology, diagnosis, and pharmacology prescribe with the same degree of safety and competency as a doctor?

Cost-effectiveness

Diminishing the prerequisite standards for prescribing is a curious action when one considers the stringent requirements of the United States’ Food and Drug Administration (FDA) and New Zealand’s Medicines Assessment Advisory Committee (MAAC) for the marketing of a new medicine, plus the increasingly stringent requirement for accreditation and credentialling of organisations and doctors.

It is claimed on the basis of a few studies that there is “international evidence on the safety, effectiveness and cost effectiveness of nurse prescribing.” But cost-effectiveness studies in relation to medications are extremely complex and difficult to validly perform. There are many factors in the short- and long-term that have to be considered. Unless prescribing is based on accurate diagnosis and sound knowledge of pathophysiology and pharmacology, it is a dangerous activity which risks increased direct and indirect costs.

Teamwork

The consultation document claims “although nurse practitioners are autonomous in their clinical practice, usually a collaborative approach ensures that referrals are made to medical or allied health colleagues as the need arises.”

This theoretical claim runs counter to the experience of independent midwifery in New Zealand. We have seen publicity about misadventures concerning delivery and the management of newborn infants due to lack of consultation when the midwife did not recognise the difficulties.
We do not know how serious this issue is, because data has simply not been recorded, and valid comparisons about outcomes cannot be made. Initially, independent midwifery was hailed as a great advance to improve choice. There is now less choice in obstetric care in this country. Not only have general practitioners with Diplomas of Obstetrics left obstetric practice, we are now told that the country is short of 1000 to 2000 midwives.

Ron Barker, a previous Director-General of Health, pointed out in 1975, “in any organisation of staff the interests of the patient must be paramount and these are best served by the intellectual stimulation of good teamwork. Teamwork involves a clear definition of the role of each member and an acceptance by all the team that each member fulfils his own role better than any other member can.”

The blurring of roles which followed the development of independent midwifery will occur across a wide area of healthcare if independent nurse prescribing is instituted. The wider consequences of this are unpredictable.

The patient’s interests

Any change in healthcare practice should be motivated by benefit to patients. Proposed changes to the delivery of healthcare need to be subjected to rational analysis and then trialled if they are still thought to be worthy. The decision to go ahead with independent nurse prescribing indicates either that the Minister of Health has received poor advice or that there is a political wish to radically alter the pattern of delivery of healthcare.

The motivation to develop independent nurse practitioner prescribing for “equivalent access to power, status and information” does not appear to be directed to patients interests. The Ministry of Health criticises the medical position that nurses should only have access to ‘dependent prescribing.’ It is stated that in the view of the Nursing Council this is “not in keeping with a modern healthcare delivery system, the best use of health care personnel, and the development of prescribing nurse practitioners.”

This is a controversial statement designed to bolster an adopted position. Whilst everyone should have the opportunity to develop their professional expertise, it must first serve the long-term interests of patients. To propose that expanding nurse prescribing is desirable because “nurse prescribers (will) benefit from the opportunity to develop and extend their skills” places the interests of patients second to a major experiment on behalf of a sectional interest.

A better alternative—‘dependent prescribing’

The Minister of Health and the Government need to think again about independent prescribing by Nurse Practitioners. We see merit in suitably qualified nurse practitioners strengthening a health team where there is overarching medical responsibility for diagnosis and consideration of general medical issues. Advising on dose-alteration of drugs in a diabetic clinic is a prime example.

Prescribing by nurses within a team or special group has its own dangers but it has inbuilt safety and quality controls which independent nurse prescribing lack. In this regard there needs to be coordination of medical, nursing, and allied health proposals...
so that independent regulators do not jeopardise the safety and competence of the system as a whole.

The current proposal for independent nurse prescribing risks serious damage to teamwork and will have unforeseen consequences on standards of safety and competence. Prescribing within a team or unit, with proper accountability and quality controls, is much more likely to be in the best interests of the people of New Zealand.

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Deaths from poisoning in New Zealand: 2001–2002
Rebecca McDowell, Jeff Fowles, David Phillips

Abstract

Aims To describe the epidemiology and toxicology of poisoning deaths in New Zealand for 2001 and 2002.

Methods Poisoning mortality data for 2001 and 2002 were collected from the Coronial Service Office (CSO) as part of the New Zealand chemical injury surveillance system.

Results There was 235 and 234 poisoning deaths in 2001 and 2002 respectively, an annual rate of 6.3 [95% CI of 5.5 to 7.1] deaths per 100,000 population for both years. Two-thirds (67.0%) of the deaths were intentional. The 25–44 year age group had the largest number of cases and highest age-specific rate (123 deaths, 11.1 [95% CI: 9.3–13.2] per 100,000 in 2001 and 119 deaths, 10.7 [(95% CI: 9.0–12.8] per 100,000 in 2002). Over two-thirds (68.9%) of the deaths were male. In 2001, the European rate was slightly higher than that for Maori but rates for the two ethnicities were similar in 2002. Geographically, West Coast District Health Board (DHB) had the highest rates. Rates increased with increasing deprivation. Nearly two-thirds (64.3%) of the intentional deaths were attributed to carbon monoxide. Methadone, morphine or heroin, and ethanol were the leading causes of the unintentional deaths.

Conclusions The rate of poisoning deaths in New Zealand is comparable with other industrial countries as is the prominence of poisoning as a leading method of suicide.

Poisonings, both accidental and intentional, are a common occurrence in New Zealand and internationally. Many countries have established surveillance systems to monitor the incidence of poisonings events. These surveillance systems (by collecting specific data on substance/product, circumstances, outcome, and specific susceptible groups) assist health professionals in the prioritising of resources for facilitating investigations and interventions, with the aim of reducing the incidence of poisoning. The surveillance systems also allow for international comparisons of poisoning rates, although some caution is necessary as the systems are often based on different methodologies. In New Zealand, a national chemical injury surveillance system was initiated in 2001.

Unfortunately, several poisoning events result in death, causing much anguish to family and friends, and adding to costs for health and other agencies. The New Zealand national chemical injury surveillance system incorporates data on fatal poisoning cases obtained from the national Coronal Services Office (CSO). These data include case demographics, toxicology reports, and the coroner’s verdict together with the causes and circumstances surrounding each death.

This paper describes the epidemiology and toxicology of chemical and poisoning deaths in New Zealand for 2001 and 2002 based on the CSO data, and compares these to international findings.
Methods

Poisoning mortality data for 2001 and 2002 were collected from the national Coronial Service Office (CSO) in Wellington as part of the New Zealand national chemical injury surveillance system. Anonymised, quarterly extracts of the CSO database containing case demographics and coroners’ findings were collated and poisoning cases identified on the basis of the coroners’ verdict and subcategory (e.g. suicide and carbon monoxide poisoning or drug abuse and solvent). Intent, address of exposure, and toxicology results were subsequently obtained manually from the coroners’ hard copy files.

Intent (intentional, unintentional/accidental, or indeterminate) was recorded according to the judgement of the coroner. Ethnicity (only one) was obtained by CSO staff from the post mortem report, Police ‘47’ report, or briefs of evidence. Toxicology data were obtained from toxicology reports, present in approximately 95% of the coroner’s files.

All substances detected were recorded with the exception of alcohol (where the blood level was less than 20 mg/100mL) and lignocaine. Where the toxicology report was absent, the substances involved were extracted from either the coroner’s summary, the pathology report, police statements, or statements of family/friends. The substance primarily responsible for each death was identified from the cause/circumstances of death recorded by the coroner; or if not specified, from the toxicology report. The NZDep2001 decile scale\(^1\) was used to measure deprivation for cases with an exposure address geocoding to at least an accuracy of ‘Street.’

The 2001/2 data, as of 30 April 2004, are estimated to be 95% complete. Rates were calculated using 2001 Census data and expressed per 100,000 population with 95% confidence intervals. Rate ratios and 95% confidence intervals were calculated where appropriate. A robust method of constructing 95% confidence intervals was used to determine ‘statistically significant differences.’\(^2\) Analyses were performed using OLAP cubes on Microsoft SQL Server 2000 and Excel 97 software programs.

Results

The number of deaths attributable to chemical injury in New Zealand for 2001 and 2002 was 235 and 234 respectively. The annual rate was 6.3 [95% CI: 5.5–7.1] deaths per 100,000 population for both years. The majority of the deaths were intentional (68.9% in 2001 and 65.0% in 2002). The associated intentional death rate for 2001 was 4.3 [95% CI: 3.7–5.1] per 100 000 population and for 2002 it was 4.1 [95% CI: 3.5–4.8] per 100,000.

Deaths by District Health Board—District Health Boards (DHBs) (Figure 1) with the greatest number of deaths for 2001 were Canterbury (31) and Waitemata (24). The highest rate was from West Coast (13.2 [95% CI: 5.1–34.0] per 100,000 population (4 deaths). 2002 findings were similar; again West Coast had the highest rate (19.8 [95% CI: 9.1–43.3] per 100,000 population, 6 deaths) and Canterbury the highest number of deaths (28), followed by Waitemata and Auckland (24 each).

DHBs (with greater than 10 deaths in a single year) which had a higher than average percentage of unintentional deaths included Auckland (47.4% in 2001 and 41.7% in 2002) and Hawke’s Bay (45.5% in 2001). However in 2002, none of the eight Hawke’s Bay deaths were deemed unintentional. We are unable to exclude the possibility that this regional difference might be explained by variation between coroners.
Deaths by age group—For both years (2001 and 2002), the greatest number of deaths and highest age specific rates occurred in the 25–44 year age group (123 deaths, 11.1 [95% CI: 9.3–13.2] per 100,000 in 2001 and 119 deaths, 10.7 [95% CI: 9.0–12.8] per 100,000 in 2002) (Figure 2). On average, nearly two-thirds (63.6%) of the deaths aged 25–44 years were deemed intentional.

There were two deaths amongst children aged less than 5 years (one in 2001 and one in 2002); both were unintentional and were due to cooking oil fires. There were also two deaths among 5–14 year olds; one resulted from intentional petrol ingestion, the other from cerebral anoxia secondary to inhalation of solvents—namely butane, propane, and isobutane. Intent was unknown for the latter case.
Deaths by sex and ethnicity—Sex was known for all deaths. For both years, significantly more were male. The associated male/female rate ratio for 2001 was 2.5 [95% CI: 0.7–8.6] and for 2002 was 2.2 [95% CI: 0.7–7.0]. In 2001, males had a slightly higher proportion of unintentional deaths than females, but this trend was reversed in 2002.

In 2001, where ethnicity was known (203/235 deaths), 82.3% of deaths (167/203) were classed as Europeans—a rate of 6.4 [95% CI: 5.5–7.4] per 100,000 population. The ethnicity specific rate for Maori was 4.8 [95% CI: 3.2–7.0] per 100,000 population and for Pacific Peoples (such as Samoan and Tongan) it was 4.0 [95% CI: 2.0–7.9] per 100,000 population.

In 2002, the percentage and ethnicity specific rate for Europeans was similar to that observed in 2001 (79.1%, 6.2 [95% CI: 5.4–7.3] per 100,000 population). There was a noticeable increase in the rate for Maori to 6.1 [95% CI: 4.3–8.6] per 100,000 population and a decrease in the rate for Pacific Peoples to 2.5 [95% CI: 1.1–5.8] per 100,000 population.

The majority of the European and Asian deaths for both years were deemed intentional (70.3% and 87.5% respectively). In comparison, only 38.5% and 40.4% of the Pacific Peoples and Maori deaths respectively were deemed intentional.

Deaths by socioeconomic status—Combined results for 2001 and 2002 show that rates were found to increase with increasing deprivation. The annual rate for cases with a deprivation score of 1 or 2 was 4.0 [95% CI: 2.9–5.7] per 100,000 population.
compared to 7.0 [95% CI: 5.3–9.2] per 100,000 population for cases with a deprivation score of 9 or 10 (i.e. the most deprived).

**Deaths by substance**—Substance data was similar between both years. Sixty-one different primary cause chemical substances were associated with the deaths, with just under half (46.7%) of the primary substances classed as ‘Household/Domestic Chemicals.’ The next most prominent substance class was ‘Therapeutics’ (31.1%) followed by ‘Chemicals/Drugs of Abuse’ (19.4%).

The main contributor to the ‘Household/Domestic Chemicals’ class was carbon monoxide. Carbon monoxide was the primary substance involved in 43.9% of the total deaths (206/469). In particular, it was attributed to nearly two-thirds of the intentional deaths (64.3%). The other leading primary substances were methadone (32), morphine or heroin (31), ethanol (23), hydrocarbon (such as petrol, butane, or LPG) (22), and amitriptyline (19) (Table 1). Methadone, morphine or heroin, and ethanol were the leading causes of the unintentional deaths.

Just under half (49.5%) of the deaths involved more than one substance. It should be noted that each case does not necessarily undergo a comprehensive screen for all possible substances. Thus, the proportion of deaths with more than one substance is a minimum estimate.

**Discussion**

There were 469 poisoning deaths in New Zealand for the years 2001 and 2002, an annual rate of 6.3 [95% CI: 5.5–7.1] deaths per 100,000 population for both years. In comparison, poisoning death rates (based on ICD-9 and ICD-10 external causes of poisoning) in 2001 for England and Wales (and Canada) were 7 per 100,000 population, \(^3\) and 8 per 100,000 population for the United States.\(^3,4\)

In a previous international comparison study by Fingerhut et al.,\(^5\) Norway (1990–94), the United States (1995), England and Wales (1993–95), Canada (1994–95), and Australia (1993–95) had annual poisoning rates of 6–7 per 100,000 population—comparable with New Zealand’s rate (1984–93). Denmark (1994–95), on the other hand, had a higher rate at 13 per 100,000 population while the rates for Israel (1993–95) and the Netherlands (1995) were lower (1–2 per 100,000 population).

Exactly two-thirds of the New Zealand poisoning deaths in 2001/2002 were intentional (suicide), the associated intentional death rate for 2001 was 4.3 [95% CI: 3.7 to 5.1] per 100,000 population and for 2002 it was 4.1 [95% CI: 3.5–4.8] per 100,000.

Suicide by poisoning has been the leading method of suicide in New Zealand, accounting for 38% of suicides between 1988 and 1997.\(^6\) The study by Fingerhut et al.,\(^5\) found that (as with New Zealand) poisoning was the leading method of suicide in England and Wales, Scotland, and Australia, accounting for between 37% and 47% of suicides.

In New Zealand, poisoning accounted for 51% of the female suicides between 1988 and 1997.\(^6\) Poisoning, however, was not the leading method of suicide for New Zealand males. The 1988–1997 data show that (among male suicides) poisoning was a close second after hanging. During this time period, 38% of the suicides were from hanging compared to 35% from poisoning.\(^6\)
Table 1. CSO data by primary substance, 2001/2002 combined

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<th>INDETERMINATE INTENT</th>
<th>ALL INTENTS</th>
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<tr>
<td>Amitriptyline</td>
<td>5</td>
<td>Cyanide</td>
<td>7</td>
</tr>
<tr>
<td>Cooking oil fire</td>
<td>5</td>
<td>Morphine or Heroin</td>
<td>7</td>
</tr>
<tr>
<td>Carbon Monoxide</td>
<td>4</td>
<td>Doxepin</td>
<td>5</td>
</tr>
<tr>
<td>Dextropropoxyphene/Paracetamol</td>
<td>4</td>
<td>Nortriptyline</td>
<td>4</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>3</td>
<td>Zopiclone</td>
<td>4</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>3</td>
<td>Codeine</td>
<td>3</td>
</tr>
<tr>
<td>Ethanol/Methanol*</td>
<td>2</td>
<td>Dextropropoxyphene/Paracetamol</td>
<td>3</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>2</td>
<td>Ethylene Glycol</td>
<td>3</td>
</tr>
<tr>
<td>Clozapine</td>
<td>2</td>
<td>Insulin</td>
<td>3</td>
</tr>
<tr>
<td>GHB** or precursors</td>
<td>2</td>
<td>Propanolol</td>
<td>3</td>
</tr>
</tbody>
</table>

* Methylated spirits
** Gamma-hydroxybutyrate
The rate for male suicides derived from the CSO data for both years was significantly higher than that for females. The associated male/female rate ratio for 2001 and 2002 was 2.5 [95% CI: 0.7–8.6] and 2.2 [95% CI: 0.7 to 7.0] respectively. This trend is apparent for suicides in general, both in New Zealand and internationally. In New Zealand, in 2001, there were 3.3 male suicides to every female suicide. And across 12 OECD countries, the average was 2.9 male suicides to every female suicide.

A further difference by sex was the prominence of carbon monoxide poisoning as a cause of death amongst males (73% versus 43% of female deaths). Carbon monoxide was by far the leading substance attributed to the CSO deaths, in particular intentional deaths (64%). Carbon monoxide is also cited as prominent amongst international poisoning deaths. In the United States, carbon monoxide causes more than 500 unintentional deaths, and over 2000 suicides per year. As in New Zealand, it is responsible for more fatal intentional poisonings than any other agent. In Australia, carbon monoxide poisoning is the most common method of suicide in young males.

Issues such as suicide risk factors and suicidal behaviour are outside the scope of this paper. However, it is worth mentioning that method restriction may not necessarily reduce overall suicide rates given that suicide is a purposive act and this approach does not address underlying risk factors. Restricting access to a particular method may just increase the use of an alternative method. However, there are several specific measures suggested for reducing the availability of vehicle exhaust as a suicide method—including fitting catalytic converters to vehicles, installation of carbon monoxide detectors which shut down engines and prevent restarting, and designing ignition systems that prevent motor vehicles from idling for more than a short period of time. Each method has limitations, but given the burden of disease, the interventions merit more careful consideration.

The proportion of intentional (versus unintentional or indeterminate) deaths were more prominent amongst New Zealanders of Asian and European ethnicities (88% and 70% respectively). In contrast, only 40% of the Maori and Pacific Peoples deaths were intentional.

For 2001/2002, there were 131 unintentional deaths in the CSO dataset, a rate for 2001 of 1.8 [95% CI: 1.4 to 2.3] per 100,000 population and a rate for 2002 of 1.7 [95% CI: 1.3–2.2] per 100,000. These rates are over twice (and in some cases three times) the annual rates for 1993–1996 (0.69 in 1993, 0.54 in 1994, 0.70 in 1995 and 0.72 in 1996) published by Yates and sourced from the New Zealand Health Information Service (NZHIS). The 2001-2002 annual rate for unintentional deaths sourced from the CSO is the same as that observed in England and Wales, and Australia for the years 1993–1995 (1.8 per 100,000) but less than that observed in the United States in 1995 (3.5 per 100,000).

The observed increase in New Zealand’s unintentional poisoning mortality rate between 1993–1996 and 2001/2002 warrants further investigation. It is unlikely that it can be completely attributed to the different data sources and associated collection methods, and thus it raises public health concerns.

Methadone, morphine or heroin, and acute ethanol poisoning were the leading causes of the unintentional deaths (accounting for 56% of these fatalities). The contribution
by methadone to poisoning deaths in New Zealand and possible contributing factors has been discussed elsewhere.\textsuperscript{12,13} Yates\textsuperscript{11} has discussed the alcohol perspective.

In addition, the observation that poisoning mortality rates were found to increase with increasing deprivation complies with findings that suicides in general are linked to low socioeconomic status.\textsuperscript{14}

While this study has reported on the main epidemiological findings associated with poisoning deaths, the data can provide for the more specific investigation of relationships between given agents and fatality rates. The CSO data has already been utilised to investigate antidepressant poisoning deaths,\textsuperscript{15} to compare the fatal toxicity index of zopiclone with benzodiazepines,\textsuperscript{16} and to investigate opioid deaths.\textsuperscript{13}

The main limitation with this study is that the data may not be 100\% complete (it is estimated to be 95\% complete) for two reasons. Firstly, some deaths may still be under investigation by coroners and the reports not yet filed at the CSO. Secondly, as poisoning deaths are identified on the basis of the verdict and subcategory assigned by the coroner (e.g. suicide and carbon monoxide poisoning or drug abuse and solvent), relevant deaths will not be identified if the coroner has been less specific (e.g. suicide and other).

The rate of poisoning deaths in New Zealand is comparable with international trends for industrial countries. So too is the prominence of poisoning as a leading method of suicide. Public health action to reduce the burden of disease from poisoning deaths in New Zealand to have the greatest impact would need to be aimed at carbon monoxide suicides, particularly amongst males aged 25–44 years.

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References:


Increased rates of trimethoprim resistance in uncomplicated urinary tract infection: cause for concern?

Dee Mangin, Les Toop, Stephen Chambers, Rosemary Ikram, Ben Harris

Abstract

Aims To assess changes in trimethoprim resistance over 2 years in bacteria causing uncomplicated urinary tract infections (UTIs) presenting to a representative group of general practitioners (GPs) in Christchurch.

Methods Seventy-six randomly selected GPs in Christchurch (the Christchurch Sentinel network) participated in the study. Using the same methodology as in the previously reported 2000 collection, midstream urine (MSU) samples were prospectively collected for standard microbiological analysis on all women between the ages of 16 and 50 years presenting with symptoms of dysuria and frequency and who had positive dipstick testing for either nitrites, leucocytes, or both. MSUs were submitted for bacterial colony counts and resistance testing of isolates present in numbers $>10^5$ cfu/ml of urine.

Results 216 dipstick positive specimens were collected in the survey period; 105 of these fulfilled criteria for significant bacteriuria. Trimethoprim resistance was found in 16 (15.2%) overall, with a resistance rate for Escherichia coli (E. coli) to trimethoprim of 17.7%. When compared to the proportions of organisms resistant in the 2000 study, there were apparent but non significant increases in the total resistance among pathogens (+6.7%) and E. coli resistance (+5.8%). Rates of antibiotic resistance of all organisms to nitrofurantoin (2.9%) and norfloxacin (0.95%) remain low. There was a statistically significant increase in resistance among all women presenting with symptoms and a positive dipstick test (+5.3%; 95% CI: 1.5%–9.1%). For a woman in this age group presenting with symptoms of urinary tract infection and a positive dipstick test, we estimate that her probability of having a trimethoprim-resistant organism in 2002 was 7.4% compared with 2.7% in 2000.

Conclusion Trimethoprim resistance of E. coli causing uncomplicated UTI appears to be rising in Christchurch. This may reflect the promotion and extensive use of this agent as first-line treatment. Whilst these data indicate that trimethoprim remains a reasonable first-line empiric treatment in this condition, this may change if trimethoprim resistance continues to rise. The apparent increase over a relatively short period (2–3 years) demonstrates the importance of regular surveillance. A third study is required to confirm whether this is a significant trend.

A previous study in 2000 (using the randomly selected Christchurch Sentinel GP Network) measured the rates of resistance to trimethoprim in organisms causing uncomplicated UTI (E. coli 11.9%, all organisms 8.5%, and intention to treat basis 2.7%). As a result of these data, both local and national guidelines have recommended the use of trimethoprim as first-line empiric treatment. Rates quoted from routinely collected community laboratory data at the same time were higher at 19% for E. coli in 2000. By 2002, this reported crude rate had risen to 21%.
In this paper, we report the resistance rates to common antibiotics of uropathogens isolated from women with uncomplicated UTI sampled prospectively using the same Sentinel Network 2 years after the first study.

**Methods**

The general practitioners from the Christchurch Sentinel Network provided samples for both collection periods. The 82 practitioners were randomly selected in 1999 as previously described. The collection period was from late spring 2001 to autumn 2002. Seventy-six GPs (93%) were available to participate in this study.

Inclusion criteria were women aged between 16 and 50 years who presented with symptoms of cystitis, supported by the presence of white cells or nitrates in the urine by dipstick, in whom empiric antibiotic treatment was to be commenced (‘intention to treat’).

Exclusion criteria were clinical evidence of pyelonephritis (temperature >38°C, renal angle tenderness, or rigors), known abnormal urinary anatomy, recent instrumentation of the urinary tract or pregnancy. Both Christchurch community laboratories were involved, performing standard midstream urine analysis (microscopy, culture, and antibiotic sensitivity determination). Results were sent back to the referring GP in the normal way and a de-identified copy sent to the study team for further analysis.

Antibiotic sensitivities were determined on all samples fulfilling the criteria for urinary tract infection. A UTI was defined as ≥20 leucocytes per mm$^3$ of urine and pure growth of ≥10$^5$ organisms per ml of a uropathogen. We chose ≥10$^5$ organisms/ml as this is a conservative and agreed definition of infection. It is noteworthy that the *in vitro* resistance rates to trimethoprim in our previous study were similar in the samples with <10$^5$ cfu/ml of a uropathogen. Antibiotic susceptibility was determined by disc testing according to NCCLS standards. Simple descriptive statistics were obtained in Excel and SAS software programs; and proportions, normal 95% confidence intervals, and tests for linear trend were performed using the CIA software program.

This repeat of the dipstick positive resistance study was part of a larger study examining the optimal use of antibiotics in women presenting with symptoms of uncomplicated urinary tract infection. The study was approved by the Canterbury Ethics Committee.

**Results**

216 dipstick positive samples were submitted; 117 out of 216 met the inclusion criteria for bacterial and white cell counts required to define urinary tract infection; and 105 of those 117 had pure growth of a pathogenic organism. The disc sensitivity testing showed the following total *in vitro* resistance rates for significant isolates as shown in Table 1: trimethoprim 15.2% (95% CI: 9.0%–23.6%), cotrimoxazole 13.3% (7.5%–21.4%), amoxycillin 42.9% (33.4%–52.3%), amoxycillin/clavulanate 2.9% (0.6%–8.1%), nitrofurantoin 2.9% (0.6%–8.1%), and norfloxacin 1% (0.02%–5.2%).

The most common infecting organisms were *Escherichia coli* (*E. coli*) (81%) and *Staphylococcus saprophyticus* (*S. saprophyticus*) (13%). Resistance varied according to the infecting organism (Table 1). *S. saprophyticus* were all sensitive to trimethoprim while 17.7% of *E. coli* were resistant.
Table 1. Resistance rates to antibiotics by organism in 2002

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotic</th>
<th>Amoxycillin</th>
<th>Amoxycillin / clavulanate</th>
<th>Trimethoprim</th>
<th>Nitrofurantoin</th>
<th>Norfloxacin</th>
<th>Cotrimoxazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>All organisms</td>
<td></td>
<td>45</td>
<td>42.9</td>
<td>3</td>
<td>2.9</td>
<td>16</td>
<td>15.2</td>
</tr>
<tr>
<td>(N=105)</td>
<td></td>
<td></td>
<td>(33.4–52.3)†</td>
<td>(0.6–8.1)</td>
<td>(9.0–23.6)</td>
<td>(0.6–8.1)</td>
<td>(0.02–5.2)</td>
</tr>
<tr>
<td>E. coli</td>
<td></td>
<td>41</td>
<td>48.2</td>
<td>2</td>
<td>2.4</td>
<td>15</td>
<td>17.7</td>
</tr>
<tr>
<td>(N=85)</td>
<td></td>
<td></td>
<td>(48.2–58.8)</td>
<td>(1.2–3.6)</td>
<td>(16.5–22.8)</td>
<td>(0.00–2.00)</td>
<td>(7.5–21.4)</td>
</tr>
<tr>
<td>S. saprophyticus</td>
<td></td>
<td>2</td>
<td>14.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(N=14)</td>
<td></td>
<td></td>
<td>(6.1–22.5)</td>
<td>(0–0)</td>
<td>(0–0)</td>
<td>(0–0)</td>
<td>(0–0)</td>
</tr>
<tr>
<td>Other*</td>
<td></td>
<td>2</td>
<td>33.3</td>
<td>1</td>
<td>16.7</td>
<td>1</td>
<td>16.7</td>
</tr>
<tr>
<td>(N=6)</td>
<td></td>
<td></td>
<td>(22.5–43.7)</td>
<td>(11.1–26.3)</td>
<td>(0–33.3)</td>
<td>(0–100)</td>
<td>(0–50.0)</td>
</tr>
</tbody>
</table>

*Including Enterobacter cloacae, Klebsiella pneumoniae, Proteus mirabilis, and Streptococcus agalactiae (gp B).
†Exact 95% confidence limits.
There was no significant difference in resistance rates nor the pattern of infecting organism by age band (Table 2).

### Table 2. Infecting organism by age in 2002

<table>
<thead>
<tr>
<th>Age band of patient (n)</th>
<th>% E. coli</th>
<th>% S. saprophyticus</th>
<th>% Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>16–21 years (14)</td>
<td>78.6 (11/14)</td>
<td>14.3 (2/14)</td>
<td>7.1 (1/14)</td>
</tr>
<tr>
<td>22–30 years (21)</td>
<td>71.4 (15/21)</td>
<td>28.6 (6/21)</td>
<td>0.0 (0/21)</td>
</tr>
<tr>
<td>31–40 years (41)</td>
<td>85.4 (35/41)</td>
<td>12.2 (5/41)</td>
<td>2.4 (1/41)</td>
</tr>
<tr>
<td>41–50 years (29)</td>
<td>82.8 (24/29)</td>
<td>3.5 (1/29)</td>
<td>13.8 (4/29)</td>
</tr>
</tbody>
</table>

When compared to the proportions of organisms resistant in the 2000 study (Table 3), there were apparent but non significant increases in the total resistance among all pathogens: 8.5 to 15.2% (+6.7%) and in E. coli resistance which rose from 11.9 to 17.7% (+5.8%). There was a statistically significant increase in resistance among all women presenting with symptoms and a positive dipstick test (+5.3%; 95% CI: 1.5%–9.1%).

### Table 3 Comparison of resistance to antibiotics in 2000 and 2002

<table>
<thead>
<tr>
<th>Resistance</th>
<th>2000</th>
<th>2002</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total resistance among pathogens</td>
<td>8.5% (8/94)</td>
<td>15.2% (16/105)</td>
<td>+6.7% Z=1.23 NS</td>
</tr>
<tr>
<td>E. coli resistance</td>
<td>11.9% (7/59)</td>
<td>17.7% (15/85)</td>
<td>+5.8% Z=0.71 NS</td>
</tr>
<tr>
<td>Total resistance among symptomatic women (intention to treat)</td>
<td>2.1% (8/374)</td>
<td>7.4% (16/216)</td>
<td>+5.3% Z=2.91 (95% CI: 1.5%–9.1%)*</td>
</tr>
</tbody>
</table>

*Significant at 5% level; NS=Not significant at 5% level.

### Discussion

The apparent increase in the overall resistance rate to trimethoprim over a 2-year period is the key finding. Using all urines fitting the conservative criteria for UTI as a denominator, the numbers are too small to determine whether this is a statistically significant trend among E. coli or among all identified pathogens—a third survey would confirm whether this is a trend within these subgroups. However, using all 216 submitted samples as a denominator, an ‘intention to treat’ analysis can be performed.

For a GP about to initiate antibiotic treatment in 2002 for a woman aged 16–50 years with symptoms of an uncomplicated urinary tract infection and a positive dipstick test for nitrites or leucocytes, the probability of that woman having a pure growth infection with a trimethoprim-resistant organism would have been 7.4%. This compares to 2.7% in the 2000 sample, and the difference is significantly different (p=0.04).

Given that many patients with symptoms of dysuria and frequency do not have positive dipsticks\(^\textit{1,9,10}\) then a GP treating on symptoms alone would theoretically
encounter an even lower rate of trimethoprim resistance. As a caveat to this, however, there is recent evidence that women with no evidence of infection using standard testing methods do respond to antibiotics and there is therefore the possibility of an undiagnosed bacterial cause with unknown resistance in this group. We note the importance of considering the likelihood of infection with Chlamydia trachomatis where there are leucocytes but no infecting organism.

This study confirms the finding in the first study that the resistance rate for trimethoprim in individual organisms is lower than that reported from the regional laboratory. For example, the Sentinel rate among E. coli was 17%, with 21% reported from opportunistically collected data at the regional laboratory in 2002. The finding of a higher trimethoprim-resistance rate among E. coli than other uropathogens is consistent with international experience. This is important when considering influences on antibiotic prescribing. Laboratory results are reported by organism so prescribers using routinely collected data as a guide will tend to look at the rate for the most common infecting organism (E. coli).

The overall resistance rates found suggest that, in Christchurch, trimethoprim still appears to be a reasonable antibiotic of first choice for empiric treatment of symptoms of urinary tract infection in women aged 16–50 years with no other complications. Put another way, if such women have a positive dipstick there is only a 1 in 13 chance they will require a second antibiotic if treated empirically with trimethoprim. However, the apparent rise in trimethoprim-resistance rate over such a short time is of concern.

Trimethoprim is currently the local recommended first-line antibiotic for treatment of uncomplicated urinary tract infection. The most clinically important resistance mechanism is coded on a plasmid and may be disseminated by highly mobile transposons that may be transferred among a wide range of organisms. Resistance, therefore, would be expected to increase over time but we do not know how quickly this will occur. This further highlights the need for regular prospective monitoring of resistance levels to assess the rate of increase and determine the ongoing clinical utility of this antibiotic, preferably at a national as well as a district level.

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**References:**


Vitamin D deficiency among patients attending a central New Zealand rheumatology outpatient clinic

Graham Chiu

Abstract

Aims To measure the Vitamin D status in patients attending a rheumatology outpatient clinic because of the known musculoskeletal and immunosuppressive effects of Vitamin D deficiency.

Methods 66 consecutive patients at a private rheumatology clinic in central New Zealand were recruited at the beginning of winter.

Results Of 66 patients, 55 patients were included in the analysis. 43 (78%) had 25OH cholecalciferol levels that were below the reference range (50–150 nmol/L), and of these 12 (22%) had levels classified as moderate to severe deficiency (<25 nmol/L).

Conclusions Vitamin D deficiency is common in this setting, and is likely to contribute to the musculoskeletal symptoms experienced in this population.

Most of our vitamin D comes from the photolytic action of sunlight in the UVB spectrum on skin; and in the absence of sunlight, non-fortified dietary sources are normally incapable of providing the daily minimal requirements to maintain levels above that required to maintain bone health (>50 nmol/L) without the consumption of large amounts of oily fish. Furthermore, there is now evidence to suggest that low vitamin D levels are associated with an increased incidence of autoimmune disease such as rheumatoid arthritis and type I diabetes mellitus, as well as an increased incidence of malignancy.

Methods

All ambulant patients capable of self-care, and attending a private rheumatology clinic in Wellington and Wanganui, were advised that there was a possibility that vitamin D deficiency could be contributing to their musculoskeletal complaints. Pathology forms for vitamin D assay were given to consenting patients from the end of May 2005 to the beginning of July 2005, and the assay was performed either by Capital Coast Health Laboratory, or Southern Community Laboratories. The reference range for both of these laboratories is given as 50–150 nmol/L, and both use the Diasorin assay kit which has a coefficient of variation between tests of 6% which approximates to +/- 12% for 95% confidence limits.

Results

Of the 66 patients recruited for this audit, 56 had a vitamin D assay performed. One patient who was taking calcitriol was excluded from the analysis. Serum 25OH cholecalciferol results are shown in Figure 1 and age distribution versus 25OH-cholecalciferol levels are shown in Figure 2.
Figure 1. Serum 25OH cholecalciferol results of patients attending rheumatology clinics at Wellington and Wanganui

Figure 2. Age distribution versus 25OH-cholecalciferol levels in patients attending rheumatology clinics at Wellington and Wanganui
The patients with the highest levels of vitamin D (>60 nmol/L) were found in the age range 40–70 years, and severe deficiency was present throughout the patient population. There were four Asian Indian patients, and they were all found in the lowest quartile; two of these had presented with bone and/or muscle pain. Three Chinese patients were in the third quartile, and the remaining patients were Caucasian.

The bulk of the patients were being treated for inflammatory or autoimmune disease, and the disease distribution is shown in Table 1.

Table 1. Diseases/conditions in patients attending rheumatology clinics at Wellington and Wanganui

<table>
<thead>
<tr>
<th>Disease/condition</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>17</td>
</tr>
<tr>
<td>Inflammatory arthritis</td>
<td>7</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>7</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td>5</td>
</tr>
<tr>
<td>Backpain and muscle pain</td>
<td>3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>2</td>
</tr>
<tr>
<td>CREST syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Enthesopathy</td>
<td>1</td>
</tr>
<tr>
<td>Exercise induced urticaria</td>
<td>1</td>
</tr>
<tr>
<td>Juvenile RA</td>
<td>1</td>
</tr>
<tr>
<td>Oligoarthritis</td>
<td>1</td>
</tr>
<tr>
<td>Post viral fatigue</td>
<td>1</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>1</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>1</td>
</tr>
<tr>
<td>SLE</td>
<td>1</td>
</tr>
<tr>
<td>Spondyloarthropathy</td>
<td>1</td>
</tr>
<tr>
<td>Tendinitis</td>
<td>1</td>
</tr>
<tr>
<td>Undifferentiated CTD</td>
<td>1</td>
</tr>
</tbody>
</table>

RA=Rheumatoid arthritis; CREST=C–calcinosis, R–raynauds, E–esophageal dysfunction, S–sclerodactyly, and T–telangectasias; SLE=Systemic lupus erythematosus; CTD=Connective tissue disease.

Discussion

Increased vitamin D deficiency has been previously reported in several at-risk settings including inpatients,5 rest homes for the elderly,6 and dark-skinned women attending antenatal clinics.7 This study also shows that ambulant patients attending a rheumatology clinic also have low levels; 22% of them had levels (<25 nmol/L) that can give arise to bone pain and muscle weakness,9 thus complicating their existing diseases.

Nine (17%) patients had vitamin D levels lower than 17.5 nmol/L which is higher than the figure of 3% reported by Skeaff9 for New Zealand adolescents and adults. It is not known whether this higher result is a reflection of Wellington’s latitude of 41.3 degrees south, or whether it is a function of the population being studied.15,16

Importantly, vitamin D is now known to have important immune functions, and low intake has been linked to rheumatoid arthritis,3 multiple sclerosis,10 and type I
Several small prospective studies have shown that vitamin D analogues have disease-suppressing effects in rheumatoid arthritis and so maintaining high non-toxic levels of vitamin D may have positive therapeutic implications for patients with inflammatory disease.

Although a reference range for bone health is given as 50–150 nmol/L by both laboratories, a minimum level of 110 nmol/L has been reported to suppress rises in parathyroid hormone in healthy elderly men and women and therefore may be a more appropriate treatment target.

It is suggested that patients attending rheumatology clinics have their vitamin D status assessed and their deficiency states corrected. Furthermore, they should be given advice on sunlight exposure relevant to their skin type and latitude of residence. Current sunlight exposure recommendations for New Zealand are based upon ultraviolet data, and need confirmation with biological studies as it is possible that (based on Northern Hemisphere studies) there is likely to be very little cutaneous vitamin D synthesis occurring during the winter months. In that case, supplementation may have to be recommended for all patients during the winter period.

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**References:**


Older patients in the nephrology clinic—should they be referred?

Sarah Lynn, Richard Sainsbury, Martin Searle

Abstract

Aim To review the outcomes of elderly patients referred to a nephrology clinic and to develop referral guidelines.

Methods A retrospective audit of patients aged 65 years or older referred over a 24-month period to a nephrology clinic. Outcomes assessed were whether a renal diagnosis was made and if there was any change in management.

Results Sixty-one patients were referred with an average age of 74 years (range 65–88 years). The commonest reason for referral was renal impairment (69%); mean estimated creatinine clearance 32 ml/min. Diagnoses included hypertensive renal disease (30%), chronic renal failure—cause unknown (18%) and diabetic nephropathy (8%). In the majority of cases, the diagnosis was clinical. Renal biopsy was performed on four patients and declined by a further two. Management usually consisted of advice regarding clinical monitoring and drug treatment (80%). The clinic visit resulted in a change of management in 50% of cases.

Conclusions Most elderly patients with renal disease have chronic pathology for which intensive investigation is not warranted. The majority of nephrology clinic referrals resulted in advice on clinical management being given to the general practitioner. Patients with severe or acute renal impairment are more likely to be investigated and offered treatment. Referral guidelines for general practitioners may aid appropriate referral.

In industrialised countries there has been an exponential rise in the number of elderly patients with identified renal disease. This is not unexpected given the ageing population, increased life expectancy, decline in renal function with age, and the elderly’s increased access to care. Advances in dialysis technology mean that life-sustaining treatment for the elderly is now feasible and an increasing number of elderly patients are being accepted onto dialysis programs worldwide.

In Australia, 45% of patients starting dialysis in 2003 were aged 65 years or older compared to 36% in 1997. The American Society of Nephrology has recognised this growth and coined the term ‘gerontologizing nephrology.’ In this era of limited resources and growing outpatient clinic waiting lists, consideration needs to be given to which elderly patients should be referred for specialist review.

National Referral Guidelines for Renal Medicine exist but are not directed specifically at the elderly. There is also a degree of uncertainty amongst general practitioners and specialists about which elderly patients to refer and the timing of referral. It is felt by some that an elevated creatinine in an asymptomatic older patient does not immediately warrant a specialist referral but opposing this is the evidence of under-referral of such patients to nephrologists.
It also needs to be recognised that a number of elderly patients with observed renal impairment do not progress. Patients who require long-term dialysis have improved outcomes if they are referred early to allow time for education and planning.\textsuperscript{8}

A retrospective case note audit was performed to assess the pattern of referral of elderly patients and their management in the clinic and to develop referral guidelines for these patients.

**Methods**

New patients aged 65 years or older attending the Nephrology Clinic at Christchurch Hospital between January 2000 and December 2001 were included in this study. The Clinic services a population of 350,000 and reviews 170 new patients each year. Patients seen following inpatient review were excluded. New patients were identified by using the Nephrology Department clinical database PROTON (Clinical Computing Plc, London, United Kingdom) and the Hospital’s Patient Management System.

The clinical record for each patient was then reviewed and data collected on the reason for referral, investigations performed, treatment given, diagnosis made, and management offered. Estimated creatinine clearance (CrCl) was calculated using the Cockcroft and Gault formula.\textsuperscript{9} The first outcome assessed was whether a definite diagnosis was made. This was considered to be an aetiologic diagnosis if made following a renal biopsy, immunological testing, or renal imaging (including angiography). All other cases were considered to be clinical diagnoses.

We next assessed what treatment was offered and whether this resulted in a change in clinical management. Treatment offered included immunosuppressive therapy, dialysis education, or advice to the general practitioner on medication or clinical monitoring. Information related to service delivery was also collected including time to clinic appointment following referral and the rate of enrolment into follow-up. Data was collected to December 2001 and numbers commencing dialysis were collected to December 2004.

**Results**

There were 68 elderly new patients referred in the study time period. This represented 18% of the clinic workload and 0.12% of the elderly population in Christchurch. Seven case notes were not available for review. The mean age of the patients was 74 years (range 65-88 years) with 57% males. Referrals from general practitioners made up 74% with most referring only a single patient. The remaining referrals came from a wide range of specialists. The mean waiting time for clinic review was 31.7 days with no difference between the two referral groups.

**Table 1. Reasons for referral**

<table>
<thead>
<tr>
<th>Reason for referral</th>
<th>Referral source</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GP</td>
<td>Specialist</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension (range 112/67–240/100 mmHg)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Proteinuria (range 0.37–7g/24hr)</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Microscopic haematuria</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

**Referrals**—There were several reasons for referral (Table 1) with some patients presenting with more than one problem. The commonest presentation was an elevated plasma creatinine (69%), with a mean serum creatinine of 0.20 mmol/L and a mean
estimated CrCl of 32 ml/min. Seven patients had a 30% improvement in the serum creatinine between the time of referral and clinic assessment.

Hypertension was mentioned in the referral in 10%, however 87% of all patients referred had a blood pressure >130/80 mmHg (mean 162/80, range 112/67–240/100). Proteinuria was the reason for referral in 13% of the patients (range 0.37–7g/24hr) with an additional 5% referred for investigation of nephrotic syndrome.

**Investigations**—Only 54% of the patients had their urine examined for blood or protein prior to referral. Following clinic review, urinalysis was performed in 97% with no other patients found to have significant proteinuria (i.e. >1g/24hr) or haematuria. In Christchurch, the general practitioners have limited access to renal ultrasound for patients without private health insurance: only 43% of patients referred had this test performed in the community while 36% had an ultrasound following clinic review. Serum protein electrophoresis was performed in 31%. Two patients had renal artery imaging performed prior to referral. Another patient was offered this investigation but declined.

**Table 2. Renal biopsy findings**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age (years)</th>
<th>Clinical presentation</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy performed</td>
<td>66</td>
<td>Nephrotic (3.3g/24hr)</td>
<td>FSGS</td>
</tr>
<tr>
<td></td>
<td>71</td>
<td>Sarcoïdosis</td>
<td>Renal sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>Nephrotic (14.6g/24hr)</td>
<td>FSGS</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>Proteinuria (3.9g/24hr)</td>
<td>FSGS</td>
</tr>
<tr>
<td>Biopsy declined</td>
<td>75</td>
<td>Nephrotic (3.5g/24hr)</td>
<td>Membranous nephropathy</td>
</tr>
<tr>
<td></td>
<td>77</td>
<td>Proteinuria (7g/24hr)</td>
<td>Diabetic nephropathy</td>
</tr>
</tbody>
</table>

FSGS=Focal and segmental glomerulosclerosis.

All patients presenting with nephrotic syndrome or proteinuria >3g/24hr were offered a renal biopsy, aside from one patient presumed to have familial focal and segmental glomerulosclerosis on the basis of a strong family history. Four patients had a renal biopsy performed and a further two patients declined this procedure (Table 2). The remaining five patients with proteinuria either had known diabetes mellitus or hypertension with no significant renal impairment and so did not have a renal biopsy.

**Diagnosis**—A range of diagnoses were made (Table 3) and included hypertensive renal disease (30%), chronic renal failure—cause unknown (18%), and diabetic nephropathy (8%). In the majority of cases the diagnosis was clinical with only 12 (20%) patients having a diagnosis made by investigation.

**Management**—In the majority of cases (80%), assessment resulted in advice to the referrer which changed management in 36% of cases. This included advice on clinical monitoring, antihypertensive treatment, stopping specific nephrotoxins, and optimising glycaemic control. Four patients were treated with oral prednisone to treat a variety of conditions: renal sarcoidosis, renal vasculitis, multiple myeloma, and focal and segmental glomerulosclerosis.

Five patients were offered dialysis education, with three commencing peritoneal dialysis and the remaining two declining to proceed with treatment. Over the next 3 years, four more patients received dialysis education. Review in the Nephrology
Clinic was organised for 30% of the patients and 11% were referred on to another specialty.

**Table 3. Diagnoses of renal disease**

<table>
<thead>
<tr>
<th>Renal diagnosis</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive renal disease</td>
<td>18 (30)</td>
</tr>
<tr>
<td>Chronic renal failure (cause unknown)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>4 (6)</td>
</tr>
<tr>
<td>APKD</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (20)</td>
</tr>
</tbody>
</table>

APKD=Adult polycystic kidney disease.

**Discussion**

This paper is a review of our practice and is the only published data in New Zealand on referral patterns of elderly patients to a nephrology service. Most of the elderly patients in our study had chronic renal disease that was asymptomatic and did not warrant intensive investigation. These patients were commonly managed by providing advice to the general practitioner and it has to be questioned whether a clinic visit is the only means of conveying this information.

The value patients place on being seen by a specialist was not determined due to the retrospective nature of the study. A proportion (25%) of patients did require further investigation and specific treatment and it is this group in particular that should continue to be referred for specialist review. We were unable to determine if the clinic visit resulted in improved outcomes long term as the follow-up was short, and we did not attempt to make any comparisons with the younger patients referred to the service.

This study highlights the low referral rates of older people with renal disease, which may also reflect the low recognition of renal disease in the community. The AusDiab study provides important and useful prevalence data that can be extrapolated to our population. It clearly showed that age is the strongest predictor of renal impairment with GFR <60 ml/min found in 54.8% of people ≥65 and GFR <30 ml/min in 1.7% of elderly.

This equates to 31,300 people in Canterbury with moderate renal impairment and 970 with severe renal impairment. These numbers would overwhelm the renal service if all were referred for specialist review. Resources for specialist assessment are limited and the gap between demand and availability is likely to expand as morbidity increases in the ageing community and quality of care improves.

Proposed referral guidelines for patients aged 75 years or older are included (Appendix 1) that would facilitate identification of those patients who require specialist review. These guidelines promote selection of patients in whom investigation is likely to yield a result (e.g. renal vasculitis); where aggressive management is important to slow the progression of disease (i.e. significant proteinuria, difficult to control hypertension); and when dialysis should be considered. These are in keeping with other national guidelines.
Patients who do proceed to dialysis need to be referred promptly. Indeed, several studies have shown that late referral for patients who require dialysis is associated with poorer outcomes.\(^8,12\) In our clinic, waiting time is not a barrier to review with the mean waiting time for a non-urgent review in this study being 1 month. Urgent referrals are seen on a same day basis where required.

Hypertensive and vascular renal disease were the most common renal diagnoses. Vascular comorbidities (such as ischaemic heart disease) which would have been useful to help determine the aetiology of the renal impairment were not routinely recorded. The high rates of hypertension suggest that the national hypertension guidelines of aiming for blood pressure (BP) <130/80 mmHg are not being adhered to and/or are difficult to achieve.\(^13\) There were relatively low rates of diabetic nephropathy.

Other studies have also shown this pattern of a higher incidence of vascular renal disease and lower rates of diabetic disease in the elderly compared with younger patients.\(^2,14\) This is worth bearing in mind as the majority of studies showing slowing of progression of renal disease have been in those with diabetic nephropathy.

Urinalysis should be performed in all patients with new or worsening renal impairment, and the low use of this test in our referral group is disappointing. This issue is not confined to older patients—as a similar rate was seen in a recent department audit of all referrals (unpublished data). Urinalysis is a simple, inexpensive test that provides important information regarding glomerular and other renal diseases, and it may identify those patients in whom a renal biopsy should be considered.

The presence of proteinuria indicates a significant risk of progressive kidney damage;\(^15,16\) proteinuria >1g/24hr was identified in 1% of people aged ≥65 in the AusDiab study.\(^10\) It has been shown in younger subjects that the rate of progression of chronic renal disease can be reduced by management of hypertension\(^17\) and the use of angiotensin-converting enzyme inhibitors (ACEI),\(^18,19\) with the greatest benefit seen in those patients with > 1g/day of proteinuria. For some patients, the use of ACEI will result in a rise in creatinine and potassium. This is allowable if it does not rise more than 30% above baseline and stabilises within the first 2 months of treatment, as these patients seem to receive the greatest benefit in renoprotection.\(^20\)

Most older patients with renal impairment need to be managed in primary care. Renal function needs to be assessed by calculating the estimated creatinine clearance—as elderly patients (particularly overweight females) can have a serum creatinine within the normal range but significantly impaired function.

To increase awareness of renal failure in the elderly,\(^21\) general practitioners are being encouraged to use the Cockcroft and Gault equation. Local laboratories are now using an equation used in the MDRD study\(^15\) to calculate creatinine clearance (as weight and age are not required). In addition, renal ultrasound is useful to detect obstructive uropathy and to confirm the chronicity of the renal impairment by measuring renal size.

Asymmetry of kidney size may indicate renovascular disease. It is unfortunate that timely access to imaging can be difficult to organise from the community and wider access to these investigations is required. Thus it is essential that preventive strategies
to delay the progression of early renal disease are promoted to general practitioners alongside the proposed guidelines.22

Renal disease in the elderly is common and further thought needs to be given to how our health service will manage this epidemic. There will be a growing need to balance the technical possibilities of treatments such as dialysis against the available resources. In 2003, there were 1699 patients receiving dialysis in New Zealand with annual treatment costs of $50,000 per patient.23 This number is increasing at a rate of 9% per annum and one-third of these patients are aged over 65 years (elderly).

The benefits of dialysis are questionable for some of these patients. Ultimately, the decision to investigate and treat needs to be individualised depending on the presence of comorbidities, social circumstances, and patient choice.

Appendix 1

Referral Guidelines:

- Acute renal impairment (i.e. rapid rise in creatinine concentration over a period of days)
- Severe renal impairment (GFR < 30 ml/min) for consideration, discussion and education on dialysis and management of nutrition, anaemia and calcium/phosphate metabolism.
- Proteinuria > 1g/24hr associated with hypertension and/or renal impairment
- Microscopic haematuria associated with hypertension and/or renal impairment
- Poorly controlled hypertension
- Absence of advanced malignancy, severe cardiac disease, dementia, or other conditions limiting life expectancy

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Correspondence: Dr Sarah Lynn, The Princess Margaret Hospital, PO Box 800, Christchurch. Fax: (03) 337 7803; email: sarah.lynn@cdhb.govt.nz

References:


The Christchurch Tissue Bank to support cancer research

Helen Morrin, Sarah Gunningham, Margaret Currie, Gabi Dachs, Stephen Fox, Bridget Robinson

Abstract

Aim To report on the development of a central resource of consented cancer tissues for researchers to use for ethically approved projects, and to describe the banking process.

Methods The development of tissue banking in Christchurch, New Zealand is described, including the number and main types of samples collected. The consent forms have evolved with several new donor options added between 1996 and 2004. Since June 2004, disposal of tissues by a karakia (blessing) has been offered. Characteristics of each tissue including amount, location in the bank, and relevant clinicopathological data have been recorded prospectively in a detailed secure relational database.

Results The changes in the consent form and donor options are described. Most donors (99.6%) consented to allow access to medical records (since May 2002); 98.3% to tissue being sent overseas (since May 2003), 97.4% to commercial research (since May 2003), and 35.6% requested disposal with a karakia. Since May 2003, 87% of donors have been Caucasian, 5.1% Maori, and the remainder composed of other categories as stated on the 2001 New Zealand census format. By March 2005, samples have been banked from more than 2000 donors. For each of the last 4 years, samples have been collected from more than 300 donors, including fresh-frozen tissue, DNA preparations, serum, plasma, and paraffin blocks. The predominant tissues are from donors with cancers of the breast, colon, urological, and gynaecological sites.

Conclusions The Christchurch Tissue Bank is a successful model for potential New Zealand-wide application, providing quality tissue samples for cancer research whilst appropriately addressing ethical, legal, and cultural aspects of their collection.

Breakthroughs in the understanding of cancer biology, the identification of prognostic factors, and the development of new treatments are increasingly dependent on access to human cancer tissues with linked clinicopathological data. Access to human tumour samples\(^1\) and a large investment in translational research are needed to advance this research.\(^2,3\) The National Cancer Institute in the US was early to recognise this and funded three centres to provide cancer tissues for research, coordinated by the Cooperative Human Tissue Network.\(^4\) Tumour banks are now well-established in Europe, the US, and Australia.\(^5-8\) The National Health and Medical Research Council (NHMRC) in Australia has recognised the importance of collecting tissue for translational research projects by awarding Enabling Grants in 2004 to support the exchange of samples across Australia via the Australasian Biospecimen Network (ABN) and to establish additional banks.\(^9\)
All tissue banks have had to overcome ethical, legal, cultural, and economic issues,\textsuperscript{10,11} with consideration also of commercialisation, confidentiality, and quality of research.\textsuperscript{12,13} The College of American Pathologists have published recommended policies for uses of human tissue in research, education, and quality control.\textsuperscript{14} With the safeguard of a Human Research Ethics Committee, use of human tissue for cancer research has become accepted in Australia.\textsuperscript{15} In New Zealand, a tissue bank must comply with international biorepository standards as well as unique national ethical, cultural, and legal guidelines for human tissues.\textsuperscript{16}

The Health and Disability Commissioners Code of Rights under Right 7\textsuperscript{17} requires written informed consent for each human sample in every research project, which has meant re-contacting the donors and obtaining fresh consent, a time-consuming and incomplete process. It has been argued that anonymised tissues could be used under stringent safeguards\textsuperscript{18} but not all agree,\textsuperscript{19} and the New Zealand Human Tissue Act is currently under review.\textsuperscript{20}

In 1996, a group of scientists and clinicians in Christchurch recognised the need both for human cancer tissues for research and for a common collection process which met the current concerns in New Zealand about patient privacy and consent. The Christchurch Tissue Bank (CTB) was set up as a collaboration between staff from the Departments of Oncology, Surgery, and Pathology at Christchurch Hospital and Christchurch School of Medicine and Health Sciences. Banking started with ethical approval to collect tissue and blood for ‘Molecular Biology Studies in Cancer’.

The Tissue Bank Board (TBB) was then established for oversight and governance. In 1997, a charitable donation funded a dedicated \textsuperscript{-80°C} freezer for long-term storage as well as a computer on which to maintain a secure relational database. The CTB was housed with the newly established Angiogenesis Research Group, and a part time tissue bank co-ordinator was appointed. Two years later, a full-time curator took over the role. The CTB is now a central repository of consented solid cancer tissues for genomic and proteomic studies, overseen by the Tissue Bank Board (TBB), and is affiliated with the ABN.

The aim of this report is to chronicle the evolution of the banking process, the development of the consent form, and the recorded options of the donors.

**Methods**

**Consent forms**—The first consent form was prepared in 1996. Since then, there have been many changes in ethics guidelines, incorporating improved inclusion of all cultural groups and changes in needs of researchers. The CTB has therefore continually made alterations to the Information and Consent Form for Tissue Banking, and applied to the Canterbury Ethics Committee for approval of each version.

To determine the specific project(s) for which the tissue can be used, a consent form for collecting and storing tissues is the key feature, which delegates authority on behalf of the donor to the TBB and the Ethics Committee. Any researcher who wishes to use the tissues must obtain separate ethics approval for each study. Tissue can then be used for more than one project, optimising use of each donor’s tissues. This facilitates studies needing many samples or rare cancers, where tumours are collected over many years, or combined with other collections.

The consent form informs donors that their gift will be tissue that is excess to diagnostic requirements from their planned surgical procedure and will not adversely affect their treatment; that the exact research which uses their tissue in the future cannot be predicted but that only projects which have gained approvals from the TBB, an accredited Ethics Committee and the Biological Safety Committee will be able to use samples. Provision is made that should any results be of benefit to the donor or their
family, they can be contacted. Donors can revoke consent at anytime and their tissue sample is removed from the CTB along with all documentation.

The Christchurch School of Medicine and Health Sciences Research Office has developed guidelines for culturally appropriate disposal of any remaining sample allocated to a project, and the option for disposal with karakia or blessing was added in 2004.

**Tissue banking process**—All patients attending the Central Pre-admission Clinic, Christchurch Hospital before surgery for cancer are considered as potential donors. They are informed of the CTB and given the opportunity to donate a part of their tissue to assist future cancer research. The medical or nursing staff then obtain written informed consent. Blood samples gifted to the CTB are taken at the same time as pre-surgical bloods, and sent to the CTB along with notification of the scheduled day of surgery.

Theatre staff are alerted by a coloured notice attached to the clinical records that consent has been given for banking. They contact CTB staff who rapidly transport the fresh specimen to the Histopathology Department. The Duty Pathologist on that day decides whether there is sufficient tissue to be banked or whether it is all needed for diagnosis. The pathologist then separates any excess tissue into ‘Tumour’, ‘Normal’, and ‘Tumour Interface’, where tumour and normal meet. The CTB prepares these fresh tissue samples for long-term storage.

The majority of tissue is snap frozen in liquid nitrogen (−196°C). The sample is then anonymised, allocated a unique CTB number unlinked to name or NHI number, then stored in secured minus 80°C freezers. Each freezer is locked, needs swipe card access, is on essential power, alarmed continuously, and has liquid carbon dioxide backup in case of failure.

On a daily basis, the Curator ensures that the banking process operates according to all governing legal, ethical, cultural, and scientific requirements, and is the primary contact for staff involved in the process, as well as for applicants requesting tissues. In addition, the Curator gives educational seminars and staff training sessions to ensure the ongoing quality of banking.

**Tissue sample types collected**—The majority of the specimens are collected from Christchurch Hospital and Christchurch Women’s Hospital, with a small number from other hospitals. The CTB aims to collect a wide range of cancer specimens with their associated clinicopathological data. Specific preparations are made depending on current project needs. Ideally, serum, plasma, DNA, fresh frozen tissues, optimal cutting temperature (OCT) blocks for immunohistochemistry, touch imprint slides for fluorescent in situ hybridisation (FISH), and paraffin-embedded blocks are collected from each patient.

For particular projects, tissue microarrays (TMAs) are constructed by taking single 1 mm cores of representative tumour from each donor paraffin-embedded block and re-embedding them in a recipient block that contains up to 120 cores. The TMAs conserve the archival paraffin blocks and enable researchers to compare gene expression and protein localisation in multiple tissues under the same conditions, and correlate with findings using the whole sample. All histochemistry and molecular detection techniques used with regular sections can also be applied to array sections, providing optimal staining conditions, faster evaluation, and more cost-effective use of multiple antibodies.

**Patient confidentiality**—A secure relational database of the clinicopathological data associated with each tissue stored in the bank is maintained to protect patient confidentiality and to facilitate optimal matching of tissue to specific research requirements. Data recorded for each specimen includes histological type, grade, size of tumour, presence of lymph node metastases, vascular or lymphatic invasion, presence of necrosis, specific data relevant to the tissue type, patient gender and age, and any pre-surgical treatment.

Only CTB staff have access to the database, and all spreadsheets generated for a project and sample allocations are de-personalised before release to approved researchers, thereby fulfilling the requirements of the Health Information and Privacy Codes. The database also provides an auditable trail from donation to allocation to a research project. Samples are tracked, and weights or volumes recorded to determine sample use and availability.

**Tissue Bank Board (TBB)**—The TBB governs the CTB. The Board meets monthly to consider any applications to use banked tissues, changes in Ethics Committee requirements, and the Curator’s monthly status report. The Board’s role is to ensure stored tissue is used appropriately for research, in the best interests of the tissue donors. It is also responsible for the physical security of the specimens and associated clinicopathological data.
Members of the Tissue Bank Board include clinical and scientific representatives from Christchurch Hospital and Christchurch School of Medicine and Health Sciences’ Departments of Oncology, Anatomical Pathology, General and Specialised Surgery, Paediatrics, Pathology and Haematology, in addition to the CTB Curator and cultural and ethics representatives. The TBB sends minutes of meetings and an annual report to the Upper South Regional Ethics Committees.

**Access to stored tissues**—To access banked samples, researchers were required to have approval of their project by a Canterbury Ethics Committee (and since 2005, an Upper South Regional Ethics Committee) or the National Ethics Committee (now the Multi-region Ethics Committee). They must also apply to the Tissue Bank Board with details of the project, and the types and numbers of tissues required. These procedures allow for review of scientific, clinical, cultural and general issues, and allocation of samples to researchers is transparent, fair, and auditable. Once Ethics Committee and TBB approval is obtained in writing, the Curator liaises directly with the research group to arrange sample delivery. Researchers are required to acknowledge the Christchurch Tissue Bank as their sample provider in all publications.

**Results**

**Consent form development**—The first consent form in 1996 was combined with an information sheet and was very simple by contemporary standards. It allowed the collection of blood and tissue, which could be used without any linked clinical information (Table 1). By 2001, the consent form had evolved to the template used in all subsequent versions. New requests for tissue from researchers lead to consideration of further changes.

**Table 1. Changes in consent and information forms for tissue banking**

<table>
<thead>
<tr>
<th>Consent form version</th>
<th>Date implemented</th>
<th>Ethics approval for</th>
</tr>
</thead>
<tbody>
<tr>
<td>V 22.03.96</td>
<td></td>
<td>Tissue and blood collection</td>
</tr>
<tr>
<td>V 02.06.98</td>
<td>16.06.98</td>
<td>Use of unlinked specimens</td>
</tr>
<tr>
<td>V 01.01.01</td>
<td>01.03.01</td>
<td>More detail, patient information sheet</td>
</tr>
<tr>
<td>V 01.05.02</td>
<td>01.07.02</td>
<td>Access medical records option</td>
</tr>
<tr>
<td>V 28 Feb 2003</td>
<td></td>
<td>Christchurch Women’s Hospital consent form</td>
</tr>
<tr>
<td>V 01.04.03</td>
<td>12.05.03</td>
<td>Use in overseas collaborations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use in commercial research collaborations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recording of ethnicity</td>
</tr>
<tr>
<td>V Sept 2003</td>
<td></td>
<td>Children’s Haematology and Oncology Centre consent form</td>
</tr>
<tr>
<td>V 1.03.04</td>
<td>11.06.04</td>
<td>Sample disposal with karakia</td>
</tr>
</tbody>
</table>

Consent form options were developed to allow the donor choice with respect to:

- Access of their medical records for treatment and survival data (Version 01.05.02)—i.e. ‘linked samples’;
- Sending tissue overseas to collaborating research groups;
- Use of tissue by collaborating commercial research interests (Version 01.04.03); and
- Offering culturally sensitive sample disposal at the conclusion of a project where applicable (Version 1.03.04).

Two donor groups needed more specific consent forms, which were still based on the standard template. Paediatric donors and/or guardians use consent forms developed
for the Children’s Haematology Oncology Centre (CHOC) and gynaecological donors use the consent form developed for Christchurch Women’s Hospital.

**Donor consent options**—The numbers of donors who agreed to the options on the consent form are shown in Table 2. A small number gave no response. The majority of patients (99.6%) were comfortable with researchers accessing their medical records held by the Canterbury District Health Board (added in 2002); 98.3% consented for samples to be sent overseas to collaborating researchers and 97.4% consented to use of their sample in collaborating commercial research projects (added during 2003). Sample disposal with a karakia or blessing was requested by 35.6% of donors, regardless of ethnicity.

**Table 2. Numbers of donors consenting to options for tissue use**

<table>
<thead>
<tr>
<th>Consent options recorded</th>
<th>Number of donors</th>
<th>Donors who consented (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to patient’s medical records</td>
<td>846</td>
<td>99.6</td>
</tr>
<tr>
<td>Tissue sent overseas to research collaborators</td>
<td>606</td>
<td>98.3</td>
</tr>
<tr>
<td>Tissue use by collaborating commercial researchers</td>
<td>581</td>
<td>97.4</td>
</tr>
<tr>
<td>Requested sample disposal with a karakia (blessing)</td>
<td>163</td>
<td>35.6</td>
</tr>
</tbody>
</table>

The invitation to record ethnicity has been offered on the consent form (Version 01.04.03) since May 2003, and uses the format of the 2001 New Zealand census. Ethnicity data records the donor’s response (Table 3). From the 553 CTB donors who recorded ethnicity, there is no difference noted between the ethnic groups with respect to their response for allowing access of their medical records, for sending samples overseas to collaborating researchers, and for being used in collaborating commercial research projects. Specimen disposal with a karakia was requested by 96% of the 28 donors who recorded their ethnicity as Maori.

**Table 3. Self-declared ethnicity of donors to the Christchurch Tissue Bank (2003–2004)**

<table>
<thead>
<tr>
<th>Recorded ethnicity</th>
<th>Number of donors</th>
<th>Percentage of donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand European</td>
<td>481</td>
<td>87.0</td>
</tr>
<tr>
<td>New Zealand European and Maori</td>
<td>12</td>
<td>2.2</td>
</tr>
<tr>
<td>Maori</td>
<td>16</td>
<td>2.9</td>
</tr>
<tr>
<td>Samoan</td>
<td>3</td>
<td>0.5</td>
</tr>
<tr>
<td>Chinese</td>
<td>5</td>
<td>0.9</td>
</tr>
<tr>
<td>Other Caucasian</td>
<td>32</td>
<td>5.8</td>
</tr>
<tr>
<td>Other Asian</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>553</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

**Tissue accrual**—The number of patients who have consented to tissue banking has increased each year from 1996 to 2001; since then, numbers have been sustained at over 300 patients annually (Figure 1).

This increase followed the change from a part-time to full-time curator. By March 2005, over 2,000 patients had gifted tissue to the CTB. The main tissue types accrued
by the CTB over the last 5 years (Figure 2) reflect both the cancer surgery performed at Christchurch Hospital, and the specialty of surgeons with an interest in banking and research.

Figure 1. Number of patients who consented to tissue banking at the Christchurch Tissue Bank each year

Figure 2. Cumulative number of main tissue types collected at Christchurch Tissue Bank (2000–2004)
The first projects required kidney, breast, and colorectal cancers. Since then, the Bank has developed into a biorepository collecting over 18 different cancer tissue types. Research interests have led to banking of urological tissues from kidney (201 samples by March 2005); prostate; bladder; and gynaecological tissues including endometrial, ovarian, and cervical samples. More recently, gliomas and paediatric samples have been collected for specific studies. Seven different research groups were accessing tissues for multiple projects at the end of 2004.

Sample preparation—Since 1996, sample preparation techniques have focused on snap-freezing (as quickly as possible) solid tumour, normal, and interface tissue to preserve molecular integrity and optimise yields of DNA, RNA, and protein. When samples were sufficient, OCT frozen blocks were also prepared for mRNA and protein localisation studies. Serum was stored for antibody analysis (Table 4).

Table 4. Sample preparation by the Christchurch Tissue Bank over time

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</thead>
<tbody>
<tr>
<td>Snap Frozen Tissue</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>OCT Tissue Blocks</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<tr>
<td>Serum</td>
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<td>✓</td>
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<tr>
<td>Slides for FISH</td>
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<td>✓</td>
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<td>Plasma</td>
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<td>Paraffin Blocks</td>
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<td>Tissue Microarray</td>
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<td>FTA Card</td>
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</table>

Sample preparation techniques have been introduced, modified, or made redundant, in response to new molecular techniques and researchers needs. Touch imprint slides for FISH were introduced in 2001 in conjunction with a project requiring prospectively collected breast tumours. Plasma was required for research into coagulation factors and was introduced together with isolation of genomic DNA from white blood cells for single nucleotide polymorphism (SNP) analysis in 2002. Banked genomic DNA was replaced by storage of Whatman FTA cards at the end of 2004. Acquisition of new equipment has enabled the construction of Tissue Microarrays commencing in 2004.

Discussion

This report covers the first 8 years of the Christchurch Tissue Bank. Tissues have now been collected from more than 2000 patients, together with clinicopathological data to provide quality research samples. During this period, the consent form has steadily evolved to reflect changes in ethical guidelines and to accommodate emerging research techniques and practices, within the parameters set by the Ethics Committee and Government regulations. The secure relational database has provided linked clinicopathological data and an auditable trail for each sample. Furthermore, the CTB
acts as an independent third party between donor and researcher, which provides a single collection process for human tissues in the institution.

The current annual rate (300–350) of accrual of CTB donors is sustainable only with a dedicated curator, and was not possible with part-time collection. Tissue donation depends on the enthusiasm and research interest of the clinical staff (including surgeons and nurses) as well as the strength of their collaboration with the scientists. The predominant tumours collected reflect this. Specimen collection is research responsive, as demonstrated by the increase in gynaecological specimens between 2001 and 2003.

The tissue banking process must involve the pathologist, to ensure diagnosis is not compromised. Banking rates after patient consent are relatively high, and are only limited by diagnostic needs. Thus for breast cancer where smaller tumours are now more common, banking rates of frozen tissue are 40%, compared with 62% for colorectal cancer and 78% for kidney.

The donor responses to accessing medical records, sending tissue overseas, and commercial research collaborations indicate that the majority of donors are comfortable with these options, and this is similar to the few reports in the literature. For example, a survey of patients involved in clinical trials of the Eastern Cooperative Oncology Group in the US found that 93.7% assented to use of their tissue for research on cancer, and 86.9% for research into other diseases.\(^{26}\) Similarly, a Swedish study of blood donors to a research bank found that 85.9% accepted surrogate decision-making by the ethics committee.\(^{27}\) When an attempt was made to gain retrospective consent to use renal transplant biopsies for research, 74% of 495 donors responded within 1 year, and the vast majority of them consented.\(^{28}\) Donors to other biorepositories overseas are reported to view involvement in commercial research collaborations as a way to achieve research in an under-resourced field.\(^{29}\)

Our results suggest that patients of diverse ethnicity are comfortable with donating tissue, but little has been reported by others. Thus we emphasise the importance of (and gratitude for) our close liaison with Māori advisors to the Canterbury District Health Board (CDHB) and the University of Otago, and the presence of a Māori representative on the TBB in developing culturally appropriate procedures.

Over the last few years, large electronically-linked networks have been formed to facilitate research which uses human tissues. The European Organisation for Research and Treatment of Cancer has created a Tumour Bank to facilitate translational research with close collaborations between clinicians and scientists.\(^{7}\) In the UK in 2003, a national collaboration was created called the National Translational Cancer Research Network (NTRAC) as part of the National Health Service ‘Cancer Plan’, to support and facilitate research in both academic and commercial centres.\(^{8}\) In the US, the National Biospecimen Network links the banks,\(^{30}\) while the International Society of Biological and Environmental Repositories (ISBER) provides information on the safe and effective management of specimen collections.\(^{31}\) The CTB is a member of the ISBER. This globalisation has shown that national ethical, legal, and economic standards vary widely, and this problem is being addressed by a number of organisations.\(^{32}\)

Australian researchers have launched a national prostate tumour bank,\(^{5}\) and have established the Australasian Biospecimens Network (ABN) in 2001.\(^{8}\) Some of the
funding from the NHMRC in Australia will support the development of electronic links to a central Infomatics Hub—so that a single request for tissue will yield information about tissues held in all linked banks in Australia, thus maximising these valuable resources. The CTB has been part of the ABN\(^{33}\) since its inception, and has worked with the members to develop tissue banking. Health research in New Zealand would benefit greatly from extension of a network within New Zealand.

Dedicated research banks have difficulty meeting competitive grant-funding criteria and a partial cost-recovery programme is fundamental to their survival, whereby researchers include tissue costs as part of their grant budgets. Partial cost recovery should cover tissue collection, storage, preparation, and data management. The CTB has been financially supported by grants through the Angiogenesis Research Group, which continues to host and support it, as well as by the CDHB and the University of Otago. The future of the CTB has recently been secured by a partnership with the Canterbury-West Coast Division of the Cancer Society of New Zealand supplemented by a partial cost-recovery programme.

The CTB is a successful model for potential New Zealand-wide application, which could be used to develop national tissue banking in regional centres using common consent forms and procedures. Now that clinical research internationally requires tissue samples as a standard of care, national ethical approval should be sought, together with consideration of national funding support as in the UK and Australia.

The CTB provides a common tissue-collecting process for new and existing projects, which is ethical, legal and culturally acceptable and operates to international biorepository standards to provide quality research samples. The sample preparation techniques provide a developmental platform for what is likely to be routine for diagnosis, prognosis, and planning therapy in the future.

The sustained rate of donations from people of diverse ethnicity, and the donor responses to the options on the consent form demonstrate the success of the banking programme. Indeed, it enables basic research, translational research, and contribution to international clinical trials, thereby supporting internationally recognised research in New Zealand.

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**Acknowledgements:** The Christchurch Tissue Bank functions through the goodwill and commitment of many staff from Christchurch Hospital and the Christchurch School of Medicine and Health Sciences. We thank all those involved, particularly all
donors, the Surgeons, the pre-admission clinic staff, and the Pathology and Operating Theatre staff.

The CTB has been kindly supported by these funding organisations:

- Cancer Society of New Zealand
- Cancer Society, Canterbury-West Coast Division
- Canterbury Medical Research Foundation
- Lottery Health
- Oncology Trust Fund
- Robert McClelland Trust
- Rotary Clubs of Christchurch

**Correspondence:** Dr Bridget Robinson, Oncology Service, Christchurch Hospital, Christchurch. Fax: (03) 364 0759; email: bridget.robinson@cdhb.govt.nz

**References:**


The case for lifelong follow-up after endovascular aneurysm repair

Carl Muthu, Malcolm Gordon, Tim Buckenham, David Lewis

Since endovascular aneurysm repair (EVAR) was first described in 1991,¹ the number of devices used in Australasia, Europe, and North America has continued to increase.²⁻⁴ Voluntary registries of EVAR patients have been established to monitor the clinical outcome of this relatively new technology and surveillance of these devices for endoleaks and mechanical failure is recommended.³ There has been controversy surrounding the durability of endovascular repair and questions raised as to the expense of a procedure that requires long-term follow-up.⁵ This case report serves to remind medical practitioners that EVAR patients are always at risk of developing late, potentially life-threatening complications.

Case report

Mr BS presented with an incidental 6 cm abdominal aortic aneurysm (AAA) detected on ultrasound. His past medical history included chronic obstructive airway disease (COPD) and ischaemic heart disease. He underwent uncomplicated EVAR in December 2000 using a Zenith stent (William A Cook Australia Pty Ltd, Perth) and was entered into the routine post-operative surveillance programme. In February 2005, his surveillance showed no evidence of endoleak and no structural problems with the graft device.

Mr BS then began a treatment course of radical radiotherapy for prostate cancer. In March 2005, over 4 years after his EVAR, he developed lower abdominal and right groin pain. He was admitted under the care of the oncologists with a suspected diagnosis of radiation cystitis. His abdominal pain did not settle and an abdominal CT scan was performed 3 days after admission which showed a large distal type 1 endoleak (Figure 1).

On careful review of the CT scan it was presumed that this was due to the distal end of the right limb of the graft becoming displaced from the right common iliac artery into the aneurysm sac (Figure 2). The aneurysm sac had expanded from 40 mm on his surveillance scan in February to 60 mm. Urgent referral was made to the vascular team and on clinical examination he was haemodynamically stable but had a tender aneurysm.

After discussion of the various treatment options with the patient (including open repair and conservative management) his endoleak was treated by a right femoral arteriotomy and endovascular placement of a 17 mm diameter, 71 mm long bridging stent (William A Cook Australia Pty Ltd, Perth). The proximal landing site was the proximal ipsilateral limb of the original graft and the distal landing site was the distal external iliac artery. An immediate post-procedure angiogram showed elimination of the endoleak. Mr BS made a good post-operative recovery and was discharged on the third post-operative day.
Figure 1. CT scan demonstrating the large endoleak (arrow)

Figure 2. Abdominal radiographs from 2004 (left) and 2005 (right) demonstrating the change in position of the right limb of the graft
Discussion

Since Parodis’ first endovascular stenting of an AAA,\(^1\) the use of EVAR has increased throughout the world. A voluntary audit in Australia designed to assess the safety of endoluminal AAA repair took only 18 months to collect 950 patient.\(^2\) The role of open versus endoluminal AAA repair is still debated in the vascular literature.\(^3,4\) Enthusiasts believe all aneurysms should be repaired endoluminally if anatomically suitable while others express misgivings about the long-term durability of EVAR.\(^5\)

EVAR is associated with a faster recovery time, lower morbidity, and probably lower mortality than open repair,\(^4,6–8\) but its long-term durability is unknown. All patients who have had EVAR require lifelong surveillance to facilitate early detection and appropriate management of complications, in contrast to patients who undergo open repair who do not require follow-up because of the low incidence of late complications.

The most common complication after EVAR is ‘endoleak.’ This is a relatively complex cluster of conditions but, in simple terms, they all involve continued flow of blood in the aneurysm sac after repair (i.e. the sac remains pressurized). Under these circumstances, the sac may continue to expand and the aneurysm can still rupture. EVAR is associated with a significant rate of secondary interventions—most commonly to treat endoleak.\(^7,9\) Most endoleaks can be successfully treated using endovascular techniques.\(^10\)

Conversion to open repair after EVAR is now uncommon.\(^11\) Large cohort studies have recorded an annual rupture rate of 1–1.5% per year after EVAR.\(^12,13\) Late ruptures may be due to other causes but there is certainly a correlation with the presence of endoleak.\(^14\) The EUROSTAR registry reported a rupture rate of 2.3% when an endoleak was present compared to 0.3% when no endoleak was detectable.\(^13\)

The unresolved uncertainties about the long-term durability of EVAR means that all patients require lifelong surveillance for evidence of graft failure and endoleak—this has implications in terms of cost, demand on radiology resources, and radiation exposure. The Christchurch Vascular Group has now performed 88 endoluminal AAA repairs and this is the first late, emergency complication in our series. As more patients undergo EVAR, doctors should be aware that these patients should never be considered ‘cured. They all require regular post-operative surveillance of their EVAR. Furthermore, any patient with abdominal, back, or groin pain and a history of EVAR should be considered for urgent referral to a vascular surgical service.

The surveillance programme at Christchurch Hospital consists of a CT scan at approximately 6 week, 6 months, and 12 months following EVAR. Thereafter, annual ultrasound imaging is performed if the 6- and 12-month CT scans both show no evidence of endoleak and a stable or shrinking sac, or if the patient has two (later) consecutive such CT results. AP and lateral abdominal radiographs are also taken to identify any mechanical failure in the graft.

In conclusion, EVAR represents a significant advancement in the treatment of abdominal aortic aneurysms. However all doctors should be aware of the need for regular surveillance following EVAR because of the risk of developing late endoleaks that may, as in this case, be life-threatening.
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References:

Dieulafoy lesion in the duodenum

George Anagnostopoulos, Steve Foley, Kris Ragunath

Case report

A 74-year-old man underwent endoscopy in our unit due to melaena. The past 6 months he had undergone two gastroscopies for the same reason (in other hospitals) but the source of bleeding could not be identified.

Careful endoscopic examination revealed a Dieulafoy lesion in the second part of duodenum (Figure 1). The lesion was treated with epinephrine injection and haemoclip placement (Figure 2). The patient remains well 6 months post-treatment with no further episodes of upper gastrointestinal bleeding.

Discussion

The Dieulafoy lesion represents a small submucosal defect with fibrinoid necrosis at its base, overlying a large, tortuous, thick-walled artery in the muscularis mucosa. It is characterised by subintimal fibrosis of the artery and absence of inflammation at the edge of the mucosal defect. Dieulafoy lesions are uncommon sources of GI haemorrhage; they predominantly occur in the proximal stomach. In 1988, McClave et al identified the first duodenal Dieulafoy lesions in four patients managed surgically.

Diagnosis is difficult because it relies on visualising active bleeding (or stigmata of recent bleeding) in whose absence a small mucosal defect overlying an artery can be
easily missed. Missed Dieulafoy lesions may be the cause of many cases of acute upper GI tract bleeding of unknown aetiology.¹

The question whether it is possible to identify patients at risk for developing and/or bleeding from Dieulafoy lesions is still unanswered. It seems that mucosal injury may unmask silent calibre-persistent arteries, at least in a subset of patients. Ischaemia due to decreased perfusion or oxygenation plays also a role in the minor mucosal injuries that expose large superficial vessels.¹

Endoscopic management has now become the standard approach for the treatment of these lesions, with success rates reported to be as high as 95%.³ Several modalities, including epinephrine injection, electrocautery, haemoclipping, rubber band ligation, or laser treatment have been used to treat these lesions. Recent data suggest that higher efficacy in terms of initial haemostasis and less recurrent bleeding is achieved by mechanical haemostatic therapy with haemoclip and band ligation compared with injection therapy.⁴

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**References:**

‘Woman bites dog’—making sense of media and research reports that claim women and men are equally violent

Janice Giles

Abstract

The media are quick to exploit research reports that appear to show women and men are equally violent. Unfortunately, while such reports contradict the observations of experienced medical workers, police, court personnel, and Women’s Refuge workers, they do influence public perceptions and may undermine policies designed to prevent and reduce male partner violence against women. This article examines research claims of women’s equivalent violence and explains why study outcomes claiming equal violence must not be accepted at face value.

We hear and read about violent acts every day in the media. Men are the perpetrators of the vast majority of these acts. That’s not news. Men’s violence is so commonplace as to be unremarkable. However, any suggestion of women’s violence achieves media prominence, whenever it arises.

Comments in both popular media and academic journals citing research that women are as violent, or more violent, than men are perennial. (For example: a television ‘documentary’ in which it is stated that ‘research shows women are more violent than men’,¹ and a television news item headlining study claims of a high incidence of violence against partners by Pacific Island women.).² Such statements are difficult to reconcile with worker experience in the field of domestic violence and partner abuse, and are of particular concern when cited in that context. This is a contentious issue and it is important not to be naïve about the implications of such comment.

Claims of ‘who hits who the most’ are debated in a sociopolitical context that allows those with the most credible ‘case’ to define the problem, or even if there is a problem, and whether it is morally worthy of solution.

This article explores how the ‘fact’ of women’s violence misrepresents the experience of women in abusive and violent relationships. Literature cited in support of this viewpoint is representative rather than an exhaustive compilation of all that is available.

Are women violent, just like men?

Numerous studies, including New Zealand studies³,⁴ that are cited in the media, make claims that women use violent acts in their relationships at least as often as men; however, any such conclusion requires further examination for the following reasons:

- The research is cited out of context and is based on studies of conflict between ‘ordinary’ couples in populations that do not have a known history of violence or abuse⁵—i.e. couples are not sourced or referred from police, Women’s Refuge, or other social agencies.
Almost all of these studies use a questionnaire called the Conflict Tactics Scale (CTS), which is not designed for application to populations with an established history of abuse, and has many limitations if applied in that context or is assumed to have been applied in that context.

Violence is a complex social problem arising from and sustained by multiple sources of oppression including race, class, and gender. Studies claiming ‘equal’ violence by men and women in intimate partnership reflect inadequate conceptualisations of violence, neglect analysis of imbalances in power between genders, and do not consider how socially-constructed gendered expectations of behaviour influence the motivations for and responses to violence.

There are important methodological differences between often gender-neutral quantitative research (which primarily relies on counting violent acts based on information supplied by individual respondents) and those studies which include a qualitative and gendered analysis.

Some researchers underestimate the potential for inaccurate or biased reporting, particularly in abusive relationships that may not yet be known as such.

Studies do not measure the outcomes of violence—i.e. the severity and/or frequency of injury, or the longer-term effects of living with fear of violence.

Citing research out of context

Violence as an expression of family conflict and violence that is used as an instrument to control or punish a partner is not differentiated. Understanding violent acts requires knowledge of such factors as motivation and consequences. When media comment suggests that research ‘proves’ women are as violent as men, the contexts are seldom provided (and may not even have been assessed as part of the research). Studies showing that women are ‘equally’ violent are based on interviews with couples (or, most frequently, with only one partner) in ‘ordinary’ relationships where violence is minor, does not escalate in severity, and injury rates are low.

Women victims of male partner violence are unlikely to be included in studies of family conflict because patterns of control, punishment, and social isolation by her partner are likely to preclude her participation. In addition, when women leave an abusive relationship or seek help, violence typically increases in lethality—but ex-partners are not included in ‘family’ studies, so these potentially high-risk relationships are excluded, as are behaviours common to abusive ex-partners such as stalking and harassment.

The Conflict Tactics Scale (CTS) is not designed for use in a ‘domestic violence’ context

The majority of claims that ‘women’s violence is equivalent to men’s violence’ are based on the use of a questionnaire: the ‘Conflict Tactics Scale’ developed in the United States of America, which counts tactics used by ‘ordinary’ couples when resolving conflict or expressing negative moods. The CTS has a long history of use and, as a consequence, may be uncritically accepted by generalist researchers in
multidisciplinary studies as a convenient tool for assessing domestic violence without consideration of CTS limitations in that context. Other researchers might use the CTS so that outcomes can be compared with international studies.

In New Zealand, the CTS has been predominantly applied to epidemiological and longitudinal studies such as the Dunedin longitudinal study, which interviewed a birth cohort of 21-year-olds, and more recently to a cohort of Pacific mothers. Internationally, there has been considerable objection to CTS based research claiming equal violence, with the majority of objections focussing on the inappropriate generalisation of outcomes to the context of domestic violence.

Using the CTS as the sole measure is not appropriate for application to populations in which violence and abuse is known to occur in the relationship (e.g. populations known to Women’s Refuge or Stopping Violence programmes) for the following reasons:

- The CTS presupposes an ‘ordinary’ relationship and ‘normalises’ conflict by enquiring what happens at times ‘when couples disagree, get annoyed with the other person, or just have spats or fights because they’re in a bad mood or tired or for some other reason’ (p217).
- The CTS counts the frequency of tactics (including violence) used for managing conflict over a previous 12-month period but is not designed to identify patterns of domination, coercion, and control.
- The CTS does not provide a context for acts of violence, which can create misleading outcomes. For example, he attempts to strangle her and she defends herself by kicking, biting, and hitting. In this example, he has committed one act of violence and she has committed three.
- The CTS most commonly finds violence that is ‘relatively minor and relatively infrequent’ and this cannot be compared to the situation in populations where there is an established history of violence, and in which men are the predominant aggressors (p215). The CTS does not count homicides, which are most commonly acts by men.
- The CTS does not measure the consequences of violence (i.e. frequency of injury or severity of injury). Men have higher rates of dangerous and severe forms of violence, repeat their violence more often, and do more damage with their violence. Relatively few women, even in mutually violent relationships, use violence that is likely to cause serious injury.
- The CTS does not assess fear of potential violence and injury, or the impact of living with ongoing fear. Women in violent relationships are afraid of their partner’s aggression, while men are seldom afraid.
- The CTS does not explore the motivation for violence (e.g. self-defence; or to control another person). Motives for men’s violence in relationship are typically to control via coercion or punishment; and assaults by men are commonly part of a pattern of intimidation and fear. Motives for women’s violence are often aimed at reducing abuse in their own lives and women’s violence is frequently in self-defence but may include ‘pre-emptive strikes’ when anticipating violence from a partner.
The CTS defines types of violence very broadly and there is insufficient differentiation between specific acts—e.g. ‘kicked, bitten, or hit your partner with a fist’ are counted as the same. Actual severity of the violent act remains ambiguous, with potential for wide variation in outcome and intention within categories.

Studies using the CTS do not count sexual coercion and sexual abuse, which are common experiences of women with abusive male partners. Consequently, if he attempts to force her to have sex and she fights back, her actions are counted as violence while his are not.

The CTS is applied retrospectively with potentially selective remembering and disclosure. Both women and men in abusive relationships tend to minimise men’s violence and remember women’s violence.

Researchers making use of the CTS have a responsibility to ensure that all reports explain why findings do not fit with hospital, police, family court, and community worker experience. Where possible, research needs to be balanced by taking different perspectives. This was done in the Dunedin studies, which undertook two separate interviews on the same day with the same group of participants. One study utilised the CTS, and the other asked questions about assault and allowed for inclusion of ex-partners. There were significant differences in outcomes, with the CTS based study showing that men and women have similar participation rates in violent acts, while the study on physical assault found more than four times as many women experienced assault by a male partner than men who experienced assault by a woman partner.

The designers of the CTS are also concerned about the misapplication of study outcomes by generalisation to other populations. They note that separate measures for context, assault, and injury are needed to demonstrate that men’s violence results in more injury, and that context is necessary to give meaning to outcomes of research that use this instrument.

The CTS has been revised (CTS2) and new studies may include scales to measure injury and sexual coercion. Qualitative methodologies that allow participants to describe and define their experience, rather than respond to a selection of possibilities chosen by others, would provide valuable data for understanding context and motivation.

**Limited consideration of gender, power, and motivation for violence in a context of intimate relationship**

Family violence research commonly includes interest in demographics such as employment, ethnicity, and age that epidemiological studies provide. Such generic studies are useful, for example, in assessing correlates of poverty and education with violence. Family violence studies tend to focus on counting violent acts; assume that men and women are equally powerful and that violent acts are equivalent; and commonly find ‘symmetrical’ violence (i.e. men and women are equally violent). In contrast, researchers who focus on ‘violence against women’ in a domestic context of ‘battering’ or ‘intimate partner violence’ claim that violence is ‘asymmetrical’, with men more likely to perpetuate violence than women. This latter form of research includes an understanding of the context of violent acts within intimate relationships.
(where power is unequal) and a wider ‘constellation of abuse’ experienced by women in relationship with a violent or abusive partner.\textsuperscript{7}

An analysis of gendered attitudes and expectations within society also provides context for understanding motivations for violent behaviour and the outcomes of violence, particularly when social attitudes support male authority over females in the family. These methodological differences (in conceptualising violence) mean that counting acts of violence in ordinary couples cannot claim to represent research on battering, and unqualified reports of equivalent violence in the media are misleading and irresponsible.

Current understanding of male partner violence against women is informed by analysis of socially constructed, gendered expectations of men and women, and the disparity in social power held by men and women as groups within society. Women’s socialisation generally discourages expressions of aggression while men’s violence, both public and private, is sanctioned by cultural beliefs that such behaviour is ‘manly’. Men’s violence is generally more humiliating, controlling, and coercive\textsuperscript{14} and, when a relationship includes systematic patterns of intimidation and control by male partners, just one violent act can generate a climate of fear that establishes male dominance and female obedience.\textsuperscript{16}

Women’s violence must be examined in the context of their partner’s violence against them; is seldom equivalent to men’s violence in intent, frequency, severity, or outcome;\textsuperscript{14} and is commonly in response to frustration, stress, or a manifestation of ‘slap the cad’, expressing moral indignation when insulted by a man\textsuperscript{11} (p216). Moreover, women are more likely to participate in minor acts of reciprocal violence in ‘ordinary couples’ because it is relatively safe to do so.

When women do use more serious violence, it is likely to be in a relationship where they are also victims of violence.\textsuperscript{9,12} Women do fight back to defend themselves although this may escalate violence, and women who use violence in their relationship often have significant histories of prior victimisation by a partner while male perpetrators do not.\textsuperscript{15,18}

**Inaccurate or biased reporting of perpetration and victimisation**

In studies of couples that are likely to include more violence and abuse (such as younger couples),\textsuperscript{10} it is useful to consider gendered dynamics of blame and self-blame that are at their most extreme in abusive relationships. Abusive men commonly minimise and deny their own abuse and violence in relationship, or define their actions as justified responses to some perceived transgression of their partner.\textsuperscript{19–21} But in a relationship with an abusive man, women are blamed and take responsibility for any conflict, perceiving their own actions as ‘causing’ their partner’s behaviour.

They excuse the abuse, minimise his violence, and focus attention on trying to make themselves better partners.\textsuperscript{22} An abusive male partner acknowledges less of his violence while his partner is likely to acknowledge every act of hers;\textsuperscript{7} and he exaggerates her violence to justify his own. This is particularly likely when women partners are young as well as earlier in the relationship.\textsuperscript{22} Such distortions may explain reported study outcomes that find couple agreement on undifferentiated scale measures but not on specific acts\textsuperscript{23} and may undermine accurate reporting even if both partners participate.
The relative severity of violence

When either women or men are victims of violence, the perpetrator is likely to be male—i.e. violence done to men is most commonly male-on-male violence.²⁴

Women are more frequently victimised by violent partners, and experience more injury and more severe injury in violent relationships,¹⁶ with assaults by men producing six times the rate of injury of assaults by women.¹² A significant New Zealand study focussed on incidences of physical assault in a previous 12-month period found that women are approximately 4.5 times more likely then men to be assaulted by a partner with 2.6 times the rate of assault, and are more severely harmed by such assaults.¹⁷

In addition to the potential for physical injury, living in fear and experiencing the psychological and emotional abuse that accompanies violence from a male partner can have extremely serious long-term mental health effects.²⁵–²⁷

The implications of assuming equivalent violence by women

Academics should be cautious when reporting on gendered violence based solely on findings of the CTS. In New Zealand, this scale has been used in major and highly reputable studies. The outcomes are entirely consistent with international studies using the CTS, but there are serious flaws in the methodology when generalised to domestic violence.

Comments made in the media that ‘research shows women are as violent as men’ must be taken seriously. Not because such statements are ‘true’, but because they influence public perceptions and subsequent responses toward women who experience violence and abuse from male partners. Such media claims invariably lack context; are based on populations of ‘ordinary’ couples (not couples whose relationship includes ‘serious’ violence); seldom include analysis of power and gender in violent relationships; and do not include injury outcomes, motivation for violence, or the meaning of the violence for either partner.

It remains important to maintain perspective and to remember that most men are not violent toward their relationship partners. Although violence by women against their partners is uncommon, women can indeed be violent and there is no intention here to excuse or condone women’s violence. However, comments in the media that women are more violent than men create exploitable distortions that have potentially serious implications for women.

A focus on women’s violence shifts attention away from men’s violence against women, and abusive men frequently claim ‘women are violent too’ to provide moral justification for their own behaviour. Public perceptions that women are just as violent as men reduce sympathy for victims on the assumption that they ‘deserved it’. Politically, the intention of those who claim that women are ‘equally’ violent may be to encourage the reduction of services and resources for women in violent and abusive relationships. As prophetically noted by Murray Straus, creator of the CTS, ‘the statistics are likely to be used by misogynists and apologists for male violence’¹¹ (p.217).

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References:


What’s happening in PHARMAC—where do all the submissions go? On the trail of gemcitabine

Andrew Simpson

**Abstract**

The process and progress of submissions to PHARMAC for funding of new treatments is unclear. There appears to be a lack of communication or transparency regarding funding applications, decisions, or expected timelines to reach an endpoint. It is difficult to have confidence in a process that lacks such definition. A recent clinician submission for funding of an oncology treatment (gemcitabine) for bladder cancer highlights these issues.

<table>
<thead>
<tr>
<th><strong>Drug</strong></th>
<th>Gemcitabine</th>
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<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Locally advanced or metastatic transitional cell carcinoma (TCC) of the urothelium.</td>
</tr>
<tr>
<td><strong>Recommended dose and duration</strong></td>
<td>Gemcitabine 1000mg/m² IV day 1, 8, and 15, with cisplatin 70 mg/m² day 2, each 28 days, receiving a maximum of 6 cycles.(^1)</td>
</tr>
</tbody>
</table>

**Clinical efficacy**

Without chemotherapy, the prognosis for patients with locally advanced or metastatic TCC of the bladder is limited with a median survival of 4–6 months.\(^2\) With chemotherapy, survival and quality of life can be increased. MVAC chemotherapy (methotrexate, vinblastine, doxorubicin [adriamycin], and cisplatin) was defined as the standard of care for the treatment of TCC during the 1980s and 1990s, with reported median survival of over 12 months.\(^3\)

However this drug regimen is associated with significant toxicity—including severe mucositis, neutropenic sepsis, and treatment-related deaths in up to 4% of patients in early reports.\(^1,3\) Research continues to define new treatment regimens that provide greater benefit with increased effectiveness (or similar benefit) with lesser toxicity than those funded at present.

Gemcitabine in combination with cisplatin has been shown in a pivotal phase III study to be equally effective as MVAC in this tumour type but associated with significantly less toxicity.
The median survival of the patients with locally advanced or metastatic TCC of the bladder treated with gemcitabine and cisplatin was equivalent to that of MVAC at 14 months, and 13% of those treated on study were still alive at 5 years.  

**Background**

The ‘cancer drug basket’ (Part V of Schedule H) was established in October 2001 as a result of a ministerial directive. ‘High cost’ cancer drugs within the basket are funded only for specific indications. Extension of funded treatment indications or addition of a new agent to the basket is considered upon application to PHARMAC.

Pharmaceutical companies submit the majority of applications to PHARMAC, although this facility is also available to individual clinicians. The request for a funded extension to the treatment indications for gemcitabine to include locally advanced or metastatic TCC of the bladder was the first clinician-sponsored application to PHARMAC for funding of an oncology drug, and as such has been watched with interest by the oncology community. This submission was forwarded to PHARMAC January 2004. CaTSOP (Cancer Treatments Sub-committee of PTAC) considered the submission in March 2004.

The committee considered that gemcitabine with a platinum analogue had equal effectiveness with current therapy (MVAC) but with markedly reduced adverse effects. It was noted that number of patients currently treated is low, but that more patients would be suitable for gemcitabine therapy due to the decreased toxicity of treatment. The committee estimated that approximately 70–90 patients would receive treatment per annum.

A preliminary pharmacoeconomic analysis has been performed but to date a final decision from PHARMAC is not yet available.

**Current situation**

New Zealand

Gemcitabine was initially licensed in December 1998 by MedSafe for use alone or in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer. In June 1999, gemcitabine was also licensed for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas. This was followed in May 2000 with licensing of gemcitabine for the treatment of patients with advanced bladder cancer (TCC).
Although licensed for use in TCC from May 2000, gemcitabine is currently not funded for this indication. Currently gemcitabine is listed in Part V of Section H (July 2005) of the Pharmaceutical Schedule for the restricted indications of:

- Advanced lung cancer (non-small cell lung cancer and mesothelioma);
- Advanced pancreatic cancer;
- Ovarian, fallopian tube or primary peritoneal cancer—post taxane therapy; and
- Ovarian, fallopian tube, or primary peritoneal cancer—initial therapy when taxane contraindicated.

International By comparison, gemcitabine has been funded for TCC in Australia since August 2001, and is used for this indication within the NHS in the United Kingdom.

**Access/supply**

Gemcitabine for use in TCC can be obtained through prescription at a cost of $1983 per cycle (3 doses calculated at average body surface area of 1.8m²), but is not able to be administered in the public health sector for this indication, although it is commonly used in public hospital oncology units for the above funded indications.

**Economic analysis**

PHARMAC’s cost-utility analysis based on the data from the pivotal study calculates a cost of $817,808 per QALY (Quality Adjusted Life Year) gained when using gemcitabine and cisplatin for advanced bladder cancer compared to the historical regimen of MVAC. This figure was generated from an incremental treatment cost calculated for cisplatin and gemcitabine over that of MVAC of $4276.60, and an estimated incremental benefit of 0.00523 QALYs gained.

The calculated incremental cost of treatment is similar to those calculated in other countries of GBP £2976 and AUD $5035 (communication Eli Lilly), however the incremental utility gained was 25 times greater in the UK study at 0.13 QALYs than that proffered by PHARMAC. If the UK utility is used for PHARMAC’s calculations, the cost decreases by the same magnitude to $32,900 per QALY.
Other issues

There is no accessible site on PHARMAC’s webpage that provides up-to-date information on drug submissions made. Recent accessing of the site reported applications that had been made up until July 2005, but does not include the submission for gemcitabine. This site also only lists the drug and the applicant, but not the treatment indication for which the submission has been made.

Comment

There are several issues that are highlighted from this first clinician-sponsored application for an oncology drug to be funded.

The first is the time to receive a decision from the process. The application was submitted early 2004, and reviewed by CaTSOP within a few months. Since that time there has been no formal decision notified, and it is unclear where the application is in the PHARMAC process. It is now over 18 months since the submission was made. During this process, gemcitabine is not available for use in advanced TCC bladder, at least not within the public system.

This lack of transparency of the process regarding submissions has also been true of subsequent clinician applications. It is also unclear from PHARMAC’s own website which submissions have been made or are being currently considered. The cited PHARMAC report in this commentary was made available under the Official Information Act and the fate of the gemcitabine application is unknown at present (9 months after the PHARMAC report).

PHARMAC’s pharmacoeconomic analysis is admittedly a preliminary analysis, however these analyses are instrumental in decisions regarding funding of new treatments. It is of concern that there is such a large discrepancy in the utility calculated by PHARMAC and that reported in a peer-reviewed journal, especially as the magnitude of the difference leads to a cost per QALY of $817,808 rather than $32,900.

Decisions to fund or not fund treatments need to be based on robust analysis. Large discrepancies between reports raise the question of the accuracy of the assumptions and calculations made. To gain confidence in the process used there needs to be complete transparency such that the assumptions made are seen to be evidence based, inaccuracies can be challenged, and the resulting calculations or decisions are robust and able to withstand scrutiny.
At a time when there are new treatments becoming available internationally and an increasing public awareness of new therapies and treatment indications, the funding of drugs within the public health system needs to be considered in a timely and evidence-based manner. Transparency is paramount if there is to be confidence in this process for all concerned.

Conflict of interest: Andrew Simpson has no conflict of interest to declare.

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8. Eli Lilly and Company (NZ) Limited. PO Box 109197, Newmarket, Auckland. URL: http://www.lilly.co.nz/


NZMJ Note: Refer to http://www.nzma.org.nz/journal/118-1225/1741 in this issue of the Journal for PHARMAC’s response.
Diseases and accidents of the toilet

This extract comes from the New Zealand Medical Journal 1905, Volume 4 (15), p188–90.

As an impecunious student, when the wardrobe were always in a state of decrepitude bordering on decay, it often struck me that there was great need of a practical handbook dealing with the various injuries and diseases to which our clothes are liable. Now that I tread the golden pathways of private practice, I find I still—though, of course, in a minor degree—labour under the same disabilities. I have therefore lately been devoting myself to the compilation of what trust will prove to be the standard text-book on this important subject. No pains have been spared to make the work as complete and up-to-date as possible. The chapter on “Plastic Repair of the Underclothes” has been especially contributed by a landlady of experience among many generations of students; while my own theories on the true cause of Paget’s “glossy elbows” and the classification of the fungi attacking the elderly top-hat are believed to be entirely new to medical literature.

The following are a few extracts which I hope may stimulate the interest of your readers, and lead them to support my forthcoming publication.

Perforating Ulcer of the Sock.—These may be due to outgrowing toe-nails or simply to senile trophic changes. In either case treatment by simple suture or the purse-string ligature is not to be recommended. Each perforation must be carefully grafted by an expert.

False Passages of the Vest.—Nine o’clock lectures predispose to this condition. The head, being hurriedly thrust into the garment, lacerates the fabric, and emerges through the posterior wall or the axilla instead of through the cervical canal. When several openings have been established, the patient’s life in the early morning becomes very burdensome. Multiple fistulae of the sleeves often co-exist. The best treatment is prolonged rest in bed, until the warmer weather permits of the garment being completely discarded.

Hairy Mole of the Shirt-cuff.—This is a very common affection. Epilation is of little value. Whitehead’s operation or excision of the bristle-bearing area only has been advocated; but complete excision ariaa the substitution of an artificial member made of celluloid is, in my opinion, more satisfactory

Idiopathic Atrophy of the pyjamas.—The cause of this is unknown, but it is probably due to some inherent viciousness of texture. A fine suit, originally coating as much as 3s. 64d., may, after a few success ye visits to the laundry, shrink to such an extent as to be almost unrecognisable. There is no treatment.

Mollities Bowleri.—This congenital disease of the bat is often not diagnosed at the time of purchase, but soon becomes apparent after a few days’ use. The symptoms are characteristic. The wearer, when wishing to salute a lady, finds that the brim, instead of remaining rigid and levering the body of the bat gracefully into the air, merely bends ineffectually towards the nose. In the slighter forms of the malady it slowly...
resumes its former position when the finger and thumb are removed, but in advanced
cases it must be remoulded into shape with the aid of a looking-glass. Treatment
Immersion in a bath of silicate of soda two or three times a week.

*Sloughing of the Posterior Foramen of the Collar-band* often proves troublesome, but
is not necessarily dangerous to the life of a shirt. Should the ordinary cardboard
diaphragm prove ineffectual to cope with the difficult, and a plastic operation is
considered inadvisable, a stout ligature should be passed through the collar and round
the transverse arch of the braces, where they bifurcate into the two posterior
descending branches.

*Prolapsus Trouseri.*—A most disconcerting accident, usually due to separation of one
of the posterior tuberosities, or “buttons,” when the fellow on the opposite side is
missing, or to rupture of the braces from violence. Simple suture and reposition is
usually successful. There is a rarer and more serious form due to complete separation
of the upper epiphysis. This usually occurs during sonic severe exertion, such as the
reduction of a dislocated shoulder by direct traction, and is most difficult to deal
with. If the patient be in a public place he had better be kept in a recumbent position,
and removed to his home in an ambulance. But should this for any reason be
impossible, temporary relief may be gained by the performance of a kind of modified
Alexander’s operation. The braces are detached from their insertions into the upper
fragment, passed beneath it, and transplanted on to the lower fragment by means of
stout safety-pins. Additional support is gained by including a portion of the
underlying deep Jaeger’s fascia. Care, however, must be taken to ascertain if this is
present before passing the pins, as in some hardy subjects it may be entirely absent.

A special chapter has been devoted to affections peculiar to evening dress, such as
xanthoma pectoris or Addison’s disease of the shirt-front, madura pump, and
inoperative volvulus of the necktie.

But enough has been said to indicate the scope of the work, and I will trespass on your
valuable space no longer.—G. H. R., *in the St. George’s Hospital Gazette.*
Death due to butane abuse—the clinical pharmacology of inhalants

Matthew Doogue, Murray Barclay

The Wellington Coroner, Mr Garry L Evans, recently investigated and reported on the deaths of six young New Zealanders due to butane inhalation (Decisions 86–91/05, 26 September 2005). These deaths occurred between January 2003 and April 2004 in people aged 15–27 years. The reports are compelling reading and strong recommendations are made about the management of drug abuse in New Zealand. These reports had widespread attention in the national media. The following is a brief overview of the clinical pharmacology of abused inhalants, in particular the properties and actions of butane.

The lifetime prevalence of inhalant abuse in New Zealanders is about 2%. The most commonly abused inhalants are solvents from adhesives, fuels, aerosol propellants, and nitrous oxide. Most abusers are adolescents and there is a high risk of death compared to other drug abuse.

Abused inhalants can be loosely grouped into three groups on the basis of their pharmacological and behavioural effects. The first two groups are the volatile alkyl nitrites and nitrous oxide. The prototypic volatile alkyl nitrite is amyl nitrite. The basis for use and abuse of the alkyl nitrites is their vasodilatory and smooth muscle relaxant effects. Nitrous oxide is a widely used gaseous anaesthetic that is also used commercially as an aerosol (e.g. in whipped cream). Nitrous oxide has a pattern of effects that include stimulant, depressant, and hallucinogenic effects. However the exact mechanism of action on the central nervous system (CNS) is poorly understood.

The third group includes volatile solvents, fuels, and anaesthetics. Volatile substances have long been used in anaesthesia and also have a long history of abuse. Notable abusers in Victorian England included Coleridge, Southey, and Wedgwood. Anaesthetic agents have evolved from ether, to halogenated alkanes (e.g. halothane), and to the currently used halogenated ethers (e.g. sevoflurane). While the mechanisms of action of volatile substances are similar, these halogenated gases appear to have additional gaba enhancing activity, which provides advantages for anaesthesia.

The mechanism of action of volatile substances remains poorly understood and their range of effects is much greater than can be elicited by specific molecular targets. Volatile substances are rapidly absorbed from the lungs and spread throughout the CNS affecting the properties of lipid membranes. The changes in cell membranes affect multiple cell-signalling processes.

A generalisation that is usually valid is the Meyer-Overton rule Potency of inhalational agents correlate directly with their lipid solubility. In anaesthesia potency is often defined by the minimum alveolar concentration required to produce an effect. The magnitude of effect is dependent on both dose and potency.

The acute affect of volatile substance abuse is characterised by rapid onset of intoxication and rapid recovery. Intentional abuse can cause the desired effects of
euphoria and disinhibition, and the undesired effects of nausea, vomiting, dizziness, ataxia and cough. Higher doses can cause drowsiness, coma, respiratory depression and seizures. Pulmonary aspiration of stomach contents, and pneumonitis can occur. Cardiac arrhythmias are often implicated in fatalities.

The chronic effects of volatile substance abuse have been characterised particularly for toluene, the solvent of “glue sniffing”. Long-term use can cause permanent cerebellar and cortical damage and chemical pneumonitis is relatively common. In addition, hepatitis, bone marrow suppression, and renal failure have all been reported. Substance-abuse during pregnancy is a particular risk given the age of the abusing population, with toluene abuse during pregnancy being consistently associated with foetal malformations.

Butane, also known as liquid petroleum gas (LPG), is widely used as a propellant in aerosols and as a fuel for LPG appliances and cigarette lighters. It is a colourless, flammable gas with a boiling point of –0.5°C. The butane causing the Wellington fatalities came from a range of sources, including air freshener, lighter fluid, a gas heater, a gas element, and butane canisters for camp stoves (x2). Butane’s relatively high volatility, with rapid evaporation from compressed liquid, permits high dose rates. It is also highly lipid soluble (logP 2.81) and thus potent. The combination of a high dose and potency facilitated lethal toxicity in these six young New Zealanders.

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Proceedings of the 180th meeting of the Otago Medical School Research Society, 3 November 2005


Drug substances in solid formulations exhibit a wide and unpredictable variety of solid-state properties, which can affect bioavailability and ultimately alter clinical outcome. These concerns have led to an increased regulatory interest in understanding the solid-state properties and behaviour of drug substances in accordance with the guidelines outlined by the Food and Drug Administration. This study looks at the different physical states (polymorphs and amorphous form) of ranitidine hydrochloride to illustrate the importance of understanding solid-state behaviour in pharmaceutical drug development.

Ranitidine hydrochloride, a H$_2$ antagonist, exists in two polymorphs, termed form 1 and 2. Our previous milling studies at room temperature indicated that ranitidine hydrochloride form 1 transformed to form 2 over a period of time. As heat was generated during the milling, a further study was carried out at 4 ± 2°C and 35 ± 2°C to compare with the room temperature studies. Solid-state properties were evaluated by X-ray powder diffraction and differential scanning calorimetry. The crystallization temperature of the amorphous form of ranitidine hydrochloride was found to be between 40°C to 60°C. In all cases, one-way transformation of form 1 to 2 was observed. Milling at 4°C led to an in situ temperature of 40°C and produced only amorphous drug; milling at ambient temperature led to an in situ temperature of about 50°C with progressive transformation to form 2 via the amorphous form and milling at 35°C led to an in situ temperature of 66°C, with more rapid transformation.

This suggests an increase in temperature of the solid material during milling in relation to its crystallization temperature as well as the duration of milling influences solid-state changes and therefore to changes in physicochemical properties and potentially in the bioavailability and stability of the drug.

Factors associated with finger and thumb injury in netball players. G Donaldson$^1$, SJ Sullivan$^1$, A Thurston$^2$, G Johnson$^1$. $^1$School of Physiotherapy, University of Otago, Dunedin; $^2$Wellington School of Medicine & Health Sciences, University of Otago, Wellington.

Finger trauma is a significant problem in netballers, comprising up to 23% of all injuries sustained by these players. Of concern is the recurring nature of finger injuries and the suspicion that individuals with hypermobility, or generalized joint laxity, may be predisposed to trauma as a consequence of an increased range of movement in the finger joints.

The purpose of this study was to examine the relationships between hypermobility, measures of hand function and traumatic digital injury in netballers. Twenty-four
netballers (mean age 28.84 ± 8.46 [SD] years) were followed up with a physical examination 3.28 ± 2.14 years subsequent to finger trauma. One sub-group (n=12) had been diagnosed with damage to the volar plate (VP), the important fibrocartilaginous structure of the proximal interphalangeal joint. The other sub-group (n=12), had been diagnosed with either single interphalangeal or metacarpophalangeal joint dislocation (JD). For each subject, the degree of joint hypermobility using the validated Beighton Hypermobility Index (BHI), along with five functional outcome measures, was determined. The BHI gives a composite score ranging from 0-9 with those subjects scoring between the values of 5-9 considered to be distinctly hypermobile.

The median BHI score for the VP subgroup was found to be 4.0 (0-7, IQR) and that of the JD sub-group, 4.5 (0-8, IQR). In the VP group, significant correlations were identified between hypermobility and localized chronic instability (0.896, \( P < 0.001 \); Spearman’s rho) and between that of hand function (-0.600, \( P < 0.039 \)).

Volar plate injuries are a relatively rare but serious injury to the hand and concern is expressed at the high incidence identified within this group of netballers. The greater likelihood of poor functional outcomes and localized chronic instability in netballers in association with hypermobility suggested by the outcomes of this study has important assessment and rehabilitation implications for this group of patients.

Naturally occurring flavonoids baicalein and baicalin as putative modulators of GABA\(_{\text{A}}\) receptors. L Huang, G Lees. Department of Pharmacology & Toxiology, Otago School of Medicine, Dunedin.

We are seeking anxiolytic drugs devoid of the undesirable side-effects typical of conventional benzodiazepines (BDZs). The GABA\(_{\text{A}}\) receptor is a member of the ligand-gated ion channel superfamily, and represents the main target of anxiolytic, hypnotic and anesthetic drugs. Baicalein and baicalin are isolated from an Asian plant, Scutellaria baicalensis, and have shown affinity for benzodiazepine (BDZ) binding sites and anxiolytic-like effects in laboratory animals. Here we address the hypothesis that both compounds are positive allosteric modulators of GABA\(_{\text{A}}\) receptor currents.

Cultured neurons were prepared from cerebral cortices of 17-18 day-old rat embryos and were used in electrophysiological experiments after 14-30 days \textit{in vitro}. Pyramidal cells were clamped at –40 mV; 500 ms pulses of GABA (3.2 \textmu M) were applied at one-minute intervals. Baicalein did not allosterically enhance the GABA-induced current in cultured rat cortical neurons (concentration range from 10 \textmu M to 50 \textmu M). Low concentrations of baicalin (< 100 \textmu M) did not modulate the GABA-induced current. A high concentration of baicalin (320 \textmu M), exerted an apparent inverse agonist effect on GABA-induced current (reduced to 52.84 ± 6.17 % of control, \( n = 4 \), \( P < 0.001 \), paired two-tailed t-test), occluded spontaneous inhibitory currents and led to a net increase in excitatory synaptic activity in the cultures. These effects were fully reversible.

Though neither flavonoid showed positive fast modulation of the GABA\(_{\text{A}}\) receptor, further studies are necessary to determine if baicalein acts as a GABA\(_{\text{A}}\) receptor antagonist, and whether the inverse agonist effect of baicalin is through the BDZ
binding site of the GABA\textsubscript{A} complex. In conclusion, in spite of their anxiolytic profiles \textit{in vivo} neither compound appears to represent a benzodiazepine agonist.

Soluble forms of the major transplantation antigens MHC class I and II are not associated with exosome structures in human or murine blood. P MacKay\textsuperscript{1}, RW Jack\textsuperscript{1}, N Koch, S LeibundGut-Landmann\textsuperscript{2}, W Reith\textsuperscript{2}, AD McLellan\textsuperscript{1}.

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Major histocompatibility complexes (MHC) are integral membrane molecules required for the activation of antigen specific T-cells and are the main molecules mediating allogeneic transplant rejection. MHC is also present as a soluble form (sMHC), which may play an important role in immune tolerance by preventing T-cell activation. Previous \textit{in vitro} studies using cultured cell lines have resulted in an assumption that the main reservoir of sMHC in biological fluids is contained within exosomes (100 nm lipid vesicles). We endeavoured to characterise sMHC from serum and confirm their association with exosomes. Surprisingly our findings showed that serum sMHC were not associated with exosomes.

Using antibodies recognising specific epitopes on MHC-II, gel permeation chromatography with or without detergent to detect an association with high molecular weight, detergent-labile structures, ultracentrifugation to investigate association with high density lipid vesicles and western blotting to determine molecular weights, we showed that serum sMHC-II differs from exosomal bound sMHC-II in five ways: serum sMHC-II is of low density, of low apparent molecular weight (50-250 kDa), is not detergent-labile, is not physically linked to MHC-I or other isotypes of MHC-II (HLA-DR or -DQ) and is capable of binding the TAL-1B5 antibody that recognises an intracellular epitope of HLA-DR \textalpha-chain which is masked by association with cellular or exosomal membranes. These characteristics were also confirmed for sMHC-I.

The concept that sMHC exists independent of exosomes in the body has exciting implications for the development of transplant therapy, treatment of toxic shock and autoimmune diseases. While varied theories attempt to provide a role for MHC-containing exosomes \textit{in vivo}, our research suggests that production of exosomes by immortalised cell lines is an artefact of cell culture and/or viral transformation and is not reflected \textit{in vivo}.

Epigallocatechin-gallate and tamoxifen: a novel drug treatment in a murine model of estrogen receptor negative breast cancer. AR Menzies, MJ Scandlyn, MJ LeNedelec, EC Stuart, RJ Rosengren. Department of Pharmacology and Toxicology, Otago School of Medical Sciences, University of Otago, Dunedin.

There is currently no effective drug treatment for estrogen receptor negative (ER-) breast cancers. We have previously demonstrated that epigallocatechin-gallate (EGCG) + tamoxifen exert synergistic cytotoxicity in MDA-MB-231 human breast cancer cells (ER-). This study aimed to determine if synergism would occur in a murine model of ER- breast cancer. Additionally, the activities of enzymes CYP19,
CYP3A and CYP1A were investigated as a potential mechanism of action, as they are important in the synthesis and metabolism of estradiol, possibly altering the production of DNA-damaging metabolites.

Athymic nude CD1 female mice were inoculated with MDA-MB-231 cells (2x10^6/50µl matrigel) and left to form palpable tumours. Mice were treated for 70 days as follows (n=20); control (5 ml/kg saline, i.p. and corn oil, orally), EGCG (25 mg/kg, i.p.), tamoxifen (50 µg/kg, orally) and EGCG (25 mg/kg, i.p.) + tamoxifen (50 µg/kg, orally). Tumour volume was measured weekly using electronic callipers. Toxicity was determined by measuring alanine-aminotransferase activity and gross organ weight. Statistics were performed using one-way ANOVA and Student-Newman-Keuls post-hoc test. Tumour growth suppression began on day 35, as the combination treatment group’s tumour volume decreased 165% from control (P < 0.05). This reduction continued to day 70 when the tumour volume was reduced by 291% (151 ± 27 mm^3 vs 439 ± 89 mm^3, P < 0.05). This was supported by a 198% (P < 0.05) decrease in tumour weight. Hepatic CYP3A catalytic activity, determined by erythromycin-N-demethylation, was increased 137% in the combination group compared to control (0.89 ± 0.05 nmol/mg/min vs 0.65 ± 0.04 nmol/mg/min, P < 0.05) However, there were no changes in hepatic CYP1A or ovarian CYP19 catalytic activity.

The results demonstrate that EGCG and tamoxifen safely suppress the growth of ER-tumours in vivo. However, modulation of drug metabolising enzymes does not play a role in this effect.

Transgelin: discovering its role in prostate cancer progression. P Prasad, J Stanton, S Assinder. Department of Anatomy and Structural Biology, Otago School of Medical Sciences, University of Otago, Dunedin.

Neoplastic changes are associated with disruption of the actin cytoskeleton as well as numerous actin-associated proteins. One such protein is the 22 kDa transformation sensitive protein, transgelin (also named SM22). Transgelin is involved in organising loose actin filaments into a viscous gel. Its expression is downregulated in breast and colon cancer. This study aimed to investigate whether transgelin expression is lost during prostate cancer progression.

To investigate this, RT-PCR was carried out on RNA isolated from human prostate cell isolates. Transgelin specific primers (experimental), beta-actin specific primers (positive control) were used along with no template and RT negative controls. RT-PCR showed that transgelin is transcribed in normal prostate cells as well as in the LNCaP prostate cancer cell line. However a serial dilution of cDNA showed a loss of the transgelin transcript at 31.25ng cDNA for LNCaP cells, but it was still present in normal epithelial cells. This demonstrated lower levels of expression in prostate cancer cells. Two peptide-specific anti-SM22 polyclonal antibodies and one monoclonal antibody, all raised to different epitopes, were used in western blotting and immunohistochemistry. Cellular localisation of transgelin was determined immunohistochemically using a standard streptavidin-biotin peroxidase method with high-temperature antigen retrieval on 5 µm formalin-fixed paraffin-embedded human prostate sections. This demonstrated transgelin expression in both stromal and glandular tissue in normal and pre-cancerous hyperplastic prostates. Homogenates of
normal stromal and epithelial human prostate cell isolates separated by SDS-PAGE demonstrated an immunopositive protein of expected size (22 kDa) on western blot. This was absent in LNCaP cells.

In conclusion, downregulation of transgelin expression occurs in prostate cancer. This suggests a role of transgelin in prostate carcinogenesis and provides evidence for transgelin as a novel target for prostate cancer diagnosis and therapy.

Cost-efficacy of TPMT testing prior to azathioprine therapy. V Priest (1,2), EJ Begg (1), SJ Gardiner (1), CMA Frampton (1), RB Gearry (1), ML Barclay (1) & DWJ Clark (2). (1)Department of Medicine, Christchurch School of Medicine, Christchurch; (2)Department of Pharmacology and Toxicology, Otago School of Medical Sciences, University of Otago, Dunedin.

Inflammatory bowel disease (IBD) is an increasing burden in Western societies. Azathioprine (AZA) is the immunosuppressant of choice for maintaining remission. Thiopurine methyltransferase (TPMT) is an enzyme involved in the metabolism of AZA and displays genetic polymorphism. Marked deficiency occurs in 0.3-0.6% of the Caucasian population, predisposing to neutropenia. TPMT activity (‘phenotype’) and genetic (‘genotype’) tests can identify individuals at elevated risk of neutropenia. This study examines whether prospective phenotype and genotype testing are cost-effective in New Zealand.

A pharmacoeconomic model was developed to predict outcomes in a theoretical population of 1,000 IBD patients over a one-year period. Inputs for the models included the prevalence of TPMT deficiency, risks of neutropenia, costs of the tests and rectifying neutropenia, and quality of life effects. Pharmacoeconomic analyses compared population outcomes with the different testing strategies.

Cost analysis showed that identification of ‘at risk’ patients by phenotyping or genotyping would save New Zealand taxpayers NZ$180,000 or NZ$11,000 per 1,000 patients, respectively. The savings from avoided neutropenia outweighed the costs of testing. The phenotyping assay was cheaper than genotyping and had a greater likelihood of preventing neutropenia (concomitant drug use and novel mutations may impair TPMT activity but would not be identified with a genotype test). Prospective testing was also beneficial for patient quality of life. Sensitivity analysis showed the results were robust with respect to changes in the inputs.

In conclusion, prospectively identifying poor metabolisers of AZA is cost-effective and pre-empts serious adverse reactions (phenotyping is currently more effective than genotyping).

The constitutive expression of HPV16 E6 in HCT116 cells leads to a reduction in E-cadherin levels that can not be counteracted by indole-3-carbinol or tamoxifen. J Shields, M Hibma. Department of Microbiology and Immunology, Otago School of Medical Sciences, University of Otago, Dunedin.

Human papillomavirus (HPV) is a prevalent sexually transmitted disease responsible for over 99% of cervical cancer cases. HPV type 16 (HPV16) accounts for about half of these cases worldwide. HPV infects the keratinocytes of mucosal and cutaneous epidermis and E-cadherin is a homophilic adhesion protein expressed on these cells. It
has previously been shown that transient expression of one of the viral oncoproteins, HPV16 E6, reduces surface levels of E-cadherin. The aims of this study are to determine if E6 regulates surface and total E-cadherin expression in an E6 expressing colon cancer cell line (HCT116), and to determine if E-cadherin reduction by E6 can be counteracted by using indole-3-carbinol (I3C) or tamoxifen (TAM), which are reported to increase E-cadherin in some cell lines.

Flow cytometric analysis, immunofluorescence and western blotting were used to measure E-cadherin levels in the stable HCT116:E6 cell line compared with wild type HCT116 (WT) cells. Levels of surface E-cadherin on HCT116:E6 were 0.49 (± 0.03; SEM n=3) times the levels of WT, as measured by flow cytometry. Immunofluorescence also showed a reduction in the amount of surface E-cadherin in HCT116:E6. Total E-cadherin in HCT116:E6 was 0.61 (± 0.11; SEM n=3) times the level in WT as measured by densitometric analysis of western blot. There was no difference in surface E-cadherin in HCT116:E6 and WT when grown in the presence of I3C (50-200 µM) or TAM (0.1-10 µM), as analysed by flow cytometry (n=3).

In summary, the cell line HCT116:E6 has a reduction in both cell surface and total E-cadherin, confirming that E6 regulates E-cadherin when constitutively expressed in cells. This in vitro study shows that I3C and TAM are unlikely to be good candidates for therapeutic agents to restore E6 mediated loss of E-cadherin.

Epigallocatechin gallate and curcumin synergistically induce G2/M-phase arrest in MDA-MB-231 human breast cancer cells. TJ Somers-Edgar, EC Stuart, RJ Rosengren. Department of Pharmacology and Toxicology, Otago School of Medical Sciences, University of Otago, Dunedin.

Previous work has demonstrated that epigallocatechin gallate (EGCG) and curcumin are synergistically cytotoxic to estrogen receptor negative (ER-) MDA-MB-231 human breast cancer cells. Therefore, this study aimed to determine the optimal treatment conditions required to achieve this synergistic effect. Optimal treatment conditions were then used to determine the time-course required to produce synergistic cytotoxicity. Additionally, this study aimed to determine whether the observed cytotoxicity was associated with alterations to cell cycle progression.

To determine the cytotoxicity time-course, MDA-MB-231 cells were plated at 35,000 cells/well and treated with 20 µM EGCG, 3 µM curcumin or both for 12 to 48 hours. Vehicle control cells were treated with 0.1% DMSO. The sulforhodamine B assay was then used to determine cell number. For cell cycle studies, MDA-MB-231 cells were plated at 100,000 cells/well and treated as above for 6 to 12 hours. Cell cycle progression was examined using propidium iodide labelling and flow cytometry. Time-course studies revealed that combination treatment with EGCG and curcumin produced a synergistic decrease in cell number. Specifically, after 48 hours of treatment with 20 µM EGCG, 3 µM curcumin or EGCG + curcumin, cell number was decreased from vehicle control by approximately 16%, 24% and 67% (mean, n=3, P < 0.05), respectively. Analysis of cell cycle progression revealed that EGCG and curcumin synergistically induce cell cycle arrest in G2/M-phase. Specifically, after 18 hours of treatment with 20 µM EGCG, 3 µM curcumin or EGCG + curcumin, the proportion of cells in G2/M-phase was increased, compared to vehicle control, by approximately 2%, 6% and 21%, respectively (n=8, P < 0.05).
Thus, EGCG and curcumin are synergistically cytotoxic to MDA-MB-231 human breast cancer cells, and the induction of G<sub>2</sub>/M-phase cell cycle arrest by these compounds appears to contribute to this effect.

**Neurotrophin-3 loss in vivo does not affect myelination at birth, but reduces myelination at three weeks in mice.** KJ Tait, AG Woolley, MJ Duxson. Department of Anatomy and Structural Biology, Otago School of Medical Sciences, University of Otago, Dunedin.

The myelin that ensheaths large calibre axons ensures rapid bi-directional signalling between the central and peripheral nervous systems. Recently, *in vitro* work provided evidence that neurotrophin-3 (NT-3), a proprioceptive neuronal survival factor, is a peripheral myelination inhibitory factor. Our aim was to test this hypothesis *in vivo* using mice null mutant, heterozygous or wild type for the NT-3 gene.

Littermates were intracardially perfused with cacodylate-buffered (0.1 M) 4% paraformaldehyde / 2.5% glutaraldehyde at either postnatal day 0 (P0, n = 16) or postnatal day 21 (P21, n = 8). The medial cord of the brachial plexus was processed and resin-embedded using standard transmission electron microscopy (TEM) protocols. Due to the perinatal lethality of the null mutation, only heterozygous and wild type animals were compared at P21. Ultrathin sections were contrast-stained and imaged using TEM. The width of myelin surrounding axons was measured, wraps of myelin (lamellae) counted, and each expressed as a ratio of axonal diameter.

For P0 animals there were no significant differences between null mutants and wild types in the proportion of myelinating axons, the myelin width, the width of the inner mesaxon cytoplasm or lamellae compaction. Random systematic samples of axons from P21 heterozygous animals revealed a reduction in myelin (myelin ratio = 0.219 ± 0.003, mean ± SEM, n = 4, \( P < 0.05 \); independent-samples \( t \)-test), compared to wild types (0.232 ± 0.003, n = 4), while lamellae compaction was unaffected. The inner mesaxon cytoplasm was also reduced in heterozygous animals (631 ± 31 nm, n = 4, \( P < 0.05 \)) compared to controls (735 ± 15 nm, n = 4).

Although *in vitro* results have suggested NT-3 as a negative regulatory factor for myelination, our *in vivo* results show that NT-3 loss causes no change in myelination at birth, and reduces myelination at P21.
Ampullary mass and obstructive jaundice

Simon Janes

A 62-year-old Caucasian man presented with abdominal pain and progressive obstructive jaundice. He was in remission for acute myeloid leukaemia. Abdominal ultrasound was normal, however endoscopic retrograde cholangiopancreatography (ERCP) demonstrated a cauliflower lesion at the ampulla of Vater (Figure 1).

Ampullary biopsy showed a tubulo-villous adenoma with high-grade dysplasia and a Whipple pancreatico-duodenectomy was performed without complication. Histological examination showed the lesion was a Brunner’s gland hyperplasia (BGH; Figure 2), with foci of moderate grade adenoma at the proximal margin. The patient has remained asymptomatic after 2 years of follow-up.

Figure 1. Polypoid duodenal lesion seen at the time of ERCP. Biopsy showed a tubulo-villous adenoma with high-grade dysplasia
Discussion

Brunner’s glands are mucus-secreting acinar glands located in the deep mucosa and submucosa of the duodenum, emptying into the crypts of Lieberkühn. The glands secrete mucus, pepsinogen, and urogastrone in response to acid stimulation. They are most numerous in the duodenal bulb, and diminish in number and size distally. The mechanism inducing hyperplasia remains unknown—coincident duodenal carcinoma and BGH has been described, but there is no evidence of malignant transformation. BGH at the ampulla of Vater has only been reported once previously.

Around one-quarter of cases are discovered incidentally during laparotomy or endoscopy, but there is no evidence suggesting that asymptomatic lesions should be removed. In the case described, suspicious imaging and biopsy results indicated radical excision. When the diagnosis is less doubtful, endoscopic removal offers a safe and cost-effective alternative to open surgery. The majority of patients gain symptomatic relief after excision, and recurrence has not been documented.

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References:


Media, medicine, and mammography

We are aware that news stories about health and medicine can precipitate dramatic changes in consumer behaviour. For example, hormone replacement therapy in New Zealand was reduced by almost 60% after the media featured news of health problems related to such treatment.

On 17 May 2005, it was announced that the singer Kylie Minogue had been diagnosed with breast cancer. This was followed by a media frenzy focussing on breast cancer in young women. Unsurprisingly, there was an unprecedented increase in bookings for mammography in Australia. The government-sponsored BreastScreen programmes in four states saw a 40% rise in screening bookings in the two weeks of the publicity. And six weeks afterwards, bookings remained more than a third higher in non-screened women. Wonder whether this surge crossed the Tasman?

Hot flushes and gabapentin

A sudden feeling of warmth and redness that begins in the chest and spreads to the neck and the face, accompanied by sweating, palpitations and anxiety—yes, a ‘hot flush’ (or flash in the United States). Most women going through the menopause experience them and they are also among the most commonly reported symptoms in women receiving systemic therapy for breast cancer, adversely affecting quality of life. Treatment with oestrogen and progestagen can ameliorate these symptoms, but may increase the risk of getting breast cancer or increase breast cancer relapse rate.

Enter gabapentin, a GABA (gamma-aminobutyric acid) analogue—a neurotransmitter. Hitherto, trial-proven benefits in menopausal patients and now also in breast cancer patients. Apparently, 900 mg/day (but not 300 mg) is effective in control of flushes in approximately half of the patients. Interestingly, the flushes were diminished by about 20% in the placebo arm. Finally, gabapentin is expensive and not available in New Zealand for this purpose.

Breast cancer and bone marrow micrometastasis

Prognosis and therapeutic options in breast cancer are defined by tumor size, histologic grade, presence or absence of lymph-node metastasis, and expression of hormone receptors. But what about bone marrow micrometastases at the time of diagnosis? Intuitively surely bad news?

A recent study incorporating the combined individual patient data from nine studies involving 4703 patients with stage I, II, or III breast cancer demonstrated micrometastasis in 30.6 percent. And their 10-year follow-up was significantly worse. However, as the patients with bone marrow micrometastasis had larger tumors and tumors with a higher histologic grade and more often had lymph-node metastases and...
hormone receptor-negative tumors, not much further useful information was produced from the bone marrow biopsy. So, not useful and psychologically harmful information for patients and their clinicians.


Treatment for Alzheimer’s disease?

Some believe that Alzheimer’s disease is associated with, or caused by, a cholinergic deficiency in the central nervous system. Hence, three cholinesterase inhibitors donepezil, rivastigmine, and galantamine are widely recommended for clinical use. The rationale for these recommendations is that evidence from randomised controlled trials has shown that all three drugs have beneficial effects on cognitive and global outcome measures. Just how strong is the evidence? Apparently not that good.

A German group have reviewed all published, double blind, randomised controlled trials comparing donepezil, rivastigmine, or galantamine with placebo in patients with Alzheimer’s disease. Apparently there are 22 such trials. The researchers conclude that “because of flawed methods and small clinical benefits, the scientific basis for recommendations of cholinesterase inhibitors for the treatment of Alzheimer’s disease is questionable.”

BMJ 2005;331:321–3

Vitamin E, cardiovascular disease, and cancer

We have recently commented upon the failure of low-dose aspirin and statins in the primary prevention of cancer. So what about Vitamin E? Vitamin E has antioxidant properties leading to the hypothesis that it can prevent the development of cardiovascular disease and cancer. There is, of course, some basic research encouraging this hypothesis. This has recently been tested in a prospective randomised trial comparing 600 IU of vitamin E and placebo on alternate days. This study, the Women’s Health Study, included 39,876 apparently health US women aged at least 45 years and followed them for over ten years.

And the results—Vitamin E taken every other day provided no overall benefit for major cardiovascular events or cancer and did not affect total mortality. These data do not support recommending vitamin E supplementation for cardiovascular disease or cancer prevention among healthy women. Another theory put to the sword.

JAMA 2005;294:56–65
PHARMAC’s response on gemcitabine and transparency

In this issue of the Journal, Dr Andrew Simpson (What’s happening in PHARMAC—where do all the submissions go? On the trail of gemcitabine. URL: http://www.nzma.org.nz/journal/118-1225/1733) discusses the clarity of PHARMAC’s process for the funding of new medicines for cancer, in particular that of gemcitabine for advanced bladder cancer.

We respond in terms of PHARMAC’s timeframes and processes; transparency and consultation; the role of cost-effectiveness for the process and that of gemcitabine; and progress to date.

New process for hospital-administered cancer treatments

For hospital-administered cancer treatments, PHARMAC currently assesses applications on behalf of district health boards (DHBs). Following that assessment, if national agreement is reached on funding, then PHARMAC will seek a contract with the supplier for the product, before consulting on a proposal and seeking the approval of the PHARMAC Board. PHARMAC also consults before declining applications.

One objective of the cancer control strategy action plan is to improve national consistency in access to cancer treatments. Hence it is important that all DHBs agree to any funding proposal. At present this requires an agreement from all 21 DHBs at the national CEO meeting, held four times each year. PHARMAC and the DHBs are currently streamlining this decision-making process.

PHARMAC receives about 30 applications for funding each year. The Pharmacology and Therapeutics Advisory Committee (PTAC) makes a recommendation about the relative priority of each application—when not referring applications to its expert subcommittees, or deferring pending further information. In general, about 20% of applications have been given high priority, 20% moderate priority, 30% low priority or fund only if cost-neutral, and for 30% PTAC has recommended they be declined. This priority rating is used both to inform PHARMAC on the use of analyst resources in conducting technology assessments and in prioritising spending.

Few cancer drug applications under the new process have been recommended as high priority, but progress has been good for those that have:

- 20 applications for cancer drugs have moved through the process since 2002 (18 in the last two years). Four applications have progressed to funding, with a number of other proposals either being considered by the Board or shortly to be consulted on.

- Advisory committees (the Cancer Treatments Sub-committee of PTAC (CaTSOp) and/or PTAC itself) have given a high priority to six applications. CaTSOp/PTAC have recommended that eight applications be declined.

- Of the six applications given a high priority, four have been funded already, and one is currently being negotiated with a supplier. The other application was reviewed very recently (September 2005).
Transparency

Transparency can be difficult in the face of commercial sensitivity. Pharmaceutical companies have consistently insisted that their applications remain confidential. There have been times when disclosure of PTAC minutes has been resisted by a company and they have been released only as the result of an Official Information Act request. Likewise the results and component assumptions of PHARMAC’s economic analyses have not generally been widely disseminated. Indeed, in order to satisfy the industry, those analyses undertaken by PHARMAC on behalf on DHB hospitals have had to be made available via a secure website (the Hospital Pharmaceutical Assessment Database (HPAD) website).

The HPAD website (http://www.pharmac.govt.nz/hpad/) has a number of economic analyses, available to DHB staff.

We acknowledge that the table of new funding applications on the PHARMAC website (http://www.pharmac.govt.nz/new_funding_applications.asp) has not included gemcitabine. PHARMAC apologises for this oversight, and will make sure that the few applications not sponsored primarily by suppliers are included.

Consultation

PHARMAC has an established consultation process for proposed changes to the Pharmaceutical Schedule, scheduled around PHARMAC’s monthly Board meetings and printing deadlines. PHARMAC consults (and is required to consult) with relevant clinical and patient groups to ensure it has all the information before making a decision.

In the case of technology assessments, PHARMAC has four levels of economic analysis: very rapid, preliminary, indicative, and detailed, with increasing external involvement. Naturally, the more detailed the analysis and the greater the consultation and discussion sought, the longer it takes to complete the assessment stage of PHARMAC’s process.

Use of economic analysis at PHARMAC

Economic analyses such as cost-utility analysis (CUA) help PHARMAC to prioritise funding where there is a constrained budget. They form only a part of the reason why funding might ultimately be approved, or declined. Cost-effectiveness is but one of PHARMAC’s nine formal decision criteria (http://www.pharmac.govt.nz/pharmaceutical_schedule_update.asp).

Because PHARMAC works in the pragmatic public policy/purchasing environment and analytical capacity is finite, there are inevitable trade-offs between precision and timeliness. The level (extent and depth) of analysis does vary according to circumstances; more definitive analysis may occur in future, according to need, competing priorities and available resources.

PHARMAC’s CUA for gemcitabine was a preliminary analysis (see the above taxonomy). Preliminary analyses typically are interim assessments using opportunistic data, and the results generated by preliminary analyses area reasonably rapid, aiming to inform decision-making within time constraints.
Further details on the role of economic analysis at PHARMAC can be found at http://www.nzma.org.nz/journal/116-1170/362/

The preliminary CUA for gemcitabine

At times the overall results of CUAs are highly sensitive to the inputs, for instance the utility estimates and the cost of treatment. PHARMAC relies on publicly available information for its CUAs.

In the case of gemcitabine, utility values generated by the supplier (Eli Lilly) and published in the UK gave a cost/QALY of about $30,000. By contrast, using the comprehensive disability weights used by the Australian Burden of Disease Study (http://www.aihw.gov.au/publications/health/bdia.html)\(^\text{10}\) (viz. the Global Burden of Diseases Study\(^\text{11}\) and Netherlands\(^\text{12}\) disability weights) gave poorer results at around $800,000/QALY. The CUA report that Dr Simpson refers to was an early draft version released to the supplier under the Official Information Act, and included both of these estimates.

PHARMAC stands behind its preliminary CUA, which noted that the >$800,000/QALY figure was imprecise, with sensitivity analyses giving a wide range of values. The PHARMAC preliminary analysis and that of the supplier\(^\text{13}\) used different methodologies and hence are difficult to compare.\(^\text{14}\) The text of the PHARMAC CUA was careful to acknowledge these differences, and stated quite clearly that the QALY gain aspect of the preliminary NZ analysis were not particularly robust. The supplier’s UK-based estimates of QALY gain were included in the PHARMAC analysis, and results based on the UK QALY data were explicitly included in the analysis’ conclusion. PHARMAC’s preliminary analysis concluded:

“Given the…imprecision of the cost-utility estimates, it cannot be said at this stage whether or not gemcitabine should be listed for the proposed indication. It may warrant additional assessment of quality of life gains (including further local clinical input) and potential for reducing the cost of the medication. More efficacy data as they become available would also be valuable. Nevertheless, at the current price, the cost per QALY is likely to be above $33,000 per QALY gained.”

A copy of the full PHARMAC preliminary CUA\(^\text{15}\) is available at the corresponding position of the full text version: http://www.nzma.org.nz/journal/118-1225/1741

Progress to date

Both the Cancer Treatments Sub-committee of PTAC (CaTSoP) and PTAC have given gemcitabine for advanced bladder cancer a moderate priority.

PHARMAC staff presented a recommendation to the DHB chief executive officers (CEOs) at the end of August on the funding of gemcitabine. PHARMAC is now actively in discussions with the supplier, and hopes to be in a position to consult on a proposal in early 2006.

The progress of individual applications is fluid. PHARMAC is happy to provide updates at any time as to where applications have progressed. For clinicians and others wanting to know the status of applications, PHARMAC can be contacted directly (contact details are on PHARMAC’s website http://www.pharmac.govt.nz/).
Steffan Crausaz  
Therapeutic Group Manager  
PHARMAC

Scott Metcalfe  
Public Health Physician  
Wellington

Conflict of interest: Scott Metcalfe is externally contracted to work with PHARMAC for public health advice. Steffan Crausaz declares no conflicts.

Endnotes and references:

1. PHARMAC and the DHBs are currently streamlining the decision-making process, by agreeing a national budget each year for hospital cancer treatments (including baseline funding for existing treatments and funding for new investments) that will be managed by PHARMAC. This will require a consistent national dataset on current usage before this process can occur. It is currently proposed that the streamlined process start from 1 July 2007.

2. Applications considered by PTAC during 2004 and 2005 to date.

3. Historically the pharmaceutical industry has lobbied for greater transparency in PHARMAC’s processes. However, when PHARMAC has consulted on making changes – such as publishing PTAC minutes as soon as signed off by the committee, or publishing hospital pharmaceutical assessments directly and openly on the PHARMAC website – the pharmaceutical industry has argued against such publication, citing right of review as a reason.

4. HPAD analyses are undertaken for DHB hospitals as part of the Hospital Pharmaceutical Assessment Process (HPAP). HPAP was established in 2002 as part of the National Hospital Pharmaceutical Strategy, to reduce duplication of work and increase discussion on the costs and benefits of new pharmaceuticals by distributing hospital pharmaceutical assessments nationally. These assessments are distributed to DHBs as confidential documents, which is at the request of and agreement with the pharmaceutical industry. PHARMAC has recently undertaken a review of the HPAP; feedback from DHBs who responded indicated that many considered that the HPAP had improved transparency, facilitated review and improved the consistency and quality of assessments. Further information on the purpose of HPAP and PHARMAC’s role in the distribution of discussion documents can be found on the PHARMAC website – www.pharmac.govt.nz/hospital_strategy.asp

5. New Zealand Public Health and Disability Act 2000, Section 49 Pharmac to consult in implementing objectives and carrying out functions

Section 4.2 Consultation.

Section 3.3.3 “PHARMAC will carry out appropriate consultation on the classification of pharmaceuticals into therapeutic sub-groups and its application of reference pricing in respect of a particular sub-group.”

Section 2.2 Decision Criteria
9. Taxonomy of economic analyses undertaken by PHARMAC

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Detailed</td>
<td>Detailed and systematic identification and synthesis of effectiveness, natural history, QoL and cost data. Follows Prescription for Pharmacoeconomic Analysis. Follows policies of Recommended Methods to Derive Clinical Inputs for Proposals to PHARMAC. Reviewed internally (PTAC for clinical assumptions, PHARMAC) and externally. 3-6 months FTE input.</td>
</tr>
<tr>
<td>Indicative</td>
<td>Interim assessment using opportunistic data but more detailed than preliminary CUA. Follows Prescription for Pharmacoeconomic Analysis. Largely follows policies of Recommended Methods to Derive Clinical Inputs for Proposals to PHARMAC. Typically reviewed internally (PTAC for clinical assumptions, PHARMAC). 4-6 weeks FTE input. Includes remodelling of supplier analyses.</td>
</tr>
<tr>
<td>Preliminary</td>
<td>Rapid assessment using largely opportunistic data. 1-2 weeks FTE input. Includes supplier analyses not yet evaluated by PHARMAC staff.</td>
</tr>
<tr>
<td>Rapid</td>
<td>First cut assessment using opportunistic data. 1-2 days FTE input. Includes supplier analyses not yet evaluated by PHARMAC staff.</td>
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Preliminary analyses are based on the principles used by PHARMAC for pharmacoeconomic evaluations as described by the Recommended Methods to Derive Clinical Inputs for Proposals to PHARMAC (http://www.pharmac.govt.nz/pdf/61396.pdf) and PHARMAC’s Prescription for Pharmacoeconomics (available online at http://www.pharmac.govt.nz/pharmo_economic.asp). These principles include: the use of overall health sector costs and direct patient costs when measuring effects on costs overall; measuring QALY gains; discounting both costs and QALY gains according to PHARMAC’s current discount rate [8%]; use of univariate and multivariate sensitivity analyses; and the systematic identification, synthesis and presentation of relevant clinical input data.

Note however that with preliminary analyses that many data are derived opportunistically, not systematically.


14. In the M-TAG/Eli Lilly analysis (Robinson et al 2004), oncology healthcare professionals were surveyed to estimate difference in quality of life between the treatment arms. The survey used willingness-to-trade-time (WTTT) as the primary measure (in weeks), reflecting the degree to which clinicians would be willing to trade reductions in life expectancy with improvements in toxicity during treatment. The total estimated WTTT included the following adverse events: febrile neutropenia requiring hospitalisation or neutropenic sepsis; alopecia (hair loss); mucositis; diarrhoea; weight loss. This gave a WTTT of 25.4 weeks, which equated to 0.13 QALYs gain (over life expectancy). However, actual utility values for each treatment arm were not derived (or at least not reported in the Robinson et al 2004 paper).

Information Act (OIA) version withholding confidential information (author's and reviewers' names and gemcitabine price information, under sections 9(2)(a) and 9(2)(b) of the OIA).
PHARMAC responds on long-acting inhalers for COPD

Dr David Jones has recently written in the Journal (http://www.nzma.org.nz/journal/118-1222/1669) about access to long-acting inhaled bronchodilators for patients with chronic obstructive pulmonary disease (COPD). We make some observations:

Tiotropium is already available but is under-used

Tiotropium has been funded for patients with severe COPD (FEV$_1$ < 40% predicted) since February this year. Details of Special Authority criteria can be found in Appendix 1 at the end of this letter.

The Pharmacology and Therapeutics Advisory Committee (PTAC) in August 2004 considered tiotropium to be beneficial$^{2,3}$ and cost-effective, and recommended that tiotropium be listed with a high priority (http://www.pharmac.govt.nz/latest_PTAC_minutes.asp).

For patients with severe COPD, tiotropium appears to be cost effective compared with other new medicines, with a cost per QALY of $8,400.$^4$ This includes major reductions in hospitalisations for COPD exacerbations (although there is an overall cost to the health sector from using tiotropium over ipratropium).

However, patients with severe COPD are not yet getting this effective treatment. The uptake of tiotropium since the February listing has been low:

- The prevalence of COPD—and numbers of patients eligible for tiotropium treatment—can be difficult to quantify,$^{5,6}$ with wide-ranging estimates according to the definitions of COPD used.$^7$ A possible range is between 65,000 and 85,000 patients with COPD,$^8$ with perhaps one-quarter having severe COPD at the level of FEV$_1$ < 40% predicted.$^9$ Hence there may be 15,000 to 21,000 patients with severe COPD (FEV$_1$ < 40% predicted).

- PHARMAC had estimated actual usage (numbers of patients using tiotropium) would be 5,900 by June 2005 (28–39% of the 15–21,000 eligible), reaching perhaps 11,200 patients by June 2007 (53–75%).

- However, HealthPAC data indicate there were 1,690 dispensings for tiotropium in June 2005, being 29% of what had been predicted.

- Currently (September 2005) there are perhaps 2,200 patients using tiotropium (2,146 dispensings), being 10–14% of eligible patients and 7% of users of both short-acting anticholinergics and long-acting beta agonists (LABAs)$^{10}$—see Figure 1 below:
Figure 1. Uptake of tiotropium for COPD in New Zealand

The uptake of tiotropium in New Zealand has been one-quarter that of Australia over the comparable time period since listing — see Appendix 2 (at the end of this letter) for further details.

Extending access to tiotropium for less severe COPD

PTAC has previously considered, at its August 2004 meeting, the clinical benefits of a commercial proposal that included widening tiotropium access to FEV$_1$ < 60% predicted. This access was more than had been recommended by PTAC’s Respiratory subcommittee, possibly doubling the number of users. PTAC was unenthusiastic about this proposal, noting a lack of evidence at the FEV$_1$ 40–59% level and commenting on the likely extra patient numbers.

Further details can be found in the minutes of PTAC’s meeting of August 2004, available online at http://www.pharmac.govt.nz/latest_PTAC_minutes.asp (item ‘Tiotropium [Spiriva] for use in COPD’ on page 8).

PTAC has now received a reapplication from the supplier to extend tiotropium access to FEV$_1$ < 60% predicted. This reapplication has been placed on the agenda for PTAC’s next quarterly meeting.

Long-acting beta agonists (LABAs)

International guidelines/guidance (COPDX/TSANZ, GOLD, NICE) to date do not differentiate between LABAs and long-acting anticholinergics in the treatment of COPD. However, as Dr Jones suggests, tiotropium may be better than LABAs for treating COPD, with some head-to-head trials showing significant FEV$_1$
improvements with tiotropium,\textsuperscript{18–20} others a trend to tiotropium but no significant differences,\textsuperscript{21–24} and possible tolerance to salmeterol.\textsuperscript{25} Some trials show little improvement with LABAs compared with placebo in some measures.\textsuperscript{20,26} This area requires a more systematic analysis.

PTAC in the past has recommended against funding LABAs for COPD. PTAC considered an application for eformoterol (as Foradil) for COPD in August 2001, which it recommended be declined because of the absence of good evidence of meaningful effects. PTAC considered the evidence for Symbicort for COPD in May 2004, which PTAC considered to be weak and did not show any clear benefit, and recommended that this application be declined.

The Cochrane review of LABAs in COPD\textsuperscript{27} was less than enthusiastic, concluding “In the few studies that could be included in this review, treatment of patients with COPD with long acting beta-2 agonists produces only small increases in FEV\textsubscript{1}. The improvement in airways function does not seem to be associated with a consistent effect on other outcomes such as health related quality of life or reductions in breathlessness.”

Finally, we are aware of at least two RCTs comparing the LABA eformoterol with ipratropium (a short-acting anticholinergic).\textsuperscript{28,29} These trials show no significance between the two drugs—in contrast to the large effects seen between tiotropium and ipratropium.\textsuperscript{2} One-third of publicly-funded LABA use in New Zealand is by patients aged 65 years and over.\textsuperscript{31–33}

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Conflict of interest: Scott Metcalfe is externally contracted to work with PHARMAC for public health advice. Sean Dougherty declares no conflicts.

Endnotes and references:


9. Patients with more severe disease with FEV1 <40% will comprise less than one quarter of patients with COPD – where in an Australian study, FEV1 <50% comprised 24% of all patients with COPD (FEV1 <70% predicted without dr-diagnosed asthma). (PHARMAC analysis of Busselton data 1994/95 from ABDS at http://www.aihw.gov.au/bod/bod_vld_by_disease/m_respiratory/m3_othresp.xls – original 1981 study from Yan K, Salome CM, Woolcock AJ. Prevalence and nature of bronchial hyperresponsiveness in subjects with chronic obstructive pulmonary disease. Am Rev Respir Dis. 1985 Jul;132(1):25-9)

10. 30,691 dispensings of short-acting anticholinergic agents during September 2005, with 31,853 dispensings of LABAs including Symbicort.


12. The supplier had requested the Special Authority criteria be amended to remove the requirement for ipratropium and to increase the FEV1 threshold. The proposed criteria from Boehringer Ingelheim would remove the need for a patient to try ipratropium initially, and also would allow access to tiotropium to those patients with less (i.e. moderately) severe COPD (with FEV1s between 40% and 60% of predicted). This would be in addition to the patients included in the criteria recommended by the Respiratory Subcommittee of PTAC.

13. The likely impact of extending access criteria on patient numbers is difficult to quantify, because of a lack of good epidemiological data. However, suggests numbers of eligible patients could at least double (analysis of Australian survey data), but how this translates to uptake is not known.

PHARMAC staff have only been able to identify epidemiological data from Australia (Busselton), which was restricted to stratifying FEV1s only as low as < 50% of predicted. Analysis suggests that of those patients with COPD (FEV1 < 70% of predicted AND absence of doctor-diagnosed asthma) – who accounted for 6.2% of adults – one quarter had an FEV1 < 50% of predicted (1.5% of adults), and one half had had an FEV1 < 60% (2.8% of adults – RR <60%/<50% = 1.92). Although the Busselton data do not extend as low as FEV1s < 40%, the above data would suggest that, under Boehringer Ingelheim’s proposed extended criteria, numbers of eligible patients could at least double.


17. PubMed search keywords tiotropium (salmeterol or eformoterol or formoterol) RCTs, date 30 September 2005


30. PHARMAC analysis of one-way encrypted NHI-annotated dispensing claims data from the PharmHouse data warehouse for inhaled corticosteroids (ICSs), inhaled long-acting beta-agonists (LABAs) and inhaled/oral short-acting beta-agonist relievers (SABAs), for the period July 1999 to June 2004. 36% of dispensings for LABAs (including Symbicort) during 2003/04 were for patients aged 65 years and over – being 55,339 LABA dispensings in patients aged 65+ during 2003/04 out of 167,695 total LABA dispensings 2003/04.

31. The endorsement criteria for eformoterol 6mcg (Oxis 6) and the Special Authority criteria for Oxis 12, salmeterol and eformoterol/budesonide (Symbicort) specify the use of LABAs for the treatment of asthma alone.

32. Selected morbidity data for publicly funded hospitals 2000/01. Wellington: New Zealand Health Information Service, Ministry of Health, 2004. Table 1, ICD10 codes J45-6 (asthma), codes J40-44 (COPD). 5% of admissions during 2000/01 for asthma were for patients aged 65+ (392/8557), whereas 71% of COPD admissions were aged 65+ (6198/8675), and any admission for obstructive respiratory disease in a patient aged 65+ is 16 times more likely to be for COPD than asthma (6198/392).

Appendix 1. Special Authority criteria for tiotropium (from 1 February 2005)

Special Authority for Subsidy

Initial application only from a general practitioner or relevant specialist. Approvals valid for 2 years for applications meeting the following criteria:

All of the following:

1. To be used for the long-term maintenance treatment of bronchospasm and dyspnoea associated with COPD; and

2. In addition to standard treatment, the patient has trialled a dose of at least 40 mcg ipratropium q.i.d for one month; and

3. The patient's breathlessness ≥ grade 4 according to the Medical Research Council dyspnoea scale (see note). Grade must be stated on the application; and

4. FEV₁ < 40% of predicted (copy of actual result and predicted value to be included in application, or values to be stated on form); and

5. Either:
   5.1 Patient is not a smoker; or
   5.2 Patient is a smoker and been offered smoking cessation counselling; and

6. The patient has been offered annual influenza immunisation.

Renewal only from a general practitioner or relevant specialist. Approvals valid for 2 years for applications meeting the following criteria:

All of the following:

7. Patient is compliant with the medication; and

8. Patient has experienced improved COPD symptom control (prescriber determined); and

9. Applicant must supply recent measurement of FEV₁ (% of predicted). Details must be attached to the application (for reporting purposes only).

Note

Grade 4 (Medical Research Council dyspnoea scale) = stops for breath after walking about 100 metres or after a few minutes on the level; Grade 5 = too breathless to leave the house, or breathless when dressing or undressing.
Appendix 2. Uptake of tiotropium in Australia

Tiotropium has been funded in Australia since February 2003 under a restricted benefit for the long-term maintenance treatment of bronchospasm and dyspnoea associated with COPD.

The uptake of tiotropium in New Zealand has been one quarter that of Australia over the comparable time period since listing. New Zealand had 2,146 dispensings (5.2 per 10,000 population) during September 2005. This compares with 43,451 dispensings (22.8 per 10,000) in Australia during August 2003, the seventh month that tiotropium was listed there – as can be seen in the following graphs.

Source: PHARMAC analysis of HealthPAC dispensing data (New Zealand), Pharmaceutical Benefits Scheme (PBS) services data (Australia), and population data for both countries.
New Zealand and Australian uptake of anticholinergic inhalers

Source: PHARMAC analysis of HealthPAC dispensing data (New Zealand), Pharmaceutical Benefits Scheme (PBS) services data (Australia), and population data for both countries.11
The advantages of notifying negative HIV results by telephone

An increased uptake of HIV testing amongst sexual health clinic attendees has been noted since the introduction of a policy allowing negative HIV results to be given by telephone.

New Zealand has experienced increasing numbers of HIV diagnoses over the last 2–3 years with a significant number of people reporting not having previously tested for HIV. Statistics reveal that of HIV-diagnosed men who have sex with other men and who reported to have been infected within New Zealand, 24 of 48 men in 2003, and 16 of 51 men in 2004 had never been tested before.¹

Over recent years, international guidelines around HIV testing have changed to underscore the importance of early knowledge of HIV status and making HIV testing more accessible and available.²,³ One recommendation is that test results be obtained more easily, for example by telephone. Anecdotally, it is commonplace for primary care settings within New Zealand to provide negative HIV results by telephone. However, the current New Zealand Ministry of Health checklist for HIV testing and pre-test discussion continues to recommend that all results are given in person and face-to-face.⁴

Until August 2004, Hamilton Sexual Health Clinic guidelines recommended ‘opt-in’ HIV testing with face-to-face results. That is, all patients attending for STI tests for the first time should be offered an HIV test with repeat testing at future visits offered according to risk, with all patients required to return to the clinic to receive their HIV test results.

For most patients, there is a brief pre-test discussion to ensure the risks and benefits of being tested and of not being tested are understood. More indepth pre-test discussion is reserved for those felt to be at high risk of a positive result. Some patients would initially agree to HIV testing but change their minds when they learned they needed to return to the clinic to collect their result—or, if tested, they did not always return for their HIV result, saying at subsequent visits months later that they assumed they would have been contacted ‘if there was a problem’.

From August 2004, in an attempt to reduce perceived barriers to testing and accessing test results, we decided to offer HIV results by telephone in line with our policy for all other STI test results. Those patients felt to be at high risk for HIV or to have particular need for further post-test discussion would continue to be encouraged to attend in person for their results.

In the first 6 months (August 2004–January 2005), 44.6% (1023 of 2291) of new and re-registered patients underwent HIV testing. One patient was diagnosed HIV-positive and received the result face-to-face. In the same 6-month period the previous year (August 2003–January 2004), 36.9% (826 of 2236) of new and re-registered patients underwent HIV testing and one patient was diagnosed HIV-positive.
During a New Zealand anonymous HIV seroprevalence study in 1991–92, 22% of those having blood taken for other tests at Auckland and Christchurch Sexual Health Clinics had voluntary HIV testing.\(^5\)

The UK Government’s national strategy for sexual health and HIV set a target for reducing undiagnosed HIV in genitourinary medicine clinics—including increasing the uptake of HIV testing to 40% by the end of 2004 and to 60% by the end of 2007.\(^6\) ‘Opt-out’, rather than ‘opt-in’ HIV testing, results in higher uptake of HIV testing\(^2,3\) so we are now trialling this within our clinic in an attempt to further increase uptake of HIV testing in those not previously tested. That is, all patients attending for STI tests for the first time are now advised that an HIV test is routinely included in the standard battery of STI tests but they may choose to decline testing.

Introducing a system of telephone HIV results helped increase uptake of HIV testing within our clinic. We have learnt it is essential that arrangements for communicating all test results are discussed and agreed with the patient, and documented at the time of testing.

Our policy continues to be that positive HIV results are always given in person. However, our experience suggests that the current New Zealand Ministry of Health guidelines around HIV testing could be updated to include the option of telephone results in some situations, in line with international guidelines. This will become increasingly pertinent with the introduction of HIV screening of lower risk populations, for example antenatal HIV screening.

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References:


**Listeria—how much do pregnant women really understand about it?**

We have recently conducted an audit at Middlemore Hospital to assess how much women understood about listeriosis. *Listeria monocytogenes* can be transmitted via food or the placenta. It is an uncommon and mild illness in healthy individuals. Pregnant women are more likely to become infected, and listeriosis can lead to preterm labour, miscarriage, stillbirth, or neonatal infection.\(^1,2\) Data from the New Zealand Food Safety Authority (2002) showed a total incidence of 0.7 per 100,000 (26 cases); three cases were perinatal and two resulted in death.\(^3\) Of note, there was a recent case of *Listeria* identified at post-mortem.

Our aims were to assess women’s knowledge of *Listeria*, improve their understanding, and refine education processes. Our standards were that all pregnant women should receive information about *Listeria*, understand this information, and comply with food safety advice. These standards were based on guidelines by the Ministry of Health\(^4\) who have published two booklets to be given to all pregnant women.

We collected data using a 2-minute questionnaire based on these booklets. The first part assessed demographics like age and ethnicity. The second part listed seven safe and seven unsafe foods, arranged randomly and derived from the pamphlets. We incorporated culturally specific foods, for example raw seafood and common foods such as takeaways. Women were asked if they thought *Listeria* was found in each food. The third part assessed whether women consumed the unsafe foods. We administered the questionnaire on a one-to-one basis to 100 pregnant and postnatal women who were found on wards and antenatal clinics.

In our sample, 58% (95% CI: 48.24–67.24) of the women had been given information. This is well below the standard of 100%. With regard to ethnicity, Europeans had heard of *Listeria* the most. In terms of understanding information, only 25.86% correctly answered all responses, which is an extremely poor result.

To draw conclusions on following food safety advice, we looked at each unsafe food individually. Raw seafood, cold cooked chicken, and meats were well-identified (92–96%) but were the highest consumed (36–45%). Soft cheeses were poorly identified (67%) and 12% consumed it. This may reflect cultural biases. Cold cooked fish and reheated takeaways were well-identified (95%), and 15% to 27% consumed it. Coleslaw was not well-identified (72%) but highly consumed (62%) by the people who correctly identified it.

We also analysed consumption of unsafe foods in all women regardless of whether they knew about *Listeria* or not. We found that raw seafood and coleslaw were eaten by 50% respectively. Cold cooked chicken and meats were also highly consumed (35% each). The least consumed foods were cold cooked fish (14%) and soft cheeses (19%). Unexpectedly, reheated takeaways were not as highly consumed (28%).
The overall strengths of our study were a large, random sample where all eligible women were approached. Our questionnaire was simple and efficient, and administered one-to-one.

Biases included not taking into account demographics such as socioeconomic status and parity. The survey was conducted over 3 weeks—this can limit how generalisable our data is. Our sample of 100 women may not exclude random error. Our questionnaire included foods, which may have been too culturally specific. For example, many non-Polynesians were unfamiliar with taro leaves as non-Europeans were with soft cheeses. In addition, interviewer bias may have occurred.

In summary, 58% of women had received information on *Listeria*, 26% of women fully understood this information, and 27%–62% of women did not comply with food safety advice.

Thus we recommend:

- Discussion of findings with relevant staff.
- Education by a three-step approach:
  - Inform patients about *Listeria*.
  - Discuss food safety. Given time constraints, a sentence like ‘stay away from foods that are not cooked or heated thoroughly or leftovers’ will suffice.
  - Written information to supplement, NOT substitute, verbal information.
- Reinforce importance of food safety at each visit.
- Provide alternatives, for example homemade coleslaw.
- Repeat audit in a year and at different hospitals.
- The existing pamphlet is simple, relevant, and well presented. Improvements may include:
  - Pamphlets in different languages.
  - Include culturally specific foods accordingly.
  - Include commonly eaten foods.
  - Include alternatives.

Listeriosis is poorly understood by our population. The education process thus needs to be modified. We understand that the booklets are due to be revised by the Ministry of Health soon. Given that these recommendations are feasible and affordable, they should be considered in the revision process.

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References:


Merck responds to PHARMAC’s article on COX-2 inhibitors

We are concerned with the portrayal of the overall COX-2 class, and, specifically, VIOXX, in the recent article Going against the flow: the impact of PHARMAC not funding COX-2 inhibitors for chronic arthritis published in the 7 October 2005 issue of the Journal (http://www.nzma.org.nz/journal/118-1223/1690).

It is simply inaccurate to suggest that there was conclusive data prior to the APPROVe study that VIOXX increased cardiovascular risk. In fact, there is much data to the contrary. The most relevant of these data, overlooked in this article, were the results of randomised controlled clinical trials of VIOXX involving more than 28,000 patients.

In the combined analysis of these trials, there were similar rates of cardiovascular events with VIOXX compared to placebo or the NSAIDs ibuprofen, diclofenac, and nabumetone and a difference only between VIOXX and naproxen. We provided the results of these studies, as well as the results of the VIGOR study, to regulators worldwide. The data from these studies were the subject of several regulatory reviews between 1998 and 2004, after which regulators repeatedly reaffirmed VIOXX’s favourable risk-benefit ratio.

In failing to acknowledge this pooled analysis, the article based its conclusions instead on a flawed cumulative meta-analysis by Juni et al which inappropriately combined comparators despite significant heterogeneity in the data’ and which omitted the bulk of placebo-controlled data.2 Most importantly, even after Merck’s voluntary withdrawal of VIOXX, regulators in the United States, Canada, the European Union, Australia, and New Zealand and others reviewed the available data on the COX-2 class and, with respect to the cardiovascular risks, still concluded that the benefits of the COX-2 class warranted their continued availability to patients.

Further, estimates of the number of patients potentially injured from VIOXX or any COX-2 inhibitor are nothing more than speculation. Determination of whether VIOXX was responsible for any patient’s injury can only be made on a case-by-case basis, since there are many risks for MI and stroke, including high blood pressure, smoking, high cholesterol, and genetics just to name a few.

The figures cited in this article from Dr David Graham are based on a series of assumptions that cannot be supported. For example, Dr Graham’s assumes in his calculations that the average relative risk from a clinical study can be extrapolated equally to patients who took VIOXX for two days or two years, an assumption inconsistent with data from the APPROVe study, the same study he used as the basis for his calculations. Dr Robert O’Neill, Director, FDA Office of Biostatistics, best summarised the danger in trying to extrapolate from a single clinical trial or epidemiologic study to the general population, saying that such estimates would be “fraught with a lot of danger and have to have many caveats placed on them.”3
It is also important to note that in the APPROVe study there were similar rates of fatalities (including CV-related fatalities) in the placebo and VIOXX groups.

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References:


Evan Robert McKenzie

Surgeon, Soldier, Paterfamilias

30870 Major Evan Robert McKenzie RNZAMC. MB ChB, FRCS, FRACS, was born in the old gold mining town of Naseby in Central Otago on 18 February 1924 and died in Timaru on 2 October 2005.

He was a true ‘son of the Church’, being the seventh child of the Reverend DN McKenzie and his wife Sarah. The family of eight children lived in various towns in the Otago and Southland Provinces as the Reverend McKenzie was ‘called’ to minister in the various parishes.

Evan, however, spent most of his childhood years in Outram, a small town on the western edge of the Taieri Plains near Dunedin.

He had his secondary education at the John McGlashan College in Dunedin, from whence he became a student at the Otago Medical School, graduating MB ChB in 1947. He lived at Knox College during his undergraduate years sharing his student life with many men who subsequently made their marks in a variety of professions and countries.

For example, in my many meetings with Ratu Sir Kamisese Mara (former President of Fiji) over the intervening years, the name of Evan McKenzie invariably came up, and it was always in the most complementary of terms. He completed his Junior Resident Medical Officer years at Dunedin Hospital in 1948–49 moving across Great King Street in 1950 to be a Demonstrator in Anatomy at the Medical School prior to his move to the United Kingdom in 1952 where he undertook his surgical training. This was the norm at that time for young Kiwis who wanted to train in surgery, He successfully negotiated the difficult examination process gaining the Fellowship of the Royal College of Surgeons. He worked at first as a Senior House Officer at the City General Hospital in Sheffield and then having become a Fellow of the College of Surgeons he was promoted to Registrar. Later, in 1954, he moved to the Sallo浦 Royal Infirmary in Shrewsbury where he was the Resident Surgical Officer.

There is no doubt that the acquisition of the FRCS was the main aim of the sojourn in the United Kingdom, but his meeting and subsequent marriage to Sylvia Killick in October 1954 proved to be his greatest achievement. That wonderful partnership of 50 years enabled Sylvia and Evan to have three daughters who in good time gave them six grandsons.
Evan and Sylvia returned to Dunedin in January 1955 where Evan was appointed to the joint appointment as Assistant Lecturer in Surgery at the Otago Medical School and Senior Surgical Registrar at Dunedin Hospital.

It was at the beginning of 1955 that young doctors such as myself first experienced the extraordinary and remarkable ability that Evan had to help and advise his junior colleagues as they made their way in their chosen profession of medicine. He was knowledgeable, he was skilled, he was dedicated to the care of his patients and to his staff, but above all he was an iconoclast whose direct and honest approach to problems and people ensured his success as he advanced in seniority.

In October 1956, Evan was appointed as Visiting Surgeon at Oamaru Hospital. He remained in Oamaru until 1961, moving north when he was appointed as Junior Consultant Surgeon at Timaru Hospital. He remained in Timaru becoming Senior Surgeon, Director of Surgery and finally Deputy Superintendent. He retired in 1989.

In the late 1960s and early 1970s he willingly responded to the appeal for surgeons to volunteer for service with the New Zealand Armed Forces in Viet Nam. Evan served as the Senior Surgeon with the 1st NZ Services Medical Team in 1968–69 and again in 1970-71. This team was deployed into the town of Bong Son in Binh Dinh Province of the then South Viet Nam. The Mission of the Team was to provide health care for the civilian sick and war wounded of the northern part of the Province, and served a population of more than half a million people.

Evan was one of a small group of senior Territorial Force Medical Officers who, by virtue of their skill and experience, enabled the New Zealand Defence Force to make such a significant contribution to the healthcare and welfare of a large rural population who had been placed under such enormous stresses during the course of a most unpleasant war. The high calibre of his surgical skills was never ever in doubt, but he also had the ability to instill an enormous degree of confidence in both his staff and his patients. He was supremely self confident, and if he ever did have any doubts about his ability to deal with a situation, such doubts were never obvious to staff or the patients. Procrastination and indecision were totally anathema to him.

It is true that very great demands are made on the medical and nursing staff in our New Zealand hospital service, but in a war environment there are the added stresses of the danger, and all of the other very unpleasant physical and emotional sensations that are intrinsic to living and working in the middle of combat activity. Evan McKenzie displayed those essential leadership characteristics of emotional and physical stamina that enabled him to not only carry out his surgical work with consummate skill, but also to provide a firm base of support for the younger team members. Thirty-five years later he is still remembered in Bong Son as ‘Bac Si (Doctor) Clean, Clean’.

His skills were also recognised by the Department of Health, when in a response to a request from our Ministry of Foreign Affairs and Trade, Evan was seconded as a Consultant to Western Samoa in 1976.

His willingness to expose himself to the risks associated with service in war zones was played out one more time when he accepted the post of Team Leader for the International Committee of the Red Cross Surgical Team in Peshawar, Pakistan in 1982.
Evan completed 28 years as a full-time surgeon for the South Canterbury Hospital Board at the Timaru Hospital, retiring finally in 1989. He ‘enjoyed’ an unusually busy retirement. The award of the Paul Harris medal recognised his very active involvement with Rotary Community activities. He continued to give service as the Honorary Medical Officer for the Racing Clubs in Timaru, Waimate, Geraldine, and Ashburton, and for the South Canterbury A&P Show. He provided the medical services for both the South Canterbury Rugby Union and the Boxing Association and maintained his long-term interest in the Defence Force by always being available to conduct the necessary medical examinations for potential recruits. Indeed, he served the wider community of South Canterbury in an unstinting and loyal manner for very many years.

His role as the ‘Paterfamilias’ was the one that I am sure gave him the greatest pleasure. Sylvia and Evan had three daughters who grew up in the splendid country environment where they had established their home. There was also the holiday house in Tekapo where the family was able to spend both their summer and winter holidays. In due time the daughters married and added six grandsons to the family. He loved his extended family very much and derived an enormous amount of pleasure from being party to the development of his grandsons into fine young men.

For the 51 years of their married life Evan enjoyed the resolute support of Sylvia. Men who spend their working days and many of their nights in the operating rooms and the hospital wards and who go off to wars, can only do so if they have a spouse who is both strong and resourceful. Evan had such a wife. Certainly it is the men who go off to the wars but the added stress and worry has to be borne by the wives who must cope on their own, hoping that their man will come back safely.

Evan McKenzie was without doubt one of the distinguished men of the New Zealand Medical Profession in the latter half of the 20th Century. He served his community as surgeon with great skill and dedication; he acted as a fine mentor for many of his junior colleagues, he responded to the call of his country to serve with the Armed Forces and the Red Cross, and above all he was a family man who loved his wife and extended family over all else.

We are all the worse off as a result of his loss.

We are grateful to Dr Brian McMahon (Dunedin) for this obituary.
Recovery after Stroke


This textbook aims to be a comprehensive guide to rehabilitation after stroke and be an essential reference for all members of the multidisciplinary stroke rehabilitation team.

This book has much to offer each member of the stroke team, from basic physiology, concepts of neuroplasticity, to sexuality, dysphagia, and depression after stroke. It was great to see some less well-recognised topics such as fatigue and sleep disorders getting included. Perhaps there is a bias more towards the physical therapies, and less for occupational and language therapies, but it only slightly detracts from the overall high calibre of the book. With my own biases, I particularly enjoyed the chapters on regeneration and central reorganisation as the sometimes difficult concepts were presented in a readily understandable way.

Almost all of the chapters are easily understood, are of appropriate length, and importantly have extensive up-to-date references to delve deeper into if you wish.

There are some omissions when I scan down the Contents page. I would have liked to see some additional space dedicated to dyspraxia, visuospatial problems, nutrition, leisure, and the impact of comorbidities which are so common in patients with stroke. These topics would have complemented those other areas which were well covered in the book.

The final chapter from the patient’s perspective was interesting and informative but I wanted more. I wanted to see a chapter on how to tie it all together—how to meld all the rehab packages together for the one patient. We are getting better at working on the individual bits (impairments and disabilities), but we have a long way to go to achieving the patient’s goal of social reintegration back into their own world. We will fail our patients unless we tackle this vital task.

After exploring all 600+ pages, I believe the editors have largely achieved their goal. It is a valuable text and I would strongly recommend it be accessible for all those working in stroke rehabilitation. Certainly my review copy will find a home on our stroke rehabilitation ward and I hope it is well used.

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Case Studies in Geriatric Medicine


Initially, I was not going to review this book but I dipped into one of the case scenarios…and now I am writing this review. In short it is good!

The authors state the text is aimed at a wide range of health professionals who provide care for older people, from interns, residents, training registrars, nurse practitioners, and geriatricians. I was initially sceptical that they could achieve their aims, but the text has both breadth and depth and I believe there is something in here for everyone.

The preface succinctly summarises some of the key principles of geriatric medicine such as atypical presentations and multiple pathologies, and drugs are sometimes “poisons.” Each of the subsequent 43 case scenarios neatly embellishes these principles, but without repetition. The cases are clearly based on real-life examples, with their associated complexities, and are followed by 4–5 questions to ponder. The question and answer format worked well for me, and the answers were very easy to read and thought-provoking. Each chapter is short and pithy, which encouraged me just to “dip into the book” when I had a spare moment. The references are up-to-date, with the one exception of the cardiovascular risks of “coxibs.”

The detractors for me are the USA-biased epidemiology and funding systems, but these are minor and easily overlooked.

I thoroughly enjoyed this book and found it to be an easy way to be updated across the breadth of geriatric medicine. Its niche is probably for trainees, nurse practitioners, and general practitioners, but I would encourage my colleagues to read it too. The case-based text lends itself perfectly as a teaching aid and it will get used in this way in our department.

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