CONTENTS

This Issue in the Journal

4 A summary of the original articles featured in this issue

Editorials

6 The price of Texas Tea: oil, that is
Alexandra Macmillan, Graeme Lindsay

10 PSA testing in asymptomatic men to diagnose prostate cancer remains experimental
Brian Cox, Mary Jane Sneyd

Original Articles

15 Using census data to travel through time in New Zealand: patterns in journey to work data 1981–2006
Hannah M Badland, Mitch J Duncan, Grant M Schofield

21 Spectrum of MECP2 mutations in New Zealand Rett syndrome patients
Anthony M Raizis, Mohammed Saleem, Richard MacKay, Peter M George

29 The CYP2D6 metaboliser status of patients prescribed risperidone for the treatment of psychosis
Lucy Dunbar, Wayne Miles, Amanda Wheeler, Janie Sheridan, Justin Pulford, Rachael Butler

35 Patients’ attitudes to the use of placebos: results from a New Zealand survey
Guo-Feng Chen, Malcolm H Johnson

Special Article

47 Psychosocial impacts of quarantine during disease outbreaks and interventions that may help to relieve strain
Sarbjit S Johal

Viewpoint

53 Do those afflicted with dementia have a moral duty to die? A response to Baroness Warnock
Phillipa J Malpas
Clinical Correspondence

61 Myocardial bridging in aborted sudden death: just an innocent bystander?
Paul Knaapen, Marco J W Götte, Carel C de Cock

64 A case of vasoactive intestinal polypeptideoma
John Sycamnias, Britta Strahl, Peter Stride, Boris Chern, Lasanthi Paranavithana

69 Medical image. An unusual case of inguinal pain
Magdalena M Sakowska, John Short, Tim Eglinton

73 Medical image. Aspiration of an incisor tooth in a poly-trauma patient
Ashraf F Hefny, Yousef El-Ashaal, Yassin B Ali, Fikri M Abu-Zidan

100 Years Ago in the NZMJ

75 Some exploded theories and forgotten remedies in medicine: part 5
(fevers, racial degeneration)

Methuselah

76 Selected excerpts from Methuselah

Letters

78 Santé! Public health lessons from France for New Zealand
Nick Wilson, Jonathan Jarman, Osman Mansoor

81 Transmission dynamics of the 1918 influenza pandemic in
New Zealand: analyses of national and city data
Hiroshi Nishiura, Nick Wilson

86 Interpretation of vitamin D status may be affected by alternative
supplementation
Peter Elder, John Lewis, Richard King, Chris Florkowski

88 Time to implement the polypill approach
Shaun Holt

90 Permitting sex selection
Martin Wilkinson

Obituaries

92 John Heywood Taylor

94 Norman Derek Walker
Notice

96 University of Otago Faculty of Medicine Freemasons Postgraduate Fellowships in Paediatrics and Child Health for 2010

Book Reviews

97 Speaking for the Dead: The Human Body in Biology and Medicine (D Gareth Jones & Maja I Whitaker)
Mark Stringer

99 Law, Mind and Brain (Michael Freeman & Oliver R Goodeno, eds)
Warren Brookbanks
In this Issue of the Journal

Using census data to travel through time in New Zealand: patterns in journey to work data 1981–2006
Hannah M Badland, Mitch J Duncan, Grant M Schofield

Little comprehensive longitudinal evidence exists regarding the association between work-related travel modes and oil prices for the New Zealand population. Examining this relationship may lead to a greater understanding regarding how best to promote sustainable transport modes, which is important for improving public health outcomes, such as increasing physical activity engagement, enhancing air quality, and reducing traffic-related injuries. Work-related travel data were obtained from the New Zealand census of population and housing conducted between 1981–2006. These travel data were compared with 2006-adjusted oil prices. Private motor vehicle was the dominant travel mode across years. The proportions of trips by public transport and active transport were low across all time points, and steadily declined. A decline in work-related sustainable transport modes over the last 25 years in New Zealand was evident. Work-related private motor vehicle travel may be sensitive to oil prices, however, further research is required to fully understand this relationship. Public health agencies should seek to advocate for infrastructure that supports sustainable transport modes.

Spectrum of MECP2 mutations in New Zealand Rett syndrome patients
Anthony M Raizis, Mohammed Saleem, Richard MacKay, Peter M George

In this study we reviewed the referral patterns, and clinical features, of patients referred for genetic testing to investigate possible Rett syndrome. Most patients did not have identifiable mutations and in these patients the clinical features were usually not typical of the expected pattern. In these patients careful clinical review together with extended genetic analysis is likely to establish another diagnosis and may uncover novel genes involved in developmental and behavioural disorders.

The CYP2D6 metaboliser status of patients prescribed risperidone for the treatment of psychosis
Lucy Dunbar, Wayne Miles, Amanda Wheeler, Janie Sheridan, Justin Pulford, Rachael Butler

This research looks at the use of a new genetic-based screen that predicts drug metabolising enzymes (substances in the body that break down foreign material, including prescribed medicines). Possible benefits of its use are outlined. The study showed less influence on the prescribing practice than might have been expected and reasons for this are discussed. The views of prescribers about how such a test could benefit decisions is presented.
Patients’ attitudes to the use of placebos: results from a New Zealand survey
Guo-Feng Chen, Malcolm H Johnson

In this study we asked GP patients a number of questions about placebo, such as whether they would consider participating in a placebo-controlled clinical trial, and why they might agree or not to do so. We also asked whether they thought it was appropriate for doctors to administer placebos in a number of clinical situations and we asked some questions about how they believed placebo might work. The majority of participants would consider participating in a placebo-controlled trial, most likely motivated by wanting to help develop new treatments or other patients. Most of our participants thought for a doctor to administer placebo was acceptable to some extent under some circumstances, although patients were not well informed about the more subtle details of the placebo effect.

Psychosocial impacts of quarantine during disease outbreaks and interventions that may help to relieve strain ((special article))
Sarbjit S Johal

The threat of an outbreak of infectious disease can provoke the implementation of public health controls measures such as quarantine. Those affected by quarantine are likely to report distress due to fear of risk perceptions. This paper outlines recommendations for the care of those asked to go into isolation or quarantine and those working with them, such as helping to identify causes of distress and helping them adapt to their situation as much as possible. This should take place at all levels of a public health response to an infectious disease threat, from public information so that people are clear as to the current situation through to individual face-to-face advice and support.
The price of Texas Tea: oil, that is

Alexandra Macmillan, Graeme Lindsay

Badland and colleagues, in this issue of the Journal, seek to make use of a link between crude oil price and transport behaviour to potentially derive a health benefit in the form of physical activity. They propose that increasing oil prices may benefit health if people are forced by economics to use more active modes of transport than the private motor vehicle.

Although their paper offers little in the way of firm conclusions, their recognition of the link between oil prices and public health deserves further attention. Furthermore, their paper highlights the difficulties of research across disciplines, in particular using empirical data from other sectors to draw conclusions of pertinence to health.

The economic, social, and environmental wellbeing of developed nations has been tied to the price of crude oil as a major commodity for at least a century. The price of oil is important for both macroeconomics (national economies) through international commodity markets—and microeconomics (household economies) through the price of transport, goods, and services.

There is growing international consensus about an impending global oil production peak, as heralded by Hubbert in 1949. Although there is uncertainty about the timing of the peak (somewhere between now and 2030), it is inevitable that a period of oil scarcity following the peak will lead to sustained increases in price, followed by a necessary transition to a “post-oil” global economy.

Abundant petroleum and coal-based energy has contributed to improved health through economic development over the past century for developed countries. Life expectancy has doubled, education has improved, and poverty reduced for most populations. Crude oil is the basis for most forms of transport fuel. Petroleum is also the chemical foundation for products such as plastics, pesticides, fertilisers, medications, solvents, and lubricants. Petroleum dependence has therefore infiltrated most industrial sectors, including the healthcare sector.

The wellbeing implications of increasing oil prices can therefore be considered in terms of direct implications for health care (through access to health services and the supply of medical equipment and pharmaceuticals), and indirect implications, mainly through economic performance, transportation, and food production. While the direct implications are likely to require contingency planning and preparedness within the health sector, it is the indirect impacts that are likely to be most socially profound.

In New Zealand, the end use of indigenous and imported barrels of crude oil is heavily dominated by transport. Sixty-three percent of the average barrel yields petrol and diesel, and almost 90% of this is used for domestic transport (including freight, public transport, and private motor vehicles).

The link between the price of crude oil and social wellbeing has been strengthened over time by the way we have designed our cities to be sprawling and reliant on
private motor vehicles for access to vital goods and services. The impact of oil prices on household economics is therefore indicated by the proportion of household budget spent on transport. This proportion is currently between 6% and 8%.\(^5\)

Transport is the third largest area of spending for households (after housing and food), and mediates household access to health services, education, healthy food, and employment. However, the household budget spent on food is also affected by oil prices, through the cost of primary food production (using pesticides and fertilisers), the cost of importing food, and the cost of transporting food from source to end use. Petroleum scarcity will therefore result in both more expensive and scarcer food, threatening the health of vulnerable communities.

These implications provide a strong contrast to the conclusions drawn by Badland and colleagues, who hint at co-benefits for health in a sustained oil price increase through increasing active modes of transport. Others have connected increasing oil prices with positive trends in motor vehicle injury and fatality (for example, Grabowski and Morrisey in 2004\(^6\)).

If car-use behaviour is indeed responsive to oil price changes, then increasing oil prices should bring relief from many of the harms of car use, including air and water pollution, injury, physical inactivity, and social disconnection. However, unless we can achieve a timely and innovative economic and social transition from oil-dependency, the inevitable increase in poverty and exacerbation of current inequalities will overwhelm any possible benefits suggested by decreasing car use.

Even when policies of social justice and universal healthcare are strongly maintained in the face of an oil crisis, the outcomes for public health are arguably mixed. This has been demonstrated by Cuba’s “Great Adjustment” of the 1990s, which followed the severance of trade with the former Soviet Union.

These mixed outcomes are not surprising when the juxtaposed effects of food scarcity, adult healthcare collapse, improvements in air and water quality, more participatory governance, an exponential increase in cycling and walking, and localised sustainable agricultural systems are taken together.\(^7\)\(^-\)\(^9\)

The paucity of empirical data and the absence of convergent analysis across sectors in the case of Cuba limit our ability to draw generalisable conclusions about the policies that are most likely to maximise the benefits and minimise the harms of a transition from oil dependency.

Badland’s comparative exercise demonstrates these issues of data and analysis at a more manageable scale. Both empirical sources of data used in the comparison are limited in their usefulness for understanding the relationship between oil prices and transport choices. The international price of a barrel of crude oil is only a surrogate for the price of petrol at the pump and neither reflects the full oil cost of car driving.

As well as influencing our choice of transport (as Badland suggests) the price of petrol changes driving behaviour (increasing the likelihood of slower, more fuel-efficient driving styles) and vehicle type (more fuel-efficient vehicles).

The census travel question has a number of flaws that seriously limit its usefulness in enhancing our understanding. Although the census question has the strength of consistency over time, only workplace travel is included, the question covers “main
mode” of travel by distance (favouring motorised modes), and only relates to census day. A great deal more collaborative work is needed here to shape data collection across disciplines to assist with drawing sensible conclusions of relevance to health.

It would certainly be erroneous at this stage to conclude that increasing oil scarcity will be beneficial for public health. In the long-term, there may indeed be benefits for human and environmental health; however, an overall benefit to wellbeing will rely heavily on the nature of the transition from oil-dependency to alternative energy sources. Peak oil is one aspect of three major interlinked public health issues of the 21st Century: climate change, energy use, and urbanisation.

It is clear that these cannot be tackled from within the health sector, or, in fact, from within any individual discipline. The kind of cross-discipline work that is currently most undertaken in public health is at the upper hierarchical level of planning, whereas a truly transdisciplinary approach\(^\text{10}\) will be required to develop policy responses to these issues that protect and promote public health, and address issues of inequity.

Such an approach will need to be defined by new processes that move from relationships between disciplines in the development of empirical data to collaborative planning within a framework of shared values.

**Competing interests:** None known.

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**References:**


PSA testing in asymptomatic men to diagnose prostate cancer remains experimental

Brian Cox, Mary Jane Sneyd

The recent reductions in prostate cancer mortality seen in some countries have been attributed to earlier detection of the cancer by PSA testing. However, the randomised controlled trials show that if any benefit from PSA testing exists it would not be seen within 7 years of its introduction.\(^1,2\) Therefore, the mortality reductions observed are likely to be due to more cases being offered curative therapy or the availability of better treatment.

In 1996, PSA testing of asymptomatic men was considered experimental and the major potential for over-diagnosis and subsequent overtreatment with major side-effects was highlighted\(^3\) and now the results of two studies have become available. These results provide conflicting evidence of the effectiveness of PSA testing in reducing mortality from prostate cancer.

The results of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial in the United States were published because, at this time, the study’s monitoring board raised concerns about the harms they identified from PSA testing in asymptomatic men,\(^2\) whereas the European Randomized Study of Screening for Prostate Cancer (ERSPC) study protocol precipitated publication when a statistically significant result was obtained from analyses conducted at regular intervals.\(^1\)

A summary of the design of these two studies is shown in Table 1. The ERSPC study was conducted in 7 countries, used various PSA cut-off points for recommendation for biopsy, varying screening intervals, and different age eligibility, with screening ceasing when the upper age of eligibility was reached.

In the PLCO trial, men aged 55–74 years were offered annual PSA testing for 6 years, combined with digital rectal examination for 4 years, or in the control arm received usual care. Active annual follow-up by questionnaire and linkage to the National Death Index was undertaken with a median duration of follow-up of 11.5 years (range 7.2–14.8). The PSA assays for each PLCO trial centre were performed by one laboratory. A cut-off of 4ng/ml was used to recommend referral to their usual doctor.

Table 2 summarises the main results of these studies. The results of the ERSPC study suggested a 20% reduction in prostate cancer mortality from PSA testing, along with other screening tests such as digital rectal examination (DRE) and transrectal ultrasonography (TRUS), in asymptomatic men after a median of 9 years of follow-up (RR=0.80, 95%CI 0.65–0.98).
Table 1. Summary of the design of the PLCO trial and the ERSPC study

<table>
<thead>
<tr>
<th>Study centre</th>
<th>ERSPC (n=162,387)</th>
<th>PLCO (n=76,693)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (years)</td>
<td>Intervention arm</td>
</tr>
<tr>
<td>Finland (n=80379)</td>
<td>55-67</td>
<td>4-yearly PSA</td>
</tr>
<tr>
<td>Sweden (n=11852)</td>
<td>50-69</td>
<td>2-yearly PSA</td>
</tr>
<tr>
<td>Italy (n=14517)</td>
<td>55-74</td>
<td>4-yearly PSA</td>
</tr>
<tr>
<td>Belgium (n=8562)</td>
<td>55-74</td>
<td>3ng/ml, 2-yearly PSA, plus DRE and TRUS, until Feb 1997</td>
</tr>
<tr>
<td>The Netherlands (n=17442)</td>
<td>55-74</td>
<td>3ng/ml, 2-yearly PSA, plus DRE and TRUS, until Feb 1997</td>
</tr>
<tr>
<td>Spain (n=2197)</td>
<td>55-74</td>
<td>4-yearly PSA</td>
</tr>
<tr>
<td>Switzerland (n=9903)</td>
<td>55-69</td>
<td>3ng/ml, 4-yearly PSA</td>
</tr>
</tbody>
</table>

a. Screening stopped at 71 years of age
b. Men with PSA values 3-3.5 ng/ml had DRE until 1998 and from 1999 if they had a ratio of free PSA to total PSA <=0.16 they were referred for biopsy
c. Men with PSA values 2.5-3.5 ng/ml had auxiliary tests (DRE and TRUS)
d. 10ng/ml initially during 1991-1994 in the pilot study and 4ng/ml until Feb 1997
e. 7 years between 1st and 2nd round of screening due to funding constraints
f. 4ng/ml until Feb 1997

The PLCO trial observed a non-significant 13% increase in prostate cancer mortality in those offered annual PSA tests (RR=1.13, 95%CI 0.75–1.70) after 7 years of follow-up for all subjects. This was not significantly altered by inclusion of available data to 10 years of follow-up (67% of subjects) or if confined to those with one PSA test, or 2 or more tests, in the previous 3 years at baseline.

The chance of a diagnosis of prostate cancer increases with the number of biopsies taken. In the ERSPC study the number of biopsies after a positive screening test varied between countries, but standardisation was recommended in 1996, whereas in the PLCO trial the decisions about biopsy and treatment were left to the man’s usual health care provider. This meant that, in the PLCO trial, any further assessment procedures and treatment were expected to be similar for both the intervention and control group.
Table 2. Summary of the PLCO trial and ERSPC study results of PSA screening for prostate cancer

<table>
<thead>
<tr>
<th></th>
<th>ERSPC (n=162,387)</th>
<th>PLCO (n=76,693)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tested with PSA</td>
<td>82%</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>not-given</td>
<td>52%</td>
</tr>
<tr>
<td>Prostate cancers</td>
<td>5,990</td>
<td>2,820</td>
</tr>
<tr>
<td></td>
<td>4,307</td>
<td>2,322</td>
</tr>
<tr>
<td>Percentage diagnosed with prostate cancer</td>
<td>8.2%</td>
<td>7.4%</td>
</tr>
<tr>
<td></td>
<td>4.8%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Number of prostate cancer deaths</td>
<td>214</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>326</td>
<td>44</td>
</tr>
<tr>
<td>Prostate cancer death rate</td>
<td>3.3</td>
<td>2.0</td>
</tr>
<tr>
<td>(per 10,000 person-years)</td>
<td>4.1</td>
<td>1.7</td>
</tr>
<tr>
<td>RR (95% CI) of prostate cancer mortality in intervention vs control groups</td>
<td>0.80 (0.65-0.98)</td>
<td>1.13 (0.75-1.70)</td>
</tr>
</tbody>
</table>

In Finland, Sweden, and Italy, randomisation of the offer of screening occurred after selection from population registers—a study of the effect of the introduction of prostate screening in the general population (the effectiveness of screening).

In the Netherlands, Belgium, Switzerland, and Spain, randomisation occurred after acceptance of the invitation to participate—a study of screening in those who accept it (the efficacy of screening). Efficacy is greater than effectiveness and effectiveness measures the overall benefit of offering PSA testing to asymptomatic men in the population. Therefore, the ERSPC study estimate of benefit is greater than would be achieved from population-based PSA testing in asymptomatic men.

In the PLCO trial 40% of the control subjects had at least one PSA test by the second year of follow-up (contamination of the controls) and this increased to 52% by the sixth year of follow-up. The contamination of the control group in the ERSPC study was not reported in the recent publication but varied from 6.7% to 36.6% among centres during 1996–2001. This resulted in a smaller relative increase in prostate cancer diagnoses between intervention and control groups in the PLCO trial (22%) compared to the ERSPC study (71%). Detailed analyses of both the similarities and differences among the different trials included in the ERSPC study are likely in the future.

The beneficial effects from randomised controlled trials of screening almost always exceed what is obtained when the technology is introduced into routine health care, as the tight controls for the decision making process and management protocols of trials tend to be lost. A greater length of follow-up of the trials will be required before more conclusive results are available. However, the contamination of the control groups in...
both studies may not have occurred equally among different risk groups for prostate cancer death, resulting in unresolvable bias.

What is now unequivocal from these two trials is the magnitude of over-diagnosis and subsequent overtreatment resulting from the PSA testing of asymptomatic men. Over-diagnosis is the detection of prostate cancer that would not become clinical disease in a man’s natural life. This is sometimes referred to as indolent prostate cancer and has been known for a long time to be very common.

This over-diagnosis has been estimated to be 48% (95%CI 44%–55%) for annual screening and 50% (46%–57%) for 4-yearly screening in men aged 55–67 years. The treatment of prostate cancer by either radical prostatectomy or radiotherapy carries significant risks such as chronic incontinence (urinary or faecal), impotence, or, in some instances, death.

In addition to significant side-effects, the treatment of many men who will not benefit produces increased waiting times and reduced accessibility to radiotherapy and surgery for other patients who may benefit from them. For example, if we accept the ERSPC study results, 1480 men would need to be screened and 48 additional cases of prostate cancer treated for each death from prostate cancer prevented over a 10-year period. Moreover, about 24 of the additional cases treated would receive treatment for a condition that would not have become clinical prostate cancer in their lifetime, and of these about 4 would have chronic incontinence or impotence.

The decision about the value of PSA testing in asymptomatic men is not solely determined by the magnitude of any reduction in prostate cancer mortality but by the balance of harms versus benefits. Despite previous claims of effectiveness, it now appears that if there is a reduction in prostate cancer mortality from PSA testing in asymptomatic men, it is likely to be small. The current results of the trials assist in resolving the controversy regarding the value of PSA testing of asymptomatic men.

The results of the randomised controlled trials might optimistically be considered to indicate that: eventually there will be a reduction in prostate cancer mortality from PSA testing of asymptomatic men 55–69 years of age; the considerable harms from such testing are bearable by patients and the health care sector, and; PSA testing of asymptomatic men should be facilitated.

Another view would be that we now have inconclusive evidence from randomised controlled trials of any decrease in prostate cancer mortality and unequivocal evidence of major harms, mainly from over-diagnosis and consequent overtreatment, so much so, that good health care should involve advising asymptomatic men against PSA testing at this time.

It is easy to understand the belief that the early detection of cancer must result in a reduction in the mortality from the disease. Historically, many clinicians and patients have been seduced by this idea many times for a variety of cancers. However, the current randomised controlled trial evidence suggests that claims of benefit from PSA testing in asymptomatic men have probably been overstated and that, as indicated by the authors of one of the trials, the recognised harms must be more rigorously considered to protect many men from iatrogenic illness.

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Using Census data to travel through time in New Zealand: patterns in journey to work data 1981–2006

Hannah M Badland, Mitch J Duncan, Grant M Schofield

### Abstract

**Aim** Little comprehensive longitudinal evidence exists regarding the association between work-related travel modes and oil prices for the New Zealand population. Accordingly, the objective of this study is to document work-related travel behaviours in New Zealand adults and oil prices over time. Examining this relationship may lead to a greater understanding regarding how best to promote sustainable transport modes, which is important for improving public health outcomes, such as increasing physical activity engagement, enhancing air quality, and reducing traffic-related injuries.

**Method** Work-related travel data were obtained from the New Zealand census of population and housing conducted quinquennially from 1981–2006. These travel data were compared with 2006-adjusted oil prices.

**Results** Private motor vehicle was the dominant travel mode across years (54.8%–79.9%). The proportions of trips by public transport (~4%) and active transport (8.9%–14.2%) were low across all time points and steadily declined. Oil prices decreased from 1981 to 1996, and increased from 1996 onwards.

**Conclusion** A decline in work-related sustainable transport modes over the last 25 years in New Zealand was evident. Work-related private motor vehicle travel may be sensitive to oil prices, however, further research is required to fully understand this relationship. Future research in this field should seek to increase levels of sustainable work-related transport modes, further understand oil price elasticity across different groups, and to determine whether behaviour changes are short-term or have a lag. Public health agencies should seek to advocate for infrastructure that supports sustainable transport modes and conduct further research in this field.

Public health and transport agencies recognise the consequences of private automobile reliance, such as reduced incidental physical activity accumulation, poorer air quality, increased injury risk, traffic congestion, oil consumption, infrastructure costs, and social inequalities.1–5

Public transport and active transport engagement (e.g. walking and cycling for travel purposes) offer solutions to these problems, yet participation in these travel modes is low in most developed countries.6,7

The increased reliance on private automobiles shown in many countries may in-part be a product of built environments being designed for private automobiles, with a substantial body of evidence existing to support this association.8–10

Economic considerations, such as the price of oil as a driver for changes in fuel costs, may also be associated with travel mode selection.11 Furthermore, the World Health Organization promotes walking and cycling as viable travel modes for short journeys.
that improve health outcomes,\textsuperscript{12} and New Zealand research indicates a large portion of the adult working population recognise they can commute to work by walking or cycling for distances less than 5 kilometres.\textsuperscript{13}

Accordingly, focusing on work-related travel behaviours holds much public health utility, as a large portion of people frequently commute to their workplace, therefore any behaviour change will likely have a far-reaching implications.

New Zealand census data offer a unique opportunity to examine temporal trends in the work-related commute and these movements can be examined against adjusted crude oil prices. Investigating this relationship will provide further evidence of the association between the long-term price of fuel and discrete travel choices.

International research has shown oil prices to be more elastic (i.e. as price of the product decreases, consumption increases, and vice versa) in the long-term when compared to short-term changes.\textsuperscript{14} Accordingly, understanding oil price and travel behaviour changes in the New Zealand population is important for informing the development of potential interventions to increase engagement in sustainable modes for work-related travel.

It is anticipated that greater participation in active transport will lead to improved population health outcomes, such as increased physical activity levels and reduced levels of obesity.\textsuperscript{15} As such, the aims of this study are to: firstly, document longitudinal work-related travel trends in New Zealand adults, and secondly, to examine these trends in relation to the change in oil price as a potential influence of travel mode selection for a discrete behaviour.

**Method**

Travel data were sourced from the New Zealand census from 1981 to 2006. The census occurs every 5 years at the start of March and is the official national population count, capturing demographic data on all individuals and households. The current analysis was delimited to individuals aged 15 years and over who travelled to work on the day of the census.

From 1981 onwards, individuals reported the main mode by which they travelled to work by responding to the question ‘On census day, what was the one main way you travelled to work—that is, the one you used for the greatest distance?’ Participants selected from pre-determined responses, and for this analysis were collapsed into: private vehicle, public transport, and walking and cycling modes. People reporting they worked at home, did not go to work on census day, or reported other travel modes were excluded from the analysis.

The international market price of crude oil per barrel for each year in US$ was established through examining historical oil costs.\textsuperscript{16} These figures were converted to NZ$ by the exchange rate at 1 March for that year and adjusted by Consumer Price Index (CPI) inflation to align the price per barrel with 2006 NZ$ values.

**Results**

Data presented in Figure 1 show private vehicles were the dominant travel mode at each time point for work-related travel for New Zealand adults, and were used between 54.8\% (1991) and 79.9\% (2001) of all journeys. Over the monitoring period, oil prices decreased substantially from of $295/barrel in 1981 to $48/barrel in 1996. Oil prices increased in 2001 and 2006 from the lower price observed in 1996, coinciding with a 1.1\% reduction in private vehicle modality for the work-related commute in 2006.
Public transport and walking and cycling engagement were low across all time points, however slight variations were present. Public transport patronage was higher in 1981 and 1986 and declined as oil prices fell. Public transport engagement remained relatively stable since 1991, with approximately 4% of work journeys made via mass transit.

Travelling by walking and cycling declined over time; 14.2% of work commute trips were made by active modes in 1981, reducing to 8.9% in 2006. Across this time, the New Zealand population increased from 3.143 million to 4.109 million residents.

Figure 1. Work-related travel modes and oil prices for New Zealand across six time-points

Conclusions

The presented data show that over time engagement in walking and cycling was relatively low and declined. Travel by private motorised modes was high, although in the last census period vehicle travel decreased slightly.

Importantly, but outside the scope of this study, automobile prices reduced substantially across this period through increased importation of cheaper Japanese cars. It is likely that increased vehicle accessibility due to lower purchasing costs have added to the greater reliance on private automobiles for commuting to an occupation, however, it is difficult to separate oil price and vehicle accessibility.
changes over time without conducting further in-depth research. Despite this, these presented data provided a useful overview of work-related travel patterns in the first instance, and also consider the changes that may occur as a result of an economic mediator over an extended period of time in employed New Zealand adults.

The trends observed in the current analysis were similar to those observed in other developed countries, and potential reasons have been identified.

Firstly, the New Zealand setting mirrors population distributions observed in other industrialised nations through the development of low-density neighbourhoods on the outskirts of major urban centres, these developments often have limited public transport access and lengthy commute distances.

Secondly, there have been considerable under investment and deregulation of public transport infrastructure over the last 2 decades in New Zealand. As a consequence, the public attitude towards mass transit may have worsened, potentially contributing to the low public transit rates observed.

Consistent with existing research, private vehicle use was the dominant form of travel for the work-related commute in New Zealand adults. Although no definitive conclusions between oil prices and travel behaviours can be drawn based on our findings, it appears that trends in travel behaviours, particularly private vehicle use, may be associated with the changing price of oil. These findings are consistent with recent research where exposure to sustained high oil prices has resulted in long-term behaviour changes, such as changing residential or workplace location.

Conversely, spikes in oil prices result in transient behaviour changes, e.g., an increase in telecommuting. Our data show that as the price of oil fell, fewer people travelled to work by public transport or active travel modes. Conversely, as oil prices began to increase, private vehicle use declined, although a lag between oil price increase and behaviour change was evident.

Non-immediate changes in travel behaviour observed in these data are consistent with observations that fuel demands change little in the year following price increases, with reduced automobile use being observed thereafter. Accordingly, increases in travel costs and favourable changes in sociocultural attitudes towards active transport and public transit may direct New Zealand adults to more cost-effective, health promoting, and sustainable travel modes over time.

Study limitations are evident. The census is taken every five years; therefore short-term elasticities, such as oil price spikes, cannot be detected, only the main mode of travel was assessed in the surveys and this may be biased towards travel modes that are faster moving, and no analysis was undertaken to examine how different socioeconomic and ethnic groups respond to oil price increases.

Other potential influences of travel modes such as community design were not examined, and it is unknown how this may interact with oil prices to influence travel modalities. It was also unknown how many people were able to commute to their place of work by active travel or public transport modes as data for residential-workplace distances and accessibility of public transport for these routes were not calculated. However, recent estimates suggest that approximately 40% of New
Zealand residents agreed that it was possible to replace car journeys with active transport modes on 2 days per week. As such, there is potential for substantial population health gains through increases in physical activity levels and air quality improvements if more people were to travel by active or public transport modes. Furthermore, it is likely that oil prices will continue to rise as extraction costs increase, and stronger relationships may become evident between oil prices and travel modes.

Future research in this field should seek to develop strategies to increase the rates of active travel and public transport engagement in working adults, further understand long- and short-term oil price elasticity across different groups, identify socioeconomic and ethnic responses, understand how infrastructure change affects travel modality, and determine the sustainability of travel behaviour change.

Public health agencies have a valuable role to play in this increasingly important field, including advocating for infrastructure that supports sustainable transport modes and contributing to the research in this field.

Competing interests: None known.

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References:
Spectrum of MECP2 mutations in New Zealand Rett syndrome patients

Anthony M Raizis, Mohammed Saleem, Richard MacKay, Peter M George

Abstract

Background Classical Rett syndrome is a severe neurodevelopmental X-linked dominant disorder affecting 1/15,000 girls worldwide. MECP2 has been identified as the predominant gene associated with Rett syndrome. Approximately 65-85% of patients with classical Rett syndrome have identifiable MECP2 mutations. In comparison, up to ~57% of patients with atypical Rett have mutations in the MECP2 gene.

Objectives To investigate the spectrum and frequency of MECP2 mutations in New Zealand Rett syndrome patients and evaluate whether available clinical criteria were sufficient to direct molecular testing for Rett syndrome.

Patients and Methods MECP2 coding regions were analysed by direct automated DNA sequencing and multiplex ligation dependent probe assay (MLPA) in samples from 74 patients referred for investigation of possible Rett syndrome. Necessary clinical criteria were examined in detail in 18 patients, with 7/18 having identifiable MECP2 mutations.

Results Fifteen patients (20%) carried MECP2 mutations, four of which were novel (one insertion mutation, one complex rearrangement and two deletions). Eleven previously described disease-causing sequence changes and several known polymorphisms were also detected. Ninety per cent of the observed point mutations were cytosine to thymidine (C to T) transitions at a CpG dinucleotide. Only three patients with MECP2 mutations displayed all major clinical criteria associated with Rett syndrome, four were atypical cases. Of the patients not having an identified MECP2 mutation, 8 out of 11 had clinical criteria consistent with variant Rett syndrome and one of these had a balanced translocation involving chromosomes 2p25 and 6p11-12.

Conclusions This is the first genetic study of Rett syndrome in New Zealand patients describing the MECP2 mutational spectrum. The relatively low observed frequency of MECP2 mutations reflects a wide spectrum of mental disability disorders. In some cases there were insufficient clinical criteria to justify referral for Rett gene testing.

Classical Rett syndrome (OMIM 312750) is a neurodevelopmental disorder, one of the most common causes of mental retardation in females and is usually due to mutations in the methyl-CpG binding protein 2 (MECP2) gene. MECP2-related disorders also include variant or atypical Rett syndrome, mild learning disabilities in females, and neonatal encephalopathy and mental retardation syndromes in males. Thus the variability of the clinical features is a significant
problem in the diagnosis of Rett syndrome, and many clinicians face a difficulty in deciding when to request genetic testing.

Atypical Rett syndrome, in which ~50% of patients have MECP2 mutations, is identified in patients previously classified as having autism, mild learning difficulties, or Angelman’s syndrome, adding to the complexity of diagnosis. In addition, many clinical manifestations of Rett syndrome only occur after the age of 3 years, rendering younger infants difficult to diagnose.

The threshold of necessary clinical criteria to justify testing is difficult to define due to the variable phenotype of variant Rett syndrome. In the study described here, we examine a cohort of 75 patients who were referred for MECP2 gene testing in order to determine the spectrum of phenotypic features observed by clinicians before referral.

Materials and Methods

The patients—The group consisted of 74 patients (71 female and 3 male) aged between 1 and 31 years, who were referred for testing as part of the investigation of global developmental delay and mental retardation. Where appropriate fragile X and Angelman’s syndrome were excluded by specific mutation analyses, particularly when the clinical features did not strongly support classical Rett syndrome.

Patient clinical information was derived from medical records after obtaining consent from the legal guardians in accordance with the conditions set out by the Multi-Regional Ethics Committee. Not all clinical features were available. Nine “necessary” clinical features were recorded which are a prerequisite for classical Rett syndrome, while for variant Rett there are six “main” criteria (Table 1).

Table 1 Diagnostic features of classical and atypical Rett
(available at http://www.genetests.org/query?dz=rett)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Classical Rett syndrome</th>
<th>Variant Rett syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Necessary</strong></td>
<td>• Normal prenatal and perinatal history</td>
<td>Inclusion</td>
</tr>
<tr>
<td></td>
<td>• Normal psychomotor development for the first six months</td>
<td>• At least three of the six main criteria</td>
</tr>
<tr>
<td></td>
<td>• Normal head circumference at birth</td>
<td>• At least five supportive criteria</td>
</tr>
<tr>
<td></td>
<td>• Postnatal deceleration of head growth in most individuals</td>
<td>Main</td>
</tr>
<tr>
<td></td>
<td>• Loss of purposeful hand skills between age six months and 2.5 years</td>
<td>• Reduction or absence of hand skills</td>
</tr>
<tr>
<td></td>
<td>• Hand stereotypes</td>
<td>• Loss or reduction of speech (including babble)</td>
</tr>
<tr>
<td></td>
<td>• Evolving social withdrawal, communication dysfunction, loss of acquired speech, and cognitive impairment</td>
<td>• Hand stereotypes</td>
</tr>
<tr>
<td></td>
<td>• Impairment or deterioration of locomotion</td>
<td>• Loss or reduction of communication skills</td>
</tr>
<tr>
<td></td>
<td>• Diagnosis often tentative until age of 2 to 5 years.</td>
<td>• Deceleration of head growth from early childhood</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Regression followed by recovery of interaction</td>
</tr>
<tr>
<td>Supportive</td>
<td>Supportive</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>• Breathing disturbances during waking hours</td>
<td>• Breathing irregularities</td>
<td></td>
</tr>
<tr>
<td>• Bruxism</td>
<td>• Abdominal bloating or air swallowing</td>
<td></td>
</tr>
<tr>
<td>• Impairment of sleeping pattern from early infancy</td>
<td>• Bruxism</td>
<td></td>
</tr>
<tr>
<td>• Abnormal muscle tone associated with muscle wasting and dystonia</td>
<td>• Abnormal locomotion</td>
<td></td>
</tr>
<tr>
<td>• Peripheral vasomotor disturbances</td>
<td>• Kyphosis or scoliosis</td>
<td></td>
</tr>
<tr>
<td>• Progressive kyphosis or scoliosis</td>
<td>• Lower limb amyotrophy</td>
<td></td>
</tr>
<tr>
<td>• Growth retardation</td>
<td>• Cold, discolored, and usually hypotrophic</td>
<td></td>
</tr>
<tr>
<td>• Hypotrophic, small, and cold feet and/or hands</td>
<td>feet</td>
<td></td>
</tr>
<tr>
<td>• Peripheral vasomotor disturbances</td>
<td>• Night-time screaming and other sleep</td>
<td></td>
</tr>
<tr>
<td>• Progressive kyphosis or scoliosis</td>
<td>disturbances</td>
<td></td>
</tr>
<tr>
<td>• Growth retardation</td>
<td>• Inexplicable episodes of screaming or</td>
<td></td>
</tr>
<tr>
<td>• Hypotrophic, small, and cold feet and/or hands</td>
<td>laughing</td>
<td></td>
</tr>
<tr>
<td>• Abnormal muscle tone associated with muscle wasting and dystonia</td>
<td>• Apparently diminished sensitivity to pain</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Evidence of a storage disorder including organomegaly</td>
</tr>
<tr>
<td>• Cataract, retinopathy, or optic atrophy</td>
</tr>
<tr>
<td>• History of perinatal or postnatal brain damage</td>
</tr>
<tr>
<td>• Confirmed inborn error of metabolism or neurodegenerative disorder</td>
</tr>
<tr>
<td>• Acquired neurologic disorder caused by severe head trauma or infection</td>
</tr>
</tbody>
</table>

**Isolation of DNA**—Genomic DNA was extracted from 5 ml of EDTA blood yielding approximately 80–100 µg. For PCR, the DNA was diluted to 20 ng/μl and 5 μl was used in a 50 μl PCR reaction.

**PCR amplification and DNA sequencing**—The PCR primers for MeCP2 gene amplification and PCR amplification conditions were done as described previously. Coding regions of the MECP2 were amplified by PCR and sequenced by automated fluorescent sequencing using the ABI Big Dye terminator kit version 3.1. Sequencing products were separated by capillary electrophoresis on an ABI 3130 genetic analyser. DNA sequence data was compared to the reference GenBank sequence AF030876.

**MLPA analysis**—MLPA was performed following the general directions provided by MRC-Holland (www.mlpa.com), using a probe set to cover the entire MECP2 gene. Amplification products were analysed with an ABI 3100 genetic analyzer (ABI). Electropherograms were analysed by GeneMapper version 3.5 (ABI), and peak height data were exported to an Excel spreadsheet (http://www.ngrl.org.uk/Manchester/Informaticspubs.htm) and quantified.

**Results**

Of 74 patients analysed for MECP2 mutations, 15 were found to have mutations, as summarised in Table 2. Four novel mutations were identified including a 44 bp deletion (c.1158_1201del44) and a single base insertion (c.695dupG).

A complex insertion/deletion was also identified by DNA sequencing (AF030876:g.22631_22614conAL078639:g.94544_94611). MLPA analysis revealed a large deletion, which was subsequently characterised and found to span exons 3 and 4 of the MECP2 gene.
Table 2. Summary of MECP2 mutations identified in New Zealand cases of Rett syndrome

<table>
<thead>
<tr>
<th>Case</th>
<th>MECP2 Mutation</th>
<th>Mutation type</th>
<th>Status</th>
<th>Dinucleotide CpG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>g.23713-22118del1596</td>
<td>Deletion</td>
<td>Novel</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>c.763C&gt;T (p.R255X)</td>
<td>Nonsense</td>
<td>Known</td>
<td>CpG</td>
</tr>
<tr>
<td>3</td>
<td>c.1158_1201del44</td>
<td>Deletion</td>
<td>Novel</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>c.880C&gt;T (p.R294X)</td>
<td>Nonsense</td>
<td>Known</td>
<td>CpG</td>
</tr>
<tr>
<td>5</td>
<td>c.916C&gt;T (p.R306C)</td>
<td>Missense</td>
<td>Known</td>
<td>CpG</td>
</tr>
<tr>
<td>6</td>
<td>c.808C&gt;T (p.R270X)</td>
<td>Nonsense</td>
<td>Known</td>
<td>CpG</td>
</tr>
<tr>
<td>7</td>
<td>c.473C&gt;T (p.T158M)</td>
<td>Missense</td>
<td>Known</td>
<td>CpG</td>
</tr>
<tr>
<td>8</td>
<td>c.1189G&gt;T (p.E397X)</td>
<td>Nonsense</td>
<td>Known</td>
<td>CpG</td>
</tr>
<tr>
<td>9</td>
<td>c.397C&gt;T (p.R133C)</td>
<td>Missense</td>
<td>Known</td>
<td>CpG</td>
</tr>
<tr>
<td>10</td>
<td>c.316C&gt;T (p.R106W)</td>
<td>Missense</td>
<td>Known</td>
<td>CpG</td>
</tr>
<tr>
<td>11</td>
<td>c.1164_1207del44</td>
<td>Deletion</td>
<td>Known</td>
<td>NA</td>
</tr>
<tr>
<td>12</td>
<td>c.695dupG</td>
<td>Insertion</td>
<td>Novel</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>AF030876:g.22631_22614conAL078639:g.94544_94611</td>
<td>Insertion/Deletion</td>
<td>Novel</td>
<td>NA</td>
</tr>
<tr>
<td>14</td>
<td>c.468C&gt;T (p.D156E)</td>
<td>Missense</td>
<td>Known</td>
<td>CpT</td>
</tr>
<tr>
<td>15</td>
<td>c.808C&gt;T (p.R270X)</td>
<td>Nonsense</td>
<td>Known</td>
<td>CpG</td>
</tr>
</tbody>
</table>

Note: Cytosine to thymidine transition mutations are listed as CpG or CpT; NA=Not applicable.

Eleven patients had known point mutations in the MECP2 coding sequence and of these 8 (89%) were due to cytosine to thymidine transition mutations within a CpG dinucleotide.

The age distribution of the 74 patients analysed is shown in Figure 1, with most referrals from paediatric services within New Zealand. Only 8 (11%) of this cohort were under the age of three and one of these had a known mutation p.R106W. As the majority of patients were over 3 years old, most would be expected to have sufficient diagnostic manifestations to confirm a clinical diagnosis of either classical or variant Rett syndrome.

Figure 1. Observed age frequency in a New Zealand cohort of patients referred for Rett gene testing.
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</thead>
<tbody>
<tr>
<td>Apparently normal prenatal and perinatal period</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Apparently normal Psychomotor development through the first 6 months</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Normal Head circumference at birth</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>N/A</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>+</td>
</tr>
<tr>
<td>Deceleration of head growth between the ages of 5 months and 4 years</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>N/A</td>
<td>-</td>
<td>N/A</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>+</td>
</tr>
<tr>
<td>Loss of acquired purposeful hand skills between the ages of 6 to and 30 months, temporally associated with communication dysfunction and social withdrawal</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
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<td>-</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Development of severely impaired expressive and receptive language, and presence of apparent psychomotor retardation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>N/A</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Stereotypic hand movements such hand wringing/squeezing, clapping/tapping, mouthing/rubbing automatisms appearing after purposeful hand skills are lost.</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>N/A</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Impairment or deterioration of locomotion/coordination between the ages of 1 and 4 years</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Diagnostic tentative until 2-5 years of age</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>karyotypic analysis</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>(2,6)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Necessary criteria are listed (left hand column).
ND = Not done
N/A = not available
Patients A1-11 = No MECP2 mutation detected
Patients B1-B7 = MECP2 mutation identified (Highlighted in grey).
Approximately 24% of the patients referred for gene testing via paediatric services had MECP2 mutations compared to 14% referred via genetic services.

Polymorphic sequence variants were also identified. The coding sequence polymorphisms identified included c.1189G>A and c.31GGA[6]+GGA[5], while non-coding intronic variants found were c.377+266C>T, c.378-241C>T, c.377+242C>T, c.378-19delT, c.378-74C>T, and c.378-109A>G.

Table 3 shows the clinical characteristics observed in a subset (18/74) of referred patients who were distributed throughout New Zealand and for whom legal guardian consent was obtained to examine clinical notes. Of these, 7/18 had identifiable mutations in the MECP2 gene. Only three of the seven having mutations displayed the full set of necessary clinical criteria associated with classical Rett syndrome.

Of the 11 patients not having MECP2 mutations, patient A9 was subsequently found to have a balanced translocation of unknown significance involving chromosomes 6 and 2 (Table 3) and at least 7/9 of the necessary Rett criteria. Patients A3, A5 and A7 displayed only 1/6 of the main criteria, and no MECP2 mutations were identified in these patients.

**Discussion**

We have analysed the MECP2 gene from the samples of 74 patients with Rett syndrome or Rett-like features. Of these patients, only 20% had MECP2 mutations. In other series, mutations were detected in 60 to 88% of those with classical Rett\(^5-7\) and ~50% of those with atypical Rett syndrome.\(^2,8\) In another study, patients were selected with mental retardation as the main diagnostic feature, and of these only 0.25% had MECP2 mutations.\(^9\)

In our series, the patients not having MECP2 mutations (80%) are probably clinically heterogeneous. Some cases may be due to mutations in either non-coding regions of MECP2 or other gene(s) e.g. CDKL5\(^10\) giving rise to Rett-like features, but others probably have acquired causes.

The mutations identified in this series are all clearly pathogenic and the high frequency of cytosine to thymidine transitions suggests that deamination of methylated cytosines is a common cause of Rett syndrome. Spontaneous deamination is likely to contribute to the high frequency of methyl-cytosine transitions to thymidine, but a number of factors have been found to accelerate deamination—e.g. cytosine protonation in response to aberrant base-pair formation or base modification.\(^11\)

Diagnosis under the age of three is difficult for Rett syndrome since many diagnostic features do not manifest until this age. Only 11% of our patients analysed fell into this category, so the majority were old enough to manifest the diagnostic features required to diagnose classical or atypical Rett syndrome.

Even when strict criteria are used Rett diagnosis can be difficult. A score of 4-8 out of the 9 necessary criteria (Table 1) has been previously observed in Japanese patients having MECP2 mutations.\(^2\) However, similar scores were observed in these patients with and without detectable mutations in MECP2. These observations illustrate the difficulties associated with interpreting diagnostic criteria.
We found that paediatric services were more likely to identify a patient having a MECP2 mutation (24%) when compared to genetic services (14%). This probably reflects the referral patterns, with most patients with mental disability disorders of this type being more likely to be seen by paediatric services before genetic services. Furthermore the higher frequency of <3 year olds seen be genetic services increases the probability of misdiagnosis.

A high proportion of referrals fell short of classical Rett syndrome ~83%. Patients A3, A5 and A7 displayed only 1/6 of the main criteria (Table 3), with no identifiable MECP2 mutations. While the criteria supporting Rett for these patients were weak and perhaps insufficient to warrant MECP2 testing, collection of DNA samples from such patients should still be considered of value as they will facilitate the identification of other genes associated with mental disability disorders.

Only a handful of other genes have been linked to Rett syndrome—e.g. CDKL5 and NTNG1.12,13 These genes are not considered a common cause of Rett. Our finding of a balanced translocation (6p11-12;2p25) in a patient with Rett-like features further supports the existence of other Rett-like genes. This patient had at least 7/9 necessary criteria with a translocation involving a chromosomal region not previously associated with Rett syndrome suggesting that a novel gene might be at this locus.

Very few of the patients in this cohort not having MECP2 mutations had been examined for high resolution karyotypic analysis. Where possible, cytogenetic analysis should be requested.

In New Zealand there is no formal policy to record and report all available necessary diagnostic criteria before referral. Currently, diagnostic criteria are recorded ad hoc and are difficult and time consuming to obtain from medical records. However, more detailed clinical information supplied to the testing laboratory may be useful for phenotypic classification of patients.

With respect to Rett-like mental disability disorders, we recommend that (where possible) clinicians in New Zealand should adopt a standardised approach to recording the nine necessary diagnostic criteria and that this information is provided with diagnostic test requests, in order to direct appropriate testing.

Competing interests: None known.

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Acknowledgements: We thank all the clinicians from across New Zealand who referred samples for genetic testing.

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References:

The CYP2D6 metaboliser status of patients prescribed risperidone for the treatment of psychosis

Lucy Dunbar, Wayne Miles, Amanda Wheeler, Janie Sheridan, Justin Pulford, Rachael Butler

Abstract

Aim To identify the distribution of CYP2D6 metaboliser status in patients who were being prescribed risperidone for the treatment of psychosis in a New Zealand-based clinical population.

Method 100 AmpliChip CYP450 Test® kits were made available by Roche Diagnostics. Clinicians in mental health services across three Auckland District Health Boards were instructed that the tests were being made available for use with patients who were being prescribed risperidone for the first time. Test results were fed back to the prescribing clinician. Data analysis was descriptive in nature; however, chi-square and independent sample t tests were employed to examine differences in age, gender, and ethnicity.

Results Data were obtained for 93 patients. Poor and intermediate metabolisers each constituted 10.6% of the sample. There were no ultra-rapid metabolisers. Statistical analysis revealed no significant between-group differences with respect to age or gender. The between-group difference in ethnicity status showed a trend towards statistical significance.

Conclusion Sample size limitations likely contributed to the finding that no statistically significant between-group differences were identified. In theory, though, for one in five patients a higher level of adverse effects might be predicted for a normal dose of risperidone, potentially leading to issues around treatment adherence or treatment failure.

Personalised prescription (the tailoring of medication type and dose to one’s genetic make-up) has recognised potential to improve clinical outcomes across a range of common disorders. Information on a patient’s CYP2D6 genetic polymorphism offers one example of how personalised prescription might be employed in practice. CYP2D6—part of a group of liver-based enzymes that have a primary role in breaking down foreign or unwanted substances—is specifically involved in the metabolism of many medications, including commonly prescribed antiarrhythmics, antidepressants, antipsychotics, and antiemetics.

The rate of metabolism of any CYP2D6-susceptible drug will vary according to phenotypic expression. Four phenotypic representations of CYP2D6 are currently recognised. These include: ultra-rapid metabolisers (UM) who have more than two copies of the relevant gene; extensive metabolisers (EM) who have two active copies; intermediate metabolisers (IM) who have one active copy; and poor metabolisers.
(PM) who have no active copies. Failure to account for this genetic variance may result in suboptimal clinical outcomes. For example, standard drug dose may not result in therapeutic plasma levels for UMs and may increase the risk of an adverse drug reaction in PMs.3

Evidence suggests these scenarios have eventuated in clinical practice.4,5 Thus, knowledge of an individual’s CYP2D6 status presents one means by which the risk of under- or over-prescribing CYP2D6-susceptible drugs may be avoided. Whilst the least problematic EM phenotype is dominant in most populations, the more problematic PM and UM phenotypes are not uncommon.3,6

Evidence suggests the PM phenotype is highest amongst Western European populations and lowest amongst Asian populations (expressed in 10% and 1% of the population, respectively) whereas the UM phenotype is highest amongst African populations and lowest amongst Western European populations (expressed in 30% and 1% of the population, respectively).6

Few studies have explored the distribution of CYP2D6 phenotypes in New Zealand-based populations. Those studies that have been conducted, however, suggest substantial differences exist in the distribution of CYP2D6 phenotypes between New Zealanders of Māori and European descent,7 and that the distribution amongst the latter group is consistent with other populations of Western European origin.8

Given the potential benefits in adopting a personalised prescribing approach, this paper presents the results of a study that sought to identify the distribution of CYP2D6 metaboliser status among patients who were being prescribed risperidone for the first time for the treatment of psychosis in a New Zealand-based clinical population. This population presents as an ideal target for possible personalised prescription based on CYP2D6 status as risperidone is primarily metabolised by this enzyme group and a number of studies have noted an increase in adverse drug reactions amongst PMs prescribed antipsychotics.4,9,10

In addition to reporting CYP2D6 distribution amongst this population, the paper also examines for age, sex and ethnic relationships that might predict the distribution and comments on health systems issues associated with CYP2D6 testing.

Method

Setting—This study was set in the Mental Health Services of the three District Health Boards (DHBs) serving the greater Auckland region: Auckland, Waitemata, and Counties Manukau. Records indicate that over 28,000 mental health clients access these services per annum.11 Of these, Waitemata DHB serves half, while Auckland and Counties Manakau DHBs serve around a quarter each. Māori are over-represented in mental health services across all three DHBs, forming 17% of the service user population,11 compared with around 11% of the DHBs’ catchment population.12 However, Pacific and Asian peoples are under-represented, respectively comprising 8.5% and 5.2% of the service user population,11 compared with 14.4% and 18.9% of the catchment population.12

Procedure—Ethical approval for the conduct of this study was obtained from the Northern X Regional Health Research Ethics Committee (Reference NTX/06/05/055). One hundred AmpliChip CYP450 Test® kits were made available at no cost by Roche Diagnostics for use between September 2006 and December 2007.

Information about these tests was provided to all clinicians occupying the positions of Senior Medical Officer, Registrar and House Officer (n=237.6 full time equivalent positions) in mental health services via a series of presentations and flyers distributed through existing networks within the three DHBs.
Email reminders were also sent to all clinicians throughout the study period. These included information on the potential benefits of the test, what was involved for clinicians and other process issues such as how the test was funded and the expected time frame for receiving results.

Clinicians were instructed that the tests were being made available specifically for use with patients who they believed were being prescribed the antipsychotic risperidone for the first time. Use of the test was not mandatory and compliance was not formally monitored; however, clinicians were encouraged to employ the test with all patients meeting the specified criteria, until December 2007 or until all 100 tests had been utilised (whichever came first).

Once appropriate patients were identified, the clinician was directed to prescribe ‘as usual’, then complete an AmpliChip CYP450 test order form which was given to the patient, who was required to visit a laboratory to have a blood sample taken. Testing was undertaken in a laboratory based in the South Island of New Zealand. Results were fed back to the prescribing clinician (in paper and electronic format) as per standard laboratory processes, so that results were available at subsequent patient visits.

Data were entered into an SPSS database (version 13). Much of the analysis was descriptive in nature; however, chi-square and independent sample t tests were employed to examine differences in age, gender and ethnicity.

Results

Overall, 42 doctors ordered 95 AmpliChip CYP450 tests for 93 patients. Two patients were tested twice, one of these by the same doctor. Duplicate data were excluded from the analysis. The average number of tests used per clinician was 2.24 (range 1–8), with just over half of all clinicians ordering only one test. The majority of tests were conducted with Waitamata DHB patients (66.7%), while Auckland DHB patients constituted 25.8% of patients tested and Counties Manakau DHB patients comprised the final 7.5%. A breakdown of patient metaboliser status is shown in Table 1.

Table 1. Distribution of patients’ metaboliser statuses (n=93)

<table>
<thead>
<tr>
<th>Metaboliser Status</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>10 (10.6%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10 (10.6%)</td>
</tr>
<tr>
<td>Extensive</td>
<td>68 (69%)</td>
</tr>
<tr>
<td>Ultra-rapid</td>
<td>Nil (0%)</td>
</tr>
<tr>
<td>No-call*</td>
<td>5 (5.3%)</td>
</tr>
</tbody>
</table>

*No-call* = could not be determined by laboratory.

Table 2 presents selected demographic characteristics for the 88 patients whose metabolic status was identifiable.
Table 2. Demographic profile of patient participants by metabolic status†

<table>
<thead>
<tr>
<th>Variable</th>
<th>Poor/Intermediate Metabolisers (n=20)</th>
<th>Extensive Metabolisers (n=68)</th>
<th>Overall (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean-age</td>
<td>37.9 +/- 19.1</td>
<td>32.2 +/- 15.6</td>
<td>33.6 +/- 16.5</td>
</tr>
<tr>
<td>% Female</td>
<td>47.1</td>
<td>40.4</td>
<td>41.9</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>% European</td>
<td>52.9</td>
<td>58.2</td>
</tr>
<tr>
<td></td>
<td>% Māori</td>
<td>19.6</td>
<td>17.9</td>
</tr>
<tr>
<td></td>
<td>% Pacific Nation</td>
<td>11.8</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>% Asian</td>
<td>15.7</td>
<td>13.4</td>
</tr>
</tbody>
</table>

†Patients with ‘poor’ or ‘intermediate’ metabolic status were grouped into a single category in order to improve the power of statistical analysis. Patients whose metabolic status could not be determined (‘no calls’) were excluded from the analysis.

Statistical analysis revealed no significant between-group differences with respect to age (t=1.17, df=87, p=0.247), gender ($\chi^2=1.60$, df=1, p=0.304) or ethnicity (NZ European vs. other; $\chi^2=3.12$, df=1, p=0.107). Given the small sample size, the failure for statistically significant differences to emerge may be the result of Type II error.

The between-group difference in ethnicity status, in particular, showed a trend towards statistical significance and may have been obtained with a larger sample size. Further study in this area is therefore warranted with larger sample sizes, before firm conclusions can be drawn regarding the relationship between metaboliser status and demographic characteristics in the study population.

Discussion

This study sought to identify the prevalence of four recognised CYP2D6 phenotypes amongst patients prescribed risperidone for the treatment of psychosis. As the EM phenotype is considered to be the ‘norm’, it was expected that the majority of participants would fall into this category. This proved to be the case as 77% of participants with an identifiable metaboliser status (n=88) were EM.

The distribution of PMs (10.6%) found by this study was also consistent with that reported in the literature and the absence of any UMs was not unexpected given that no people of Arabian or African descent were present in our sample (UMs are rare in non-Arabian or -African populations).

This study further sought to identify possible age, gender or ethnicity differences in the distribution of CYP2D6 phenotypes. No statistically significant differences were identified in any of these domains; however, sample size limitations likely contributed to this result, especially with regard to ethnicity.

Thus, whilst our findings concur with a study by Roberts et al where the prevalence of PMs among Māori was similar to that found in New Zealand Caucasians, caution should be taken not to over generalise this finding. On this note it is perhaps worth...
acknowledging that four of the five ‘no call’ subjects were of Māori or Pacific ethnicity, suggesting the question of different distribution for Māori and or Pacific remains a possibility that deserves exploration.

These data, alongside those of Lea et al, do suggest that a wider spread sampling of New Zealand Māori and Pacific people in New Zealand is warranted to see if these are racial differences which would have relevance for treatment planning. This would best be studied through an epidemiological based survey of the incidence of CYP2D6 polymorphisms in the New Zealand population.

The incidence of PMs (10.6%) and, to a lesser extent, IMs (10.6%) reported in this study is such that one could expect that knowing a patient’s metaboliser status would be useful in the personalising of dose and possibly medication choice. These findings indicate that, in theory, for one in five patients, a higher level of adverse effects might be predicted for a normal dose of risperidone, potentially leading to issues around treatment adherence or treatment failure. It is well recognised in the literature about personalised prescription that the phenotype can never be the sole determinant of a clinician’s dose choice.\textsuperscript{2,14} However, knowing this piece of information could reduce some of the intangibles.

Further exploration of the interaction between prescribing clinicians’ knowledge of their patient’s metaboliser status and dosing decisions is warranted. It is proposed that a randomised controlled trial would provide the most suitable methodology, where under one condition, clinicians receive the Amplichip test results and under the other, patients are untested. Data should be collected confirming receipt of test results and dosing decisions made subsequently. Test results should be ordered at first contact with the patient and received in accordance with standard laboratory turnaround times, for example within 24–48 hours.

To conclude this paper, it is worth noting a systemic issue identified during the data collection process. The Amplichip assay is a one-off test that provides clinical information relevant for the rest of the patient’s life. This feature of the assay, however, presents a challenge for health record systems and especially the storing and accessing of laboratory test results. Standard laboratory information display systems, such as Concerto, display tests in chronological order, the latest first. For most purposes this is effective. For these one-off-enduring-tests it is a potential problem since this result becomes imbedded in a host of results and unless carefully looked for cannot assist the doctor in personalising drug/dose.

Competing interests: This work was sponsored by Roche Diagnostics through an unrestricted research grant.

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Acknowledgements: This work was sponsored by Roche Diagnostics through an unrestricted research grant. We the research team are grateful for their support, their encouragement and their liaison with the laboratory where the AmpliChip CYP450 Tests® were performed. We are also grateful to Peta Hardley and Sarah Renals for their assistance at various stages of the project and to the many staff across the three participating District Health Boards who assisted in accessing patient documentation.

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References:
Patients’ attitudes to the use of placebos: results from a New Zealand survey

Guo-Feng Chen, Malcolm H Johnson

Abstract

Aims To examine how amenable patients are to the use of placebos in clinical practice, their willingness to participate in a placebo-controlled clinical trial (PCT), and to examine patients’ beliefs about the placebo effect.

Methods A cross-sectional questionnaire survey was administered to 211 general practice patients of two primary care clinics in socioeconomically divergent areas of the Auckland region, New Zealand. The questionnaire obtained self-report of willingness to accept various clinical uses of placebo as measured by the Attitudes to Placebo Treatments Scale (APTS), willingness to participate in a PCT including reasons for or against participation, and beliefs about the placebo effect.

Results The APTS score (M=22.34, SD=7.93) for the entire sample showed that patients were accepting of placebo use in certain clinical situations, even the use of placebo as a diagnostic tool. Patients seem to consider placebo use more appropriate when it is for the benefit of the patient, at the patient’s request, or when there seems to be no available alternate treatment. Placebo use was considered inappropriate when its use was seen to be for the benefit(s) of the physician or where placebo use seemed dangerous. 59% of the patients surveyed indicated willingness to participate in a PCT.

Conclusion Many patients are amenable to the use of placebos, suggesting that the major issues of placebo use (deception and lack of informed consent) are tolerated by the patients surveyed. Many were prepared to participate in a PCT particularly in order to support the development of new treatment and help other patients. However, patients seem to have misguided beliefs about the placebo effect, underestimating the effectiveness of the placebo and attributing placebo effects to personality. Generally, patients lack understanding of the placebo effect.

The administration of placebo as an intervention in clinical practice has been well-documented. Studies have shown that many physicians do not hesitate to administer a placebo intervention in various clinical situations.1–6 In a Danish study of 545 clinicians, as many as 86% reported use of placebo interventions at least once, and 48% to have used placebo interventions more than ten times within a year,4 while 60% of a group of 89 clinicians in Israel used placebos and over 30% did so more than once a month.5 In a very recent study of a United States sample of internists and rheumatologists about half of the 679 respondents acknowledged prescribing placebo treatment.6

Although apparently quite widely occurring, the use of placebo interventions in clinical practice is generally regarded as unethical because it fails to include informed consent, and often involves deceit of a patient.7 Unfortunately, we have little information about the attitudes of patients to placebo treatment or their understanding...
of the construct. The limited literature suggests that along with health professionals, patients are not well informed and generally lack awareness of the placebo effect.\(^3\),\(^8\),\(^9\)

In one study surveying 300 rheumatology inpatients about their beliefs regarding the placebo effect in the treatment of chronic pain, the authors found that patients had little knowledge of the placebo effect and tended to underestimate it, and concluded that more attention should be directed to better understand patients’ views of the placebo construct.\(^8\)

As evidence grows for a biologically active basis for placebo action mediated by expectation and conditioning processes in conditions such as pain,\(^10\)–\(^13\) Parkinson’s disease,\(^14\)–\(^17\) and depression,\(^18\)–\(^21\); along with evidence that much of the efficacy of some “real” treatments is attributable to placebo effects,\(^22\)–\(^24\) arguments for the use of placebo in clinical practice are likely to grow.\(^10\),\(^25\)–\(^27\) However, even if health professionals are ready to “exploit” placebo power, the question of whether placebo administration is acceptable to patients and the impact that placebo administration might have on the healing encounter is unknown.

Without sound knowledge of how patients generally view the use of placebos, no one can answer this question with certainty. Clearly, we need additional information to predict the likely impact of the use of placebos on patients’ perceptions of their medical experience. Therefore, shifting the research focus to examine patients’ attitudes to placebo use will benefit the existing literature.

At this point in time, the one circumstance in which placebo can be ethically administered is in the context of a clinical trial in which the participant is informed about the possibility of receiving a placebo rather than the procedure or pharmaceutical being investigated.\(^10\),\(^28\),\(^29\) Although there has been much recent discussion regarding the ethics of placebo administration in this circumstance,\(^29\)–\(^31\) there is little systematic evidence regarding consumer views of placebo use, other than one qualitative study of Japanese laypersons that found the use of placebo was related to more negative attitudes toward participating in medical research.\(^32\)

We examined whether patients were amenable to the use of placebo in various clinical situations, their willingness to participate in a PCT including their reasons for or against participation, and their beliefs about the placebo effect.

**Methods**

**Questionnaire**—We developed a questionnaire on beliefs about placebo and attitudes to the use of placebos in clinical practice and in clinical research. We sought information on basic demographics, willingness to participate in a PCT, attitudes to the use of placebos, and beliefs about the placebo effect. Placebo was briefly defined in the questionnaire as: ‘an inactive treatment such as a sugar pill that looks like the real pill and is given in the same way as a real pill’. Additionally, we asked whether patients had chronic or acute conditions.

Attitudes to the use of placebo were investigated using the APTS, a 10-item questionnaire adapted from an earlier study examining doctors’ attitudes to the deliberate use of placebo as treatment.\(^1\) However, the earlier study only examined the APTS as individual items. For the present study we wished to accumulate an overall score.

For each of the ten items, participants are asked to express what they believe is the right action for a medical practitioner to take. Prior to the main statistical analyses, the factor structure of the APTS was examined using principal components analysis. Initial results using varimax rotation suggested a two factor solution but with five items loading above .35 on both factors and eigenvalues of 3.27 and 0.34 for the factors.
As the scree plot and eigenvalues suggested a single factor, an oblique rotation (direct oblimin) was used. From this analysis, it was concluded that a single factor solution with nine items that had an eigenvalue of 3.81 and explained 42% of the total variance was appropriate. Factor loadings are shown in Table 2. Item 1 had an extremely low factor loading compared to the other nine items and was not included when the total score was calculated.

The Cronbach’s alpha for the APTS is .822. The individual scores are summed to give an overall score ranging from 9 to 45. A higher score would mean that the participant is more amenable to the use of placebos.

**Recruitment**—Consecutive general practice patients waiting to see their doctors were recruited from two clinics with different socio-economic populations in the Auckland area of New Zealand. The inclusion criteria for participation were; (1) patients had to be over 18 years old; (2) patients were required to be literate in English. Of the approximately 440 patients approached who consented to participate, 211 returned completed questionnaires, a response rate of 48%.

**Statistical methods**—Statistical analysis was carried out using version 12 of the Statistical Package for Social Science (SPSS). The significance level was set at .05 for all statistical tests. P-values less than 0.05 and 0.01 were reported. To compare group differences in means of the APTS, independent samples t tests were used. The associations between continuous variables of interest were determined using Pearson correlation coefficients. Factor analysis was used to examine the psychometric properties of the APTS.

**Results**

Table 1 shows the basic demographics of the entire sample. The uneven gender ratio probably reflects the general pattern that females visit their physicians for advice and treatment more frequently than males.\(^{33,34}\) The age of the sample no doubt results from the impact of age on health. The number reporting tertiary level education (47%) is slightly higher than the 40% of adults that reported having tertiary qualifications in the 2006 New Zealand census,\(^{35}\) perhaps because some people will engage in tertiary education without receiving a qualification.

**Table 1. Demographic data for the total sample**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency (SD in years)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>49.7</td>
<td>(17.4)</td>
</tr>
<tr>
<td>Male</td>
<td>54.4</td>
<td>(18.2)</td>
</tr>
<tr>
<td>Female</td>
<td>48.3</td>
<td>(16.9)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>49</td>
<td>(23)</td>
</tr>
<tr>
<td>Female</td>
<td>162</td>
<td>(77)</td>
</tr>
<tr>
<td><strong>Medical condition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>92</td>
<td>(44)</td>
</tr>
<tr>
<td>Chronic</td>
<td>119</td>
<td>(56)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some high school</td>
<td>88</td>
<td>(42)</td>
</tr>
<tr>
<td>Finished high school</td>
<td>24</td>
<td>(11)</td>
</tr>
<tr>
<td>Tertiary level</td>
<td>98</td>
<td>(47)</td>
</tr>
<tr>
<td>Item</td>
<td>Question</td>
<td>Factor Loading</td>
</tr>
<tr>
<td>------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>1</td>
<td>Should a doctor consider putting a bandage on a painful area (especially of a child) to reduce both pain and anxiety, even if this bandage will have little known direct effect on the injury?</td>
<td>0.131</td>
</tr>
<tr>
<td>2</td>
<td>A doctor suspects a patient of pretending to be sick. Should the doctor consider the use of placebo to find out if their pain is real or not?</td>
<td>0.673</td>
</tr>
<tr>
<td>3</td>
<td>An elderly patient suffering from arthritis is getting too many painkillers. It is best for the patient if medication is reduced, but the patient refuses to take fewer pills. Placebo pills could be used for half the medication to obtain the desired reduction. Should the doctor consider their use?</td>
<td>0.711</td>
</tr>
<tr>
<td>4</td>
<td>A new patient arrives at a doctor’s office and expects a prescription. If the doctor refuses, there is the chance that this patient will not return and will seek another doctor. To maintain contact with this patient should the physician consider prescribing an unnecessary medication until the doctor can achieve a good doctor-patient relationship?</td>
<td>0.411</td>
</tr>
<tr>
<td>5</td>
<td>An over-weight patient wishes to lose weight. Should a doctor consider the use of a placebo rather than use a weight-loss drug, hoping this patient might avoid the risk of later addiction or other side effects?</td>
<td>0.782</td>
</tr>
<tr>
<td>6</td>
<td>All standard treatments have failed with a patient. Should a doctor consider it acceptable to use a placebo describing it as a “new treatment, not yet on the market but known to be effective” to calm the patient?</td>
<td>0.679</td>
</tr>
<tr>
<td>7</td>
<td>A patient complains of ongoing headache. The doctor realizes the headache started when one of their family members died. Should the doctor consider the use of a placebo medication to treat this pain which is probably due to emotional factors related to the death of the relative?</td>
<td>0.756</td>
</tr>
<tr>
<td>8</td>
<td>A patient is a moderate smoker (10-15 per day) and wishes to stop immediately but lacks the willpower to do so. He has come to his doctor believing pills are available that hold back the urge to smoke. Should the doctor consider prescribing a placebo to help him quit smoking?</td>
<td>0.631</td>
</tr>
<tr>
<td>9</td>
<td>A patient that has incurable cancer has read a story in the newspaper that indicates that placebo treatment can be effective. The patient seems to understand the idea of placebo treatment. Should a doctor prescribe a placebo if the patient asks for the placebo?</td>
<td>0.461</td>
</tr>
<tr>
<td>10</td>
<td>A doctor has a difficult patient who upsets the other staff members at the doctor’s office. The patient seems to think they can be seen immediately whenever they wish. Their relatively harmless condition is unlikely to be helped by any treatment. Do you think the doctor should prescribe a placebo, hoping that this might provide some relief from this patient for himself and his staff?</td>
<td>0.651</td>
</tr>
</tbody>
</table>
Frequency—The results of the responses to the individual items on the APTS for the entire sample, expressed as percentages are shown in Table 2 while Table 3 presents the means and standard deviations of the APTS. Items 1, 3 and 9 were found to be the most appropriate uses of placebo. In item 1, 27% would definitely consider use in this way, while over 78% would consider use in this way on at least rare occasions. In item 9, over 32% would definitely consider use in this way, while over 68% would consider use in this way on at least rare occasions.

In item 3, over 53% would consider use in this way on at least rare occasions. Items 4, 6 and 10 were found to be the most inappropriate uses of placebo. In item 4, over 72% would definitely not consider use in this way, while 82% would either consider it definitely not appropriate or only as a last option. In item 6, over 36% would definitely not consider use in this way, while over 64% would either consider it completely inappropriate or only as a last option. Finally, in item 10, over 48% would definitely not consider use in this way, while over 71% would either consider it completely inappropriate or only as a last option.

Examination of individual scoring patterns for the APTS showed only one participant considered all uses of placebo were definitely not appropriate and one considered that all uses were definitely appropriate. While there was a tendency for participants to be either more or less agreeable to the various uses of placebo, 117 participants discriminated the various possible uses and responded definitely appropriate to at least one use and definitely not appropriate to another.

**Table 3. Means and standard deviations of the APTS of the whole sample, by gender and by medical condition**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean APTS scores</th>
<th>(SD)</th>
<th>t test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire sample</td>
<td>22.34</td>
<td>(7.93)</td>
<td></td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24.31</td>
<td>(8.37)</td>
<td>P&lt;.05</td>
</tr>
<tr>
<td>Female</td>
<td>21.75</td>
<td>(7.72)</td>
<td></td>
</tr>
<tr>
<td>Medical condition:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>21.78</td>
<td>(7.68)</td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>22.77</td>
<td>(8.12)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Comparisons of group differences were made for gender and medical conditions. The mean and standard deviation of the APTS score for the entire sample was 22.34 and 7.93 respectively. Male participants (M=24.31, SD=8.37) had significantly higher mean APTS scores than female participants (M=21.75, SD=7.72), \( t \) (209) =1.99, \( p<.05 \). However, chronic and acute patients did not significantly differ on the APTS scores.

Table 4 presents the correlations between the variables total APTS scores, age, and education. Age correlated positively with total APTS scores (\( r=0.14, p<0.05 \)), and level of education correlated negatively with total APTS scores (\( r=-0.29, p<0.01 \)).
Table 4 Intercorrelations between the APTS and demographic variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>(1)</th>
<th>(2)</th>
<th>(3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) APTS</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>(2) Age</td>
<td>.137*</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>(3) Education</td>
<td>-.287**</td>
<td>-.409**</td>
<td>--</td>
</tr>
</tbody>
</table>

Willingness to participate in a placebo-controlled trial—Table 5 shows the responses of willingness to participate in a hypothetical PCT. Overall, 59% of the entire sample would be willing to participate in a PCT. The reasons most often given were:

- The wish to support the growth of new treatments/help other patients;
- The possibility of remaining unmedicated; and
- Believing that even a placebo may help them.

The reasons most often given by unwilling participants were:

- Wanting to know if they were really receiving medication;
- Fearing that not receiving medication may worsen their condition or slow their improvement; and
- Knowing that long-term drug treatment is required.

Eighty seven percent of the patients stated that they would not lose trust in their physician if asked to participate in a PCT. No significant findings were found for the influence of sociodemographic variables - gender, medical condition, age, or education on the decision to participate or not in a clinical trial.

Patients’ beliefs about the placebo effect—Table 6 shows the responses to patients’ beliefs about the placebo effect. Over 65% were unsure that placebos would work in general. More interestingly, less than 5% either agreed completely or agreed for the most part that placebos, in general can cause bad side effects. Less than 17% either agreed completely or agreed for the most part that a placebo can provide complete pain relief. Over 21% agreed completely or agreed for the most part that the effect of a placebo can last as long as that of the real treatment. Less than 9% either disagreed completely or disagreed for the most part that the effectiveness of a placebo was dependent on the personality of the patient. Over 5% either agreed completely or agreed for the most part that two placebos can be more effective than one.
Table 5. Willingness to participate in a placebo-controlled trial for the entire sample

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes (%)</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Would you be willing to take part in a placebo-controlled trial?</td>
<td>59.0</td>
<td>41.0</td>
</tr>
<tr>
<td>If yes, please go to 2; if no please go to 3.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 I would take part in a placebo-controlled clinical trial because:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) want to support the growth of new treatments/help other patients</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>b) would receive more medical care</td>
<td>29.0</td>
<td>71.0</td>
</tr>
<tr>
<td>c) I would be able to talk to my physician more often</td>
<td>18.2</td>
<td>81.8</td>
</tr>
<tr>
<td>d) My family/friends would want me to take part</td>
<td>12.2</td>
<td>87.8</td>
</tr>
<tr>
<td>e) To please my physician</td>
<td>5.1</td>
<td>99.9</td>
</tr>
<tr>
<td>f) I think that even a placebo might help me</td>
<td>36.4</td>
<td>63.6</td>
</tr>
<tr>
<td>g) I would have the chance of being unmedicated/medication free</td>
<td>39.8</td>
<td>60.2</td>
</tr>
<tr>
<td>3 I would not be willing to take part in a placebo-controlled clinical trial because:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) I fear that not receiving medication might worsen my condition or slow my improvement</td>
<td>64.9</td>
<td>35.1</td>
</tr>
<tr>
<td>b) I know that long-term drug treatment is required</td>
<td>20.0</td>
<td>49.0</td>
</tr>
<tr>
<td>c) My physician has told me of the need of drug treatment</td>
<td>47.2</td>
<td>52.8</td>
</tr>
<tr>
<td>d) I am against the use of placebos in general</td>
<td>24.3</td>
<td>75.7</td>
</tr>
<tr>
<td>e) I want to know whether I am really getting medication</td>
<td>80.0</td>
<td>20.0</td>
</tr>
<tr>
<td>f) I don’t want to have to make such decisions</td>
<td>39.1</td>
<td>60.9</td>
</tr>
<tr>
<td>g) I have had bad experience with placebos before</td>
<td>4.3</td>
<td>95.7</td>
</tr>
<tr>
<td>h) It would be too much effort</td>
<td>27.5</td>
<td>72.5</td>
</tr>
<tr>
<td>i) Placebos are useless</td>
<td>13.4</td>
<td>86.6</td>
</tr>
<tr>
<td>j) My family/friends would not want me to take part</td>
<td>17.2</td>
<td>82.8</td>
</tr>
<tr>
<td>k) I would be afraid of taking placebo</td>
<td>25.7</td>
<td>74.3</td>
</tr>
<tr>
<td>4 Would you lose trust in your physician if he/she asked you to take part in a placebo-controlled clinical trial even if he/she has explained to you the purpose of the trial</td>
<td>13.5</td>
<td>86.5</td>
</tr>
</tbody>
</table>

Table 6. Patients’ beliefs about the placebo effect

<table>
<thead>
<tr>
<th>Item</th>
<th>Belief</th>
<th>Agree completely</th>
<th>Agree mostly</th>
<th>Unsure</th>
<th>Disagree mostly</th>
<th>Disagree completely</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Placebos work in general</td>
<td>1.9</td>
<td>17.9</td>
<td>65.2</td>
<td>10.2</td>
<td>4.8</td>
</tr>
<tr>
<td>2</td>
<td>Generally, placebos can cause bad side effects</td>
<td>0.5</td>
<td>4.3</td>
<td>37.2</td>
<td>35.3</td>
<td>22.7</td>
</tr>
<tr>
<td>3</td>
<td>A placebo can provide complete pain relief</td>
<td>2.5</td>
<td>14.4</td>
<td>47.0</td>
<td>19.8</td>
<td>16.3</td>
</tr>
<tr>
<td>4</td>
<td>The effect of a placebo can last as long as that of the real treatment</td>
<td>3.9</td>
<td>17.5</td>
<td>56.1</td>
<td>13.7</td>
<td>8.8</td>
</tr>
<tr>
<td>5</td>
<td>The effectiveness of a placebo is dependent on the personality of the patient</td>
<td>18.1</td>
<td>47.1</td>
<td>26.7</td>
<td>5.7</td>
<td>2.4</td>
</tr>
<tr>
<td>6</td>
<td>Two placebos can be more effective than one</td>
<td>1.0</td>
<td>4.4</td>
<td>49.3</td>
<td>23.3</td>
<td>22.0</td>
</tr>
</tbody>
</table>
Discussion

Principal findings—The present study is the first to utilize the individual items in a scale, and is the first to be used with a patient population. The high reliability coefficient of 0.82 for the APTS suggests that it was appropriate to use with a patient population. The mean score of 22.34 (out of 45) for the entire sample provided evidence that overall, patients were quite conservative about the use of placebos. However, examining the individual items on the APTS (Table 2), it was clear that patients in the present study were amenable to the deliberate use of placebo manipulations in some situations although their lack of knowledge regarding the finer details of the placebo effect provides a context for this finding.

Interestingly, males had a significantly higher overall score than females (24.3 and 21.8), suggesting that male patients in general are more likely to view the use of deliberate placebo manipulations as more appropriate than female patients.

Two interesting but not unexpected patterns emerged from examining the individual items on the APTS. Firstly, placebo use was considered more appropriate when it was used for the benefit of the patient, was at their request, or when there seemed to be no available alternate treatment. Secondly, placebo use was considered inappropriate when it was used for the benefit(s) of the physician or in situations where it seemed use was dangerous and without possible benefits to the patient.

Overall, on four of the ten items, over 50% of the participants surveyed would consider the use of placebo on at least rare occasions, and on three other items over 40% would consider the use of placebo on at least rare occasions. These results clearly show that many patients are amenable to the use of deliberate administration of placebo in some circumstances.

Even though the use of a placebo as a diagnostic tool is dubious, over 51% of the patients surveyed would consider use in this way on at least rare occasions as revealed by responses to item 2. This indicates that patients are unaware that use of placebo as a diagnostic tool is ineffective and inappropriate. The percentage of patients that responded definitely not appropriate to the items ranged from 16.2% to 72.0%.

The percentage of patients that responded definitely appropriate to the items ranged from 4.3% to 32.5%, which may reflect a degree of conservatism on the issue of placebo use.

Theoretical framework—The concept of paternalism is defined as an action taken by one person in what he takes to be the best interest of another without the explicit consent of the person to be benefited. The results from the present study indicated that in many situations patients appear to be paternalistic in their attitudes to the deliberate use of placebo manipulations. Interestingly, it has been argued that acceptance of a placebo by a physician can encourage other kinds of deception in medicine.

This might suggest that patients who are accepting of the use of placebos are likely to be accepting of other kinds of deception in medicine. However, the primary question in how patients react to complex situations such as placebo interventions is whether the primary expectation of the patient is “First, tell me the truth” or “First make me feel better.”
One explanation for why so many patients in the present study considered the use of placebos to be appropriate could be because patients' judgments are based on the primary expectation of making the patient feel better. The majority of the placebo manipulations on the APTS are suggested with the benefits of the patient in mind. Thus, it is conceivable that a large proportion of the patients surveyed believed that placebo manipulations would in some way benefit the patients involved.

**Willingness to participate in a PCT**—The present study found that 59% of the patients surveyed were willing to participate in a hypothetical PCT. This finding is considerably higher than that of the 44% found in the sample of schizophrenia patients.\(^3\)

In our study, one cannot preclude the possibility that approving participation may represent an altruistic, socially desirable response, particularly as participants were not actually asked to participate. This is reflected by the fact that all of the participants who reported preparedness to participate would do so to support the development of new treatments/help other patients. This is interesting, because the concepts of contributing to medical knowledge and having the opportunity to help other patients in research trials are typically underemphasised in participant information and consent forms.\(^3\)

The present finding would strongly suggest that covering these areas more fully in consent explanations may facilitate patient involvement in PCTs. Of equal importance, more explicit focus on the altruistic aspects of participation should clarify the meaning and purpose of these trials and may guide patients to a more informed level of understanding from which their decisions can be made. For example, it would be inappropriate for researchers to emphasize the benefits of the trial without also acknowledging the personal risks involved for each patient.

It is encouraging to note that only 9% would participate to please their physicians, and only 18% would participate to talk to their physicians more often. These results indicate to some extent that patients are quite independent in their decision making regarding participation in a PCT. The fact that only 13.5% of the patients surveyed would lose trust in their physician if asked to take part in a PCT further suggests that patients are generally open to discussions about such trials.

**Beliefs about the placebo effect**—The finding that only 5% believed that placebos can cause bad side effects is significant because this would suggest that up to 95% of those patients involved in placebo trials that experience a marked improvement or side effects may conclude that they are receiving the active drug. Interestingly, only 8% disagreed that the effectiveness of a placebo was dependent on the personality of the patient. Such beliefs may be perpetuated by the general view that placebos would only cure illnesses that are all-in-the mind. These findings are consistent with a previous study examining rheumatology inpatients’ beliefs about the placebo effect.\(^8\)

Overall, the results clearly indicate that patients are not well informed and have misconceptions about the placebo effect.

**Strengths and weaknesses of study**—The findings from the present study are limited by a number of issues. Firstly, the study is geographically restricted, as only two health clinics were sampled in the Auckland region albeit from different socio-

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\(^8\) Overall, the results clearly indicate that patients are not well informed and have misconceptions about the placebo effect.
economic areas. Secondly, there may be bias in those that chose to complete the questionnaire.

Finally, caution is warranted in interpreting these findings, as a problem inherent in all research using open questionnaires is that the response possibilities are specified and that the respondents may be biased to give socially acceptable answers. For example, in this study we asked patients to respond to a theoretical situation. Were they offered a placebo in a genuine clinical situation their response might of course be quite different and future research might fruitfully take up the challenge of such an investigation.

Implications—Many studies have shown that placebo manipulations are widely utilized in medical practice. However, some researchers have advocated banning the use of placebos because of the deception involved in administration and the possible harm to the physician-patient relationship.10,39

The present study reveals that many patients are amenable to the use of placebo manipulations particularly when they are used at the patient’s request, for the benefit of the patient or when there is no other available alternate treatment. Obviously, from a patient’s point of view, there must be occasions when an appropriate prescribed placebo will be less harmful and perhaps more beneficial than a complex and incompletely understood drug. For example, when the physician is dealing with patients with a history of substance abuse or when patients have to be withdrawn from certain addictive drugs.

In such cases, giving placebo without obtaining informed consent, may well contribute to the patient’s well-being, and in addition would not imply that the physician is withholding a possibly beneficial medical treatment. However, discovery of placebo use could still contribute to loss of confidence by the patient in the medical practice and the widespread use of placebos in clinical practice without informed consent could undermine the contribution of expectation to therapeutic outcome not only for placebos but also for “real” therapeutics.

The findings from the present study strongly support the need to examine important issues of deception, informed consent and appropriateness of placebo use in research and in clinical practice. Programs to educate patients should be developed to overcome the current misperception and misunderstanding of placebos. Similar surveys in other geographical areas may reveal cross-cultural differences, while similar studies on specific patient populations may also reveal interesting differences or similarities.

Competing interests: None known.

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References:
Psychosocial impacts of quarantine during disease outbreaks and interventions that may help to relieve strain

Sarbjit S Johal

Abstract

The threat of outbreak of infectious disease such as non-seasonal influenza A (H1N1), commonly referred to as Swine Flu, can provoke the implementation of public health control measures such as quarantine. This paper summarises the psychosocial consequences that may follow for patients and health care and other front-line workers when using quarantine controls. Those affected by quarantine are likely to report distress due to fear and risk perceptions. This distress can be amplified in the face of unclear information and communication that is common in the initial period of disease outbreaks. This paper outlines recommendations for care of those in quarantine and those working with them, such as helping to identify stressors and normalising their impact as much as possible. This should take place at all levels of response, from public information and communication messages to individual face-to-face advice and support.

Occasions arise where the use of quarantine procedures may be necessary to protect public health. Quarantine refers to restricted movement of those who have been exposed to a contagious disease but who may or may not become ill, whereas isolation applies to restricted movement of persons that are known to be ill with a contagious disease.

Modern quarantine includes a range of disease control strategies that may be used individually or in combination, including: short-term voluntary home curfew, restriction on the assembly of groups of people, cancellation of public events, closure of mass transit systems, and other restrictions of travel.

When planning to care for those in quarantine, one must take account of the multiple psychosocial impacts that the experience of quarantine may have upon patients and their families, workplaces, and communities.

This paper gives an overview of the issues that have arisen when using quarantine to manage infectious disease outbreaks in the past and offers some insights and guidance into how to help manage the psychosocial impact of such restrictions.

Issues concerning people in quarantine or isolation and their families

Maunder et al (2003) reported the results of a study in Toronto, Canada concerning the establishment of a leadership command team and a SARS isolation unit. Patients with SARS reported fear, loneliness, boredom, and anger and they worried about the effects of quarantine and contagion on family members and friends.

Identifying recent contacts for quarantine also provoked fears that the patient would be resented. Staff members were also adversely affected by fear of contagion and of infecting family, friends, and colleagues.
Caring for healthcare workers as both patients and colleagues was emotionally difficult for all involved, and uncertainty and stigmatisation were dominant themes for both staff and patients.

The wider hospital inpatient system was also affected in that there was a need for quarantine upon discharge, or delayed discharge. Patients who were without SARS nevertheless were deprived of family visits and experienced insomnia, anxiety, and interpersonal friction with staff. Limited access to external resources which would normally provide comfort such as books, music, and toiletries also resulted in difficulty. Asian patients also reported stigmatisation and racist reactions in the community because the outbreak was thought to have originated in China.

These findings were also supported by Tansey et al (2007) in a study examining one-year outcomes and healthcare utilisation in survivors of SARS. Many patients experienced social stigmatisation and loss of anonymity and many described the emotional strain of quarantine and isolation.

**Issues concerning staff—as healthcare workers and patients**

Staff can often have complex and conflicting thoughts and feelings about working during a public health emergency. Healthcare staff asked to work during the SARS outbreak in Toronto in 2003 reported feeling conflicted between their roles as healthcare providers and parents, feeling professional responsibility but also feeling fear and guilt about potentially exposing their families to infection.¹

Robertson et al (2004) interviewed 10 healthcare workers in Toronto who were quarantined at home for 10 days because of their exposure to SARS and were willing to discuss their experiences. They described experiences that could be categorised as loss, duty, and conflict.

Robertson et al found that workers who treated SARS patients described the likelihood of contracting SARS as ‘bad luck’ or ‘fate’ and spoke of the risk pragmatically. Being in quarantine and the need to have to restrict physical contact, to wear a mask, and to remain at home has far-reaching consequences, including loss of intimacy and social contact, culminating in physical and psychological isolation. For example, close family members would no longer hug the healthcare worker.

Parents had to confront changes in normal roles and routines, creating stress for entire families. Most found it difficult to explain the situation to their children without provoking more fear. Healthcare workers felt a duty to protect their children from being taunted or stigmatised by association. Spouses were physically isolated, for example, partners slept in separate rooms and were subjected to further pressure as they assumed responsibilities involving the outside world, such as school runs and shopping, as well as normal routine activities.

In addition to the physical isolation, healthcare workers experienced isolation and stigma as a result of their exposure to SARS. Although most workers rationalised this as a lack of understanding about the illness or the risks involved, all described feeling angry and hurt. Even after the outbreak had been contained and individuals’ quarantine had ended, workers remained acutely aware of others’ reactions. To avoid the negative response, one worker even denied being a healthcare worker from Toronto.
The psychological consequences of exposure to SARS were expressed in both physical and psychological symptoms. Participants reported emotional strain, sleeping problems and physical symptoms such as shortness of breath and headaches, which they attributed to continually wearing protective masks.

A predominant theme in the SARS literature is whether healthcare workers have a duty to treat high-risk patients. While none of these participants in the Robertson et al study refused to perform their duties, the fear and anxiety associated with the risk of contracting SARS was prominent in their minds.

Robertson et al also found that although their duty as healthcare workers was performed, the dual role of both healthcare worker and family member caused several conflicts. Participants were particularly concerned about infecting family and friends they considered vulnerable.

Conflict was also reported between workers who continued working in high-risk situations and the so-called ‘non-essential’ staff members who remained at home and were paid. However, the sense of camaraderie that prevailed amongst those who continued to work and the social contact of working together were seen as positive developments.

Further to these Canadian reports, a study of emergency department staff in Taiwan during the SARS outbreak of 2003 also found that healthcare workers were worried about their anticipated overtime hours if other staff were quarantined, as well as the stigma of the illness and the health of their families and themselves.

More recently, Taylor et al found considerable impact on those people affected by quarantine measures during the Australian equine influenza outbreak in 2007. Sixty-four percent of survey respondents believed that reduced contact and movement restriction measures were being followed less strictly by others than by themselves. A significant proportion also indicated problems with reduced contact, quarantine and isolation: 13% indicated problems with visitors or visiting others, 13% reported feeling isolated, and 9% indicated general emotional distress.

The importance of clear and transparent information in managing perceptions of public health risks

Staff frequently reported feeling angry about the spread of SARS and the lack of (or conflicting), information given by management and public health authorities. Many learned of their quarantine through media coverage before their managers informed them. Many could not reach public health authorities for information although others realised that the lack of reliable information was a result of SARS being a new condition and that the authorities and management were doing their best to respond to emerging new information.

The lack of clear guidelines on how to minimise infection at home and in quarantine can add to individuals’ fears of contaminating family members and to their uncertainty regarding effective risk control. This uncertainty has been argued to add to individuals’ sense of unease and increased their perception of personal danger.

As can be seen above, the importance of clear and unambiguous information in a disease outbreak is paramount. At a broader level, Brahmbhatt and Dutta’s 2008
review of behavioural analogues apparent in health and economic emergencies illustrates that there is a need for coherent, consistent, and easily accessible information from public health authorities, infection-control experts, and healthcare management.  

Recent theoretical work on information cascades and herding behaviour suggests that in situations of obscure information (such as the early stages of a disease outbreak), people may rationally look to the behaviour of others as a source of information. This process can lead large numbers of people to the same incorrect conclusions and unhelpful decisions.

It seems reasonably likely that under the conditions of high uncertainty, poor information, rapid change and emotional stress that exist during an infectious disease outbreak, individuals could arrive at significantly biased subjective assessments on key factual issues, at least for a time. This could lead to an over-estimation of the infection risk and to making less than optimal decisions regarding preventative actions, such as not complying with quarantine restrictions, fleeing, or quitting their jobs prematurely.

Public opinion surveys taken during SARS suggest that people at times held excessively high perceptions of the risk of becoming infected with SARS, or if infected, of dying of the disease. However, other survey evidence also indicates that people are constantly trying to update and improve their subjective probability estimates.

All of this means that the role of information and communication in public health policy and response becomes pivotal. Accurate and timely information needs to be released through official sources to help reduce unwarranted panic and emotional distress and to help people form more realistic probability assessments of subjective risk.

In the early stages of a limited disease outbreak, there may be considerable uncertainty as to whether it will turn into an epidemic or merely disappear. Authorities may often adopt a ‘wait and see’ approach, especially if an official announcement may trigger the kinds of severe trade and travel restrictions that were imposed on India during the 1994 Surat plague outbreak.

However, against these possible benefits must be balanced against the increased risk of the outbreak turning into a full blown epidemic because of secrecy and delays in launching public health measures or in calling for international assistance.

Modern developments in the plethora of non-official sources of information (e.g. rumours via cell phone or the Internet) mean that unless authorities take proactive steps to ensure otherwise, inaccurate sources of non-official information may undermine credibility, fostering even greater panic, uncertainty and possible foreign sanctions.

A transparent and credible public information strategy at all levels is likely to be the best way to minimise unwarranted panic and increase adherence to public health measures through mobilising the public as a partner in controlling the disease outbreak. An example of this is the information strategy adopted by Singapore during the SARS crisis.
Recommendations and possible interventions

For people in quarantine or isolation: The experience of stress should be taken to be understandable as a universally experienced response to extraordinary life circumstances. Stressors should be identified, articulated and normalised as much as possible. Ensure that the affected person has someone they can talk to who they trust and is knowledgeable about the situation.

For most people the range of normal reactions, such as anxiety and preoccupation should not be viewed as pathological but should be understood and perhaps realigned in order to help adaptation to public health measures.

Psychological advice and pharmacological interventions addressing inability to sleep should be readily available as sleep deprivation is likely to exacerbate other difficulties.

Early on in the SARS crises, the mode of transmission of the disease was unknown and all person-to-person contact was minimised. However, some people in quarantine reported that healthcare workers insisted on spending time with and giving emotional support to them, and this helped to reduce their feelings of fear, anxiety and isolation.

People in isolation or quarantine experience a range of economic and practical problems. Although most of these problems fall outside the health or front-line worker’s expertise and control, the worker can help affected people to obtain needed services by referring them to appropriate agencies through civil defence and welfare agency contacts.

Measures to reduce the negative impact of social isolation could include creative solutions to increase effective interpersonal communication, and efforts to provide accurate information to the media to reduce stigmatising reports. Possible tools for improved communication with loved ones could include access to the internet for email and teleconferencing software such as Skype.

Telephone contact is likely to be highly acceptable and helpful though this would have to be considered within the physical limitations of the quarantine areas. Access to newspapers and television may help people maintain a sense of connectedness with the outside world.

For staff members: The acute stress of working with potentially highly infectious patients should be recognised and acknowledged. Easily accessible practical advice on coping strategies and stress management at work and at home may be useful. Service managers may want to liaise with organisational EAP or occupational health providers concerning this. Other technical advice such as infection prevention control is readily available at the Ministry of Health website.

Authorities can positively support efforts to reduce the job stress that is generated by increased workload and assignment to unfamiliar tasks. In past quarantine episodes, occupational health staff have developed pamphlets identifying signs of anxiety and stress and information about support resources which were distributed to every nursing unit involved in quarantine measures.

For those healthcare professionals or other front-line staff working in dangerous conditions, accessible and timely referral paths should be developed for the few who
may require mental health services. For example, a confidential telephone support line set up by staff with knowledge and training to be made available for those staff members in quarantine. Just the knowledge that support is available may suffice for many resilient staff members. There is also an opportunity for leadership by example where service-managers advocate and use peer-support.

Issues regarding stigma for health workers or front-line staff involved in quarantine responses are understandable and are likely to subside only when public information and role modelling by authorities at all levels are improved.

Many of the psychosocial consequences described above can be predicted and measures put in place to address them during pre-emergency times. Other issues may come to light during the event. For example, people being transported from airports to quarantine areas before having uploaded their baggage can be without personal items such vital medication for days. Other issues such as boredom or lack of food can lead to quarantine rules being breached. Ongoing assessment of need is crucial if we are to help people to comfortably comply with these public health restrictions.

**Competing interests:** None known.

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**References:**

Do those afflicted with dementia have a moral duty to die? A response to Baroness Warnock

Phillipa J Malpas

Abstract
In October 2008 Baroness Warnock, medical ethicist and veteran British governmental advisor, claimed that an individual afflicted with dementia may have a moral duty to die when their continued living “wastes” the lives of others and the resources of the National Health Service. Her comments were widely publicised and largely condemned by those who responded.

In this paper I consider the comments made by Baroness Warnock. She claims that some individuals and groups within society may have a moral duty to die when their lives become burdensome either to themselves or to others. I conclude that no-one has a moral duty to die, but especially not those who are afflicted with dementia.

Our population is rapidly aging and more people now die of serious chronic diseases instead of acute illnesses. Health care resources are under increasing pressure. In New Zealand, people over the age of 65 currently make up around 12% of the population but they use 37% of total public health expenditure. In 2008 nearly 41,000 people had dementia; by 2050 it is predicted that over 44,000 new cases of dementia will occur each year.

We need to address how we will care for those who are near the ends of their lives; especially as that care will increasingly require more human and health care resources.

In October 2008 Baroness Warnock, medical ethicist and veteran British governmental advisor, claimed that individuals afflicted with dementia may have a moral duty to die when their continued living “wastes” the lives of others and the resources of the National Health Service. Her comments were widely publicised and largely condemned by those who responded.

Warnock stated the following in the interview she gave to the Church of Scotland’s Life and Work magazine:

If you’re demented, you’re wasting people’s lives—your family’s lives—and you’re wasting the resources of the National Health Service. I’m absolutely, fully in agreement with the argument that if pain is insufferable, then someone should be given help to die, but I feel there’s a wider argument that if somebody absolutely, desperately wants to die because they’re a burden to their family, or the state, then I think they too should be allowed to die.

Actually I’ve just written an article called “A duty to die?” for a Norwegian periodical. I wrote it really suggesting that there’s nothing wrong with feeling you ought to do so for the sake of others as well as yourself. If you’ve an advanced directive, appointing someone else to act on your behalf, if you become incapacitated, then I think there is a hope that your advocate may say that you would not wish to live in this condition so please try to help her die. I think that’s the way the future will go, putting it rather brutally, you’d be licensing people to put others down. Actually I think why not, because the real person has gone already and all that’s left is just the body of the person, and nobody wants to be remembered in this condition.
Warnock’s comments are not made in isolation. Over the past two decades many commentators have both supported and criticised the claim that some members of society may have a moral duty to die,\(^5,6\) and not just those who are afflicted with dementia.\(^7\) Indeed John Hardwig claimed there “can be a duty to die even when one would prefer to live”.\(^8\)

Should we pay any attention to the claims that some individuals or groups may have a duty to die, or should we dismiss such claims as the misguided comments of individuals out of touch with society and reality?

Although it is easy to reject the comments made by Warnock and others as offensive it is important to look at what they say because their comments may have practical and conceptual implications for those near the end of life. For instance: in policy decision making, or in (not so) subtle societal pressuring of those near the end of life to ‘hurry up and die’.

This issue is far from theoretical. If we accept the claim that individuals do have a duty to die we may shift the burden of proof to now requiring those same individuals justify their continued existence.\(^9\) Making explicit what was said and responding to it critically and deliberatively advances informed debate.

What exactly is Warnock stating in her interview? She makes a number of different claims:

- Those who are afflicted with dementia are wasting the lives of their families and so may have a duty to die
- Those who are afflicted with dementia are wasting precious health care resources and so may have a duty to die
- Assisting another individual to die is morally appropriate if that person is suffering unbearably and wants help to die
- If someone feels they are a burden on their loved ones, they should be allowed to die. Warnock is not clear whether this means they should be actively assisted to die (euthanasia), or whether their decision to voluntarily stop eating and drinking, to have medical treatment withdrawn, or to invoke a DNR order (letting die), should be respected
- If a person has an advance directive stating they do not wish to continue living if they were to become incapacitated by dementia, their advocate should be authorised to request assistance for the person to die (it is not clear whether this implies that a health professional should hasten their death)
- If personhood (the “real person”) is lost we are justified in putting those persons who are incapacitated “down”

Warnock raises an important point about the ethical permissibility of assisting competent individuals who are suffering unbearably to die. She quite clearly advocates euthanasia or physician-assisted suicide for those persons who make an explicit request for death.

The focus of this paper however is not on the ethical (im)permissibility of euthanasia or physician-assisted suicide, but rather on critically discussing two claims she makes:
first; that individuals afflicted with dementia have a duty to die because they are a burden on their families, and second; that because individuals with dementia are not persons but merely bodies, we (who exactly?) are morally justified in ending their lives.

Before discussing her two claims, it is important to be clear exactly what is meant by the terms, ‘duty’ and ‘moral duty’ for these are crucial to the claims she makes and the conclusions she reaches.

**Duties**

Philosopher Joel Feinberg states that “a duty, whatever else it be, is something required of one”. In other words if we have a duty, we are required to do or to refrain from doing something.

A duty may be imposed by law such as one’s duty to pay taxes and debts, or as in New Zealand, to register on the electoral role in order to vote. Similarly I have professional duties that oblige me to perform certain tasks—turning up prepared to lectures and marking student’s assignments on time. These duties issue from the legally binding contract I have with my employer to carry out certain professional requirements.

A duty may also be required by morality. Thus I have duties that compel me to follow or refrain from certain actions that are derived from moral rules. For instance, I have moral duties to tell the truth, to refrain from harming innocent others, to keep my promises, and respect the property of others. Some of these are also legal duties.

It has been argued I also have moral duties to give to the poor, or to participate in biomedical research. Essentially if I have a moral duty I am required by moral reason to act or refrain from acting in certain ways. I owe something important to others. If I do not fulfil the demands of my moral duties I act immorally and can be judged morally blameworthy.

Central to having and therefore fulfilling my duties to others is my capacity to understand what is required of me. If I do not have the capacity to reason and reflect on what it means to have duties to others; to understand how my actions impinge on those around me; and the ability to communicate with others, I do not and cannot have duties to others. This is because I am not responsible for my actions (or indeed my omissions).

What this means is that some individuals and groups in society have no duties (either moral or legal) to others. These are the most vulnerable members of our community. I will comment on this further where I discuss the issue of personhood.

**Individuals with dementia have a duty to die because they are a burden on their families**

When Warnock claims that individuals with dementia have a moral duty to die, what specifically is she saying? *Prima facie*, it would appear that if someone had a duty to die it meant morality required that their lives ought to end (presumably sooner rather than later). They are obliged to die. In fact if the individual did not fulfil their duty to die they would be morally blameworthy.
Is it possible morality might demand such a duty of us? Warnock’s claim would seem to issue from two positions: first that we have important filial duties that emerge from the special ties we have with our families, and second that we have a duty not to become a burden on the health care system (I will not address this latter duty).

What kind of duties do we have to members of our family? At the heart of the family are the relationships we have with others—to our siblings, our parents, and extended family members, and them to us. Generally these relationships are defined by love and nurturance, respect, reciprocity, and seeking the good of the other.14

It has been suggested that grown children have special duties to their parents for several reasons: as parents do so much for their children, children owe their parents in return. Parents do good things for their children, therefore children have a debt of gratitude, and the relationship between children and their parents is one of friendship—“the duties between grown children and their parents are the duties of friends.”15

Very little however, has been written on the duties elderly parents may have to their grown children, especially in relation to a putative duty to die. This area requires more critical thought and discussion.

Warnock claims that elderly individuals afflicted by dementia may have a duty to their families to die when they become a burden on them (financially and emotionally). However, we are not required by the dictates of morality to sacrifice so much for others that our lives become impoverished.

In other words, our duties to others are not so demanding that we must give to the point of exhaustion so that our lives and goals are adversely affected. Of course there is a valid question here about how much we ought to give, and obviously some families and individuals are in a position to give far more than others.

But even if we have reached the point where we cannot give any more to our family—either financially or emotionally—it does not follow that another must now make plans to end their life because duty demands it.

I noted earlier that what is central to most families are the special ties of love, nurturance, respect and reciprocity that bind us together. It is therefore rather surprising to claim that these same ties also demand that when the going gets tough, those who are a burden should get going (and die).

Warnock comments, “if you’re demented, you’re wasting people’s lives—your family’s lives—and you’re wasting the resources of the National Health Service”. The word ‘wasting’ is surely instructive here.

Warnock suggests that the fact I am afflicted with dementia implies my family’s lives will be ruined, leading to her assertion that it would be better for them if I was dead. And there is evidence that for some families, the financial and emotional costs of caring for those relatives with dementia is burdensome and onerous.16,17

But dementia is not a ‘one size fits all’ condition. An individual’s progression of dementia can pass through a number of different stages from very mild cognitive decline, where an individual can live reasonably independently with some assistance, to very severe cognitive decline where verbal abilities are lost, the individual requires
assistance with every facet of care and they lose basic psychomotor skills such as walking, sitting, and head control.  

Although there is considerable overlap between the various stages of dementia it is surely mistaken to categorize all those afflicted with dementia as wasting the lives of their families, or placing unreasonable sacrifices on them, requiring at the end of the day, a duty to die.

Many individuals will remain involved and interested in their families and will continue to contribute as loving and productive members. Others will require assistance that will be gladly and unselfishly given by their families.

**Individuals afflicted with dementia are not persons but merely bodies**

Warnock states:

> I’m absolutely, fully in agreement with the argument that if pain is insufferable, then someone should be given help to die, but I feel there’s a wider argument that if somebody absolutely, desperately wants to die because they’re a burden to their family, or the state, then I think they too should be allowed to die.

Receiving assistance to die because suffering is unbearable, and being allowed to die *(how exactly is one allowed to die?) because one believes one is a burden are two very different claims. I may believe I am a burden to my family because I require considerable care but that does not entail a duty to die.

Warnock continues:

> If you’ve an advanced directive, appointing someone else to act on your behalf, if you become incapacitated, then I think there is a hope that your advocate may say that you would not wish to live in this condition so please try to help her die. I think that’s the way the future will go, putting it rather brutally, you’d be licensing people to put others down. Actually I think why not, because the real person has gone already and all that’s left is just the body of the person, and nobody wants to be remembered in this condition.

It is what she claims at the end of this passage that is illuminating and disturbing. What Warnock actually seems to be suggesting is that being a person is what really matters in the context of those elderly afflicted with dementia. It is not that I have a duty to die because I have dementia and am a burden on others; rather, it is because I am no longer a person. I am just a body. It is important therefore to consider what it means to be a person.

What does it mean to be a person, and if you are not a person, what might follow? Philosophically speaking, the issue of personhood is a complex and contentious one. Generally speaking, persons are those entities who have the capacity to reason and reflect, to have preferences, to be able to communicate with others, to interact socially with others, to have feelings, to experience pleasure and pain, to be conscious (the ability to consider oneself as oneself), and self-aware (awareness of oneself existing over time).

> These are the capacities that contribute to making human life valuable. They accord us respect, protection, concern and understanding. To be a person then is to matter morally; and to have rights against, and duties to others. Non-persons do not and can not have duties or responsibilities to others.
“To identify individuals as persons is to bring them into the same moral category as ourselves and to judge someone to be a pre-person or a non-person is to distance them in some sense from ourselves”.19

As noted earlier, how we understand the importance and relevance of these capacities is challenging. What if I have feelings and experience pleasure and pain yet I am not self aware? Am I still a person? If the capacity to reason and reflect is all that is required to be respected as a person, then many individuals will never become persons and many will lose their personhood status at some point in their lives.

There is a further point to be made about whether individuals could be more or less of a person depending on their capacities: is there some kind of hierarchy of capacities – do some confer greater importance than others? In other words, could some persons be considered more or less important than others simply on the basis of the capacities they possess?

Harris19 argues that if what we are really asking is what kinds of lives are ultimately valuable, we will answer that it is the lives of those who can value his or her own existence. We are still left though with the important question of how we understand those lives when the individual cannot value his or her own existence.

What are we to make of the individual afflicted with dementia who cannot reason or reflect, has no capacity to consider oneself over time anymore, and who does not value his or her own existence? What indeed! According to Warnock such a person is just a body, a shell, of little concern or consequence. Coupled with the fact that such a person wastes precious resources (both human and health care), and is a burden on their family is enough to justify Warnock’s charge that individuals with dementia should be assisted to die.

But this has nothing at all to do with any moral requirement to die. It would appear to have far more to do with attempting to justify ending the lives of individuals whom society views as worthless, burdensome, and of little value.

Warnock claims that it would be morally permissible to end someone’s life because they are no longer a person. She steps beyond respecting a competent, autonomous individuals advance directive not to endure living a certain way (which many individuals have some sympathy for), to claiming that dementia negates personhood and that alone is sufficient reason to justify ‘assisting’ them to die.

Warnock is not clear how we assist such individuals to die. Do we fail to provide nutrition and hydration; do we withdraw or withhold medical treatment so that death will be hastened; or do we introduce a lethal threat such as a fatal bolus? What if there is no medical treatment to withhold or withdraw?

Warnock surely steps on dangerous ground for there are many others who also stand perilously close to those who are afflicted with dementia in terms of lacking personhood. If those with dementia are non-persons—bodies—who waste precious, scarce resources then what of those who also take up valuable resources who are also not persons?

For instance, those in persistent vegetative states, those in a coma, the very young and the severely cognitively disabled? Perhaps they too have a duty to die. But this cannot
be the case for as Warnock has suggested those with dementia are not persons. If they are not persons—merely bodies—they cannot have a moral duty to die.

It would seem then that what Warnock is really suggesting is that certain individuals ought to die, not because they have any moral duty, but rather because they are burdensome as they waste valuable human and health care resources. And allegedly because they are merely bodies with little or no value to the rest of us, their death is preferred to their living. Coming to such a conclusion is abhorrent for it attempts to justify terminating the lives of the most vulnerable and powerless under the guise of moral duty.

I argue it is not morally appropriate to place so much importance on the concept of personhood in the context of thinking about the moral status of those elderly afflicted with dementia. The more important moral duty here is the duty of care to those who are vulnerable and near the end of their lives.

In responding to Hardwig’s claim that “we fear death too much”, Hentoff pithily states, “my sense is we do not fear bioethicists enough”. Those with dementia have no moral duty to die; but perhaps they have much to fear from certain others.

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Myocardial bridging in aborted sudden death: just an innocent bystander?

Paul Knaapen, Marco J W Götte, Carel C de Cock

Without notable prodromes or chest trauma, a previously healthy 17-year-old adolescent male collapsed while playing soccer. Upon arrival of the paramedics, ventricular fibrillation was diagnosed for which he was successfully defibrillated followed by immediate restoration of circulation.

Apart from a transient borderline prolongation of the QT interval, there were no significant electrocardiographic abnormalities. He was transferred to our clinic and hypothermia was induced for a period of 24 hours to limit the extent of cerebral injury.

Only a mild elevation of serum troponine T levels was detected during serial blood examination and electrolytes levels and inflammation markers were within normal limits. In addition, toxicological tests were negative. A couple of days after admission, the patient regained consciousness but unfortunately suffered from postanoxic encephalopathy mainly characterised by persistent short-term memory loss. His relatives reported no cases of sudden death in next of kin.

After echocardiographic evaluation, which did not reveal any pathology, the diagnostic work-up was extended by contrast-enhanced cardiovascular magnetic resonance imaging. The latter confirmed the echocardiographic findings and displayed normal cardiac function without structural cardiac abnormalities. Particularly, there were no signs of arrhythmogenic right ventricular or hypertrophic cardiomyopathy and anomalies of the proximal course of the coronary arteries were excluded. Late contrast-enhanced images did not display any myocardial scar.

Given the transient mildly prolonged QT interval, although likely attributable to the post-resuscitation ischemic conditions of the heart, genetic testing for long QT syndromes types 1 to 3 was performed and yielded negative results.

Finally, coronary angiography was performed, which revealed marked bridging of the left descending coronary artery (Figure 1 including video clip). An extensive period of electrocardiographic observation did not show signs of ischemia, even during tachycardia with heart rates up to 180 beats per minute.
Myocardial bridging of the coronary arteries is an anomaly characterised by a segmental course of the vessel that runs intramurally. During systole the artery is compressed and on angiography a dynamic phasic obstruction is observed also referred to as ‘milking’. This condition is relatively common and generally considered benign as myocardial perfusion is a predominant diastolic process.

Nonetheless, myocardial ischemia and sudden death have been linked to myocardial bridging. A causal role, however, between bridging and sudden death has been difficult to establish owing to the anecdotal nature of available reports and the high prevalence of concomitant pathology such as hypertrophic cardiomyopathy and atherosclerotic coronary artery disease. Furthermore, diagnostic evaluation of alternative potential fatal cardiac pathology has not always been thorough in these observational studies.

Although case series have explored the value of coronary stenting and surgical bypass grafting or myotomy, these treatment strategies should still be considered experimental. Due to the lack of prior symptoms and absence of electrocardiographic signs of ischemia in our patient, we favoured a conservative therapeutic approach regarding the coronary anomaly and implanted a cardioverter defibrillator.
So the question remains whether myocardial bridging is just an innocent bystander or the actual perpetrator in this unfortunate young male.

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A case of vasoactive intestinal polypeptideoma

John Sycamnias, Britta Strahl, Peter Stride, Boris Chern, Lasanthi Paranavithana

Vasoactive Intestinal Polypeptideomas (VIPomas) are very rare tumours with an annual incidence of 1 in 10 million and a 10-year survival rate of 25%. We describe a case with instructive features as follows:

- The patient has survived 12 years without surgical treatment for the VIPoma in spite of hepatic metastases on the initial presentation.
- The diagnosis can be obscured by the ability of neuroendocrine tumours to secrete multiple hormones.
- The addition of glucocorticoid therapy to octreotide can be life-saving when intractable diarrhoea leads to severe metabolic problems.
- Intercurrent diseases can be successfully treated on their own merits, without considering the prognosis to be poor.

Initial case presentation and investigations

A 56-year-old male presented interstate 12 years previously with a 6-month history of progressively worsening explosive diarrhoea without blood or mucus. He had a weight loss of 10 kg in 6 months, but no associated sweating, hot flushes, or respiratory symptoms. He was a moderate drinker and smoker, denied recent overseas travel, and there was no family history of inflammatory bowel disease or malignancies. Current therapy included ranitidine, diclofenac, and allopurinol. Examination revealed an obese, afebrile man of 150 kg with multiple skin tags. There was no evidence of acromegaly, thyroid enlargement, fundal abnormalities, or abdominal organomegaly. Cardiovascular and respiratory examination was unremarkable.

CT demonstrated at least three liver lesions (Figure 1) and a pancreatic mass. (Figure 2). Two 24-hr urine collections without dietary restrictions revealed a moderately elevated 5HIAA at 39 and 34 µmol/24 hours. Fine needle biopsies of the liver and pancreatic lesions were performed and the histology showed well-differentiated epithelial cells with abundant cytoplasm and eccentric nuclei consistent with a neuroendocrine carcinoid tumour, but immunohistochemistry was not performed. Metastatic carcinoid disease was diagnosed.
Figure 1. CT demonstrating a multitude of calcified metastatic liver lesions

Figure 2. Pancreatic head lesion and several calcified liver lesions

Treatment and progress

The patient moved to Queensland in 1999. Octreotide 150 mcg SC twice daily was commenced but soon ceased due to intolerable side effects including nausea and hot flushes. Persistent diarrhoea, even while using octreotide, necessitated the use of spironolactone for hypokalaemia, plus large doses of loperamide. The next CT scan showed progressive disease; hence palliative chemotherapy with weekly 5-Fluorouracil was administered, given as two 12-week cycles with a 6-week break.

A trial of octreotide 50 mcg daily was tolerated; therefore the dose was gradually increased over the next few months with reasonable symptomatic control. Type 2 diabetes was diagnosed when the patient developed polydipsia, polyuria, lethargy, blurred vision, and a fasting sugar of 10.8 mmol/L. The diarrhoea deteriorated again, therefore octreotide was increased to octreotide LAR 30 mg (a slow-release preparation) monthly, with octreotide 150 mcg SC daily.

His condition deteriorated. Stool output increased to 7500 ml per day with increasing dehydration and, despite the use of outpatient fluid supplements and bicarbonate, he developed renal failure and hypokalaemic acidosis. He required ICU admission where his chart recorded “Patient has profuse diarrhoea with metabolic mayhem”. At this stage his potassium was 2.4 mmol/L, bicarbonate 8 mmol/L, pH 7.28, and stool output was 1000 ml per hour. An octreotide infusion (120 mcg daily) was commenced with total parenteral nutrition, re-hydration, pancreatic enzymes, loperamide, cholestyramine, folic acid, vitamin B+C, electrolyte replacement, and DVT prophylaxis was initiated.

Colonoscopy did not detect any abnormality and a stool culture grew non-pathogenic Blastocystis hominis. Surgical opinion was, “in desperation, a palliative resection of the pancreatic head and the right lobe of the liver could be considered”. However, because platelet serotonin level was within normal range and the diagnosis of
carcinoid was made only on a fine needle biopsy, alternative diagnoses were considered.

**Alternative diagnosis**

The patient was investigated for alternative diagnoses in 2001 and the detection of elevated levels of VIP at 440 pmol/L and 303 pmol/L (RR <50pmol/L) supported a diagnosis of VIPoma. The ability of neuroendocrine tumours to secrete many hormones is demonstrated by the raised urinary 5HIAA and intercurrent raised levels of glucagon 215 ng/L (RR 71–150 ng/L) and pancreatic polypeptide 170 pmol/L (RR <50pmol/L). Therefore hydrocortisone 100 mg QID was commenced. Stool output rapidly decreased while his urine output increased.

Soon he became fluid overloaded, requiring dramatic reduction of his IV fluids. Hydrocortisone was changed to prednisolone, initially 100 mg daily and then reduced to 50 mg daily, and finally substituted with dexamethasone. The octreotide infusion was ceased and octreotide 200 mcg SC QID commenced. An OctreoScan showed multiple foci of intense radiotracer in the liver and para-aortic regions consistent with metastatic neuroendocrine tumour and a three-phase CT scan confirmed the liver and pancreatic lesions.

**Recent progress.** Therapy since 2001 included:

- A trial with an experimental radioisotope Y⁹⁰ SMT 487 (Novartis)—3 doses over 3 months with some symptomatic relief.
- Various doses of octreotide (including octreotide LAR), loperamide, and steroids including pulse methylprednisolone. Octreotide had been prescribed nearly continuously for 10 years.
- Two 12-week cycles (with a 6-week break) of 5-Fluorouracil with folinic acid tried with minimal benefit.
- Methotrexate 10–15 mg weekly for several months as a steroid sparing agent because dexamethasone caused serious problems including numerous petechial haemorrhages, proximal myopathy and weight gain to 165 kg with associated sleep apnoea.
- CT scans of the abdomen have detected essentially unchanged calcified hepatic metastases over an 11 year period, and, a primary pancreatic lesion. He remains in reasonable health with no evidence of disease progression in 2008.

**Comorbid conditions**

Multiple other problems have occurred over 10 years and been treated on their own merits as follows:

- Morbid obesity up to 211 kg treated with laparoscopic gastric banding following unsuccessful dietary restrictions.
- Total knee replacement 2002.
- Diverticular disease and a colonic tubular adenoma removed on colonoscopy 2005.
- CLO test negative gastritis detected on endoscopy 2005.
- Resumptive pulmonary embolus diagnosed on the basis of dyspnoea, hypoxia,
and positive d-dimer, though both CTPA and VQ scan were prevented by body habitus. Anticoagulation was commenced.

VIPoma—clinical features and pathophysiology

VIPomas are rare endocrine tumours that secrete excessive amounts of VIP, causing large-volume watery diarrhea in 100% of patients, hypokalemia in 80–100%, dehydration in 83%, hypochlorhydria in 60%, and flushing in 20%. VIP is a 28-amino-acid peptide neurotransmitter, first described by Bloom\(^1\) in 1973, that stimulates small-intestinal chloride secretion.\(^2\)

Eighty to 90% of adult VIPomas are located in the pancreas, and between 37 to 68% have hepatic metastases detected on initial presentation.\(^3\) Five percent of patients have the multiple endocrine neoplasia syndrome type 1 (MEN1) with other endocrine tumours. The secretory diarrhea produced has a low osmotic gap. An osmotic gap of >125 mOsm/kg is indicative of an osmotic diarrhea, while a gap of <50 mOsm/kg suggests a secretory diarrhea.\(^4\)

Over 90% of VIPomas, contain high concentrations of somatostatin receptors, therefore somatostatin receptor scintigraphy using a radiolabelled modality is useful for the detection of metastatic disease.\(^5\)

Current therapeutic options

Many authorities recommend early surgery for both the pancreatic primary tumour and hepatic metastases. Ghaferi reported 39 cases, with a mean follow-up time of 40 months; 17 patients had documented survival times between 2 months and 10 years and 1 patient had survived 20 years following a distal pancreatectomy for localised disease.\(^6\) Rothenstein presented 193 various neuroendocrine tumours and recommended initial surgery, including removal of hepatic metastases if possible, with 5-year survival of 85.9% after curative surgery compared to a 5-year survival of 41.3% of those who did not have curative surgery.\(^7\)

Surgical resection of hepatic metastases will not cure the majority of cases, but can palliate symptoms of hormone hypersecretion and prolong survival. Octreotide will control the diarrhea in 87% of patients\(^8\), though the inhibitory effect of octreotide on secretion of insulin, growth hormone and glucagon may cause problems. The use of steroids is often not mentioned in current reviews of VIPoma management,\(^8\) but successful responses of individual cases have been reported, and steroids will control most of the non-responders.\(^9\) Alternative therapies include interferon alpha, streptozocin, doxorubicin, temozolomide, radiofrequency ablation,\(^12\) cryo-ablation, peptide receptor radiotherapy,\(^14\) or orthotopic liver transplantation.

The median survival of patients with VIPomas is 103 months, with a 10-year survival of 25%. Zimmerman reported a single case 9-year follow-up, and Nguyen reported a 10-year follow-up in two patients, who (like our patient) also had hepatic metastases at presentation, where therapy included chemo-embolisation. Hepatic metastases are usually associated with a less favourable prognosis.
Conclusions—the “take home” message

- Prolonged survival with a VIPomas is possible with aggressive management of the hormonal effects of the tumour and of tumour growth.
- Prolonged survival is less frequent without tumour surgery and with hepatic metastases on presentation.
- The correct diagnosis may be confounded by the ability of neuroendocrine tumours to secrete more than one hormone.
- Steroids are usually beneficial if diarrhoea is not controlled by octreotide.
- Comorbidities should be treated on their own merits.
- Methotrexate may be a useful agent in helping control symptoms and tumour growth while sparing steroid use.

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An unusual case of inguinal pain
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Clinical
A fit and well 29-year-old presented with worsening catamenial right inguinal pain of 4 months duration. She had undergone six previous laparoscopies for pelvic endometriosis, most recently in 2006 in addition to a previous laparoscopic ventrosuspension (plication of round ligaments). Examination revealed exquisite tenderness over the right inguinal canal; no masses were palpable. Urine and blood tests were unremarkable including a negative pregnancy test.

A magnetic resonance imaging (MRI) scan was performed (Figure 1) and the patient underwent excision of the lesion under general anaesthetic (Figure 2). Histology is shown in Figure 3.

Figure 1. Axial T1-weighted MRI with fat suppressed
Figure 2. Surgical exploration right inguinal region

![Image of surgical exploration right inguinal region]

Figure 3. Histology of the excised lesion

![Image of histology of excised lesion]

What is the diagnosis?
Round ligament endometriosis

The MRI showed a multi-loculated 27×11 mm lesion within the right inguinal canal with high T1 signal (Figure 1) consistent with endometriosis. The section of the round ligament containing the lesion (Figure 2) was surgically excised. Histology demonstrated areas of endometrial-type epithelium with focal organising haemorrhage within the tubular fibrous and smooth muscle structure of the broad ligament.

Discussion

Endometriosis affects 5–10% of women of reproductive age. It is characterised by functional ectopic endometrial tissue, which can be symptomatic of dysmenorrhoea, dyspareunia, non-catamenial pain, and subfertility. Ectopic deposits are commonly found within the pelvis affecting the ovaries, uterosacral ligaments, peritoneum, pouch of Douglas, and rectovaginal septum.

Less commonly, extrapelvic endometriosis can be located in the abdominal wall, bowel, liver, urinary tract, lung, pleura and central nervous system. Inguinal canal endometriosis is a rare extrapelvic location. In this patient, the history of ventrosuspension is notable, although its role in the development of inguinal endometriosis is unclear.

Since the first case of inguinal endometriosis was described by Cullen in 1896, 85 cases have been reported worldwide. Presentation is typically symptomatic of catamenial groin pain at a mean age of 38 years. Examination may reveal a painful, palpable inguinal mass.

In about a quarter of patients, presentation is associated with a groin hernia. Over 90% of cases involve the right groin, but the reason for this predilection is unclear. Bilateral involvement is rare. Correct preoperative diagnosis is made in less than half of patients.

Current treatment involves surgical excision of the extraperitoneal portion of the round ligament and laparoscopy for intraperitoneal evaluation if it has not already been performed.

Competing interests: None known.

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References:

Aspiration of an incisor tooth in a poly-trauma patient
Ashraf F Hefny, Yousef El-Ashaal, Yassin B Ali, Fikri M Abu-Zidan

A 27-year-old male fell from a height of 3 metres. On arrival at the Emergency Department, his Glasgow Coma Score (GCS) was 4/15, pulse rate 80 bpm, and blood pressure 190/110 mmHg. He had bleeding from the nose and mouth, was missing an upper incisor tooth, and had surgical emphysema on the left side of the chest.

Endotracheal intubation was carried out and a left-side chest drain was inserted. Trauma CT scan showed cerebral oedema and multiple left-sided rib fractures with mild haemothorax.

Two days later, a repeat chest X-ray in ICU showed a sharp radio opaque shadow in the right bronchus (Figure 1).

Figure 1. Chest X-ray showing a sharp radio opaque shadow in the right main bronchus (arrow). An incisor tooth was removed by bronchoscopy (inset)

On reviewing the admission X-rays and CT scan, the same shadow was seen in the trachea, to the left side of the endotracheal tube (Figures 2 & 3).

Bronchoscopy was performed and an incisor tooth was removed from the right bronchus.
Aspiration of teeth may occur following facial injury.\textsuperscript{1} In our patient the tooth was originally in the trachea, to the left side of the endotracheal tube, but later moved to the right bronchus. An undiagnosed retained foreign body can be fatal. In the early stages, it can cause airway obstruction, overwhelming sepsis, and acute respiratory distress syndrome. Later on, it can cause unresolved pneumonia, lung abscess, recurrent haemoptysis, and bronchiectasis.\textsuperscript{2}

Our case emphasises the importance of early suspicion and being more observant on the original plain radiograph and CT scan, when a tooth has been lost in poly-trauma patients with any facial injuries and never assume it has been expelled.

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Some exploded theories and forgotten remedies in medicine: part 5 (fevers, racial degeneration)

Published in NZMJ 1909;7(29):51– and written by Dr De Lisle, District Health Officer for Hawke’s Bay. Read before the Annual Meeting of the B.M.A., Napier.


In comparatively recent times the heads of all fever patients were shaved. The theory being that the fever existed in the head, and it was necessary to keep it cool. This is an exploded theory and the practice is almost forgotten.

The theory that all inflammatory diseases needed dantiphlogistic treatment, mercury to salivation, venesection, cupping, counter-irritation, et hoc genus omne, has exploded. It is difficult to believe it in these days, but a cousin of mine was, in 1840, plucked in his examination for the diploma of the London College of Surgeons because he told the examiner that he would not bleed in a case erysipelas.

Even in these days there were men ahead of their time. Graves desired that the epitaph on his tombstone should be: “He fed fevers.” In the thirties there was a physician at St. Thomas’ Hospital who treated his fever cases much as they would be treated today. The students considered that he was an old woman, would not go round the wards with him, and took out their lectures on the practice of physic at the adjoining hospital, Guy’s. A gentleman I once knew who qualified in 1836 told me that he thought himself unfortunate to be appointed clinical clerk to this physician, but observed that he had a smaller death-rate than other members of the staff, and that while the patients of other men were sitting over the fire spitting, his patients were out of the hospital and at work.

Many of the older practitioners who had been brought up in the old treatment and had adopted the new, considered that the practice was right in both cases, but that constitutions had changed, and the men of the present day were weaker and had degenerated. We hear a great deal about the degeneration of our race, but I for one do not believe that there is any evidence of it. They were men of a stalwart race who won Agincourt, and on the four hundredth anniversary of that day four hundred and eighty out of six hundred equally stalwart men galloped to their death at Balaklava, drawing from our Gallic neighbours who witnessed it—a people none too generous in their appreciation of us—the compliment: “C’est magnifique,” adding, however, but perhaps more in sorrow than in censure, “Mais ce n’est pas la guerre.” And from the Russians we received the dubious compliment: “A lot of lions led by asses.”

Scarcely more than two years after India was reconquered by a handful of our race, one brigade of blue-jackets making the record march of one hundred and four miles in four days, dragging their guns and fighting on the way. Does this point to race degeneration? It is true that this happened fifty years ago, but what is half a century in the history of a nation.
Antithrombotic therapy in atrial fibrillation (AF)

Atrial fibrillation is a common cardiac arrhythmia that increases the risk of stroke by a factor of five.

Vitamin K antagonists and antiplatelet agents reduce the risk of stroke in subjects with AF by two-thirds and 20% respectively. However, because of the perceived difficulties—need for monitoring, drug interactions, and fear of haemorrhage—warfarin is used in only about half of AF patients and aspirin is used instead. In this study the triallists investigated the hypothesis that the addition of clopidogrel to aspirin would reduce the risk of vascular events in patients with AF.

They randomised AF patients to clopidogrel 75 mg daily and low-dose aspirin or placebo and aspirin. As expected the combination was significantly better at preventing strokes. However, the combination was significantly worse at producing major haemorrhage.

An editorial notes these results and points out that “the annual rates of stroke among participants receiving clopidogrel and aspirin (2.4%) or aspirin alone (3.3%) were notably higher than those reported among patients at high risk for stroke who received high-quality vitamin K-antagonist therapy (approximately 1.1 to 1.3%).”


Moxifloxacin, a new drug for the initial treatment of tuberculosis

Clinicians in third world countries have little interest in whether clopidogrel is better or worse than aspirin and/or warfarin. Newer, and of course, better statins or atypical antipsychotics are also of little concern to them. However, a new drug active against tuberculosis does command attention. And the fourth-generation fluoroquinolone moxifloxacin might prove to be just that.

In this randomised trial from Brazil 170 sputum smear positive patients were given isoniazid, rifampicin, and pyrazinamide at standard doses and were assigned to receive either moxifloxacin (400 mg) with an ethambutol placebo (n=85), or ethambutol (15–20 mg/kg) plus moxifloxacin placebo (n=85), 5 days per week for 8 weeks.

At 8 weeks, sputum culture was negative in 80% of the moxifloxacin cohort compared with 63% of the ethambutol group (p=0.03). There were 8 adverse reactions in each group. A promising start.


Interaction between proton pump inhibitors and clopidogrel?

A potentially important issue as both are commonly used. In particular, clopidogrel is used to prevent recurrence of myocardial infarction. The authors of this paper state...
that most proton pump inhibitors inhibit the bioactivation of clopidogrel to its active metabolite. Apparently clopidogrel bioactivation is mediated by hepatic cytochrome P450 isoenzymes, with cytochrome P450 2C19 playing a major role. And some proton pump inhibitors can inhibit this cytochrome. Does this matter in clinical practice?

In this case-control study the researchers demonstrate that it does. They show that in such patients—those with myocardial infarction treated with clopidogrel and proton pump inhibitors—there is an increased risk (odds ratio [OR] of 1.27) of reinfarction. However, pantoprazole is not an inhibitor of the cytochrome and the OR for reinfarction with pantoprazole treatment is 1.02.


Compulsive gambling or hypersexuality after drug treatment of idiopathic Parkinson disease (PD)

This topic has aroused some interest recently and this paper from the Mayo Clinic reviews the Minnesota experience over a 2-year period. The authors point out that in the literature pathologic gambling has been linked to dopamine agonist treatment: pramipexole, ropinirole, pergolide, cabergoline, or bromocriptine. In contrast, only rare cases of pathologic gambling has been associated with carbidopa/levodopa monotherapy.

In their study of 267 patients with PD they found 7 (2.6%) who developed such compulsive behaviour. These 7 patients amounted to 18.4% of 38 patients taking therapeutic doses of dopamine agonists. The compulsive behaviour was not found among untreated patients, those taking subtherapeutic agonist doses, or those taking carbidopa/levodopa alone. Fortunately the behaviour abated with cessation and dose reduction of the dopamine agonist therapy.


“Doc in a box” clinics in the United States

A time for an update on these retail medical clinics in drugstores, the Walmart chain, and other non-traditional locations in the United States.

They are usually staffed by nurse practitioners under some medical oversight, and confine themselves to a limited range of services such as sale of drugs for common infections and wounds, tests, and vaccinations.

The California Healthcare Foundation has reported that there are more than 1000 such clinics in 37 states and patient satisfaction is high—generally >90%. Patients like the extended hours, walk-in with no appointment, prompt service, and low costs. Apparently the cost is significantly lower than the cost of attending a doctor or an emergency department. All valid points, and also likely to take the pressure off emergency departments. However it makes one feel somewhat uncomfortable that significant underlying pathology might be missed.

Santé! Public health lessons from France for New Zealand

Public health workers in New Zealand often look for lessons from English-speaking countries. However, there are many potential lessons from other countries. Here we reflect on our in-the-field observations from visiting France in three major areas of public health: good nutrition, facilitating physical activity, and tobacco control. We supplemented our field observations (most recently for January 2009) with selected Medline and Google Scholar searches (conducted in March 2009).

- **Good nutrition**—In the south of France the more Mediterranean diet appears to provide significant health benefits.¹ This diet is generally focused on vegetables, fruits, legumes, and cereals (with olive oil as the major source of fat), and is in contrast to the typically atherogenic and thrombogenic diet in New Zealand.²

  A Mediterranean diet that emphasises plant foods over meat may also be more climate friendly by generating less greenhouse gases.³ The French also eat relatively less (at least compared to Americans) and portion sizes are smaller.⁴ Indeed, some authors have noted the irony that “although the French eat less than Americans, they seem to eat for a longer period of time, and hence have more food experience”.⁴

  French parental behaviour is also more favourable towards monitoring and restricting their children’s food intake than US counterparts.⁵ Workplaces often employ chefs in France to ensure that cafeteria food is of high quality. Schools even have nutritionists and poorer parents only pay a portion of the cost of school lunches.⁶ In contrast, New Zealand appears to have gone backwards in recently re-allowing “junk food” to be sold at schools.⁷ While New Zealand has no legal constraints on food marketing, France has at least required health warnings on “fast food” advertisements.

- **Facilitating physical activity**—Urban design in France (and Europe more generally) with densely populated towns and cities appears to favour walking and cycling relative to New Zealand cities. Walking is also supported by having efficient metro systems in major cities and cycling is promoted by having public cycle sharing schemes—e.g. in Paris and Lyon.⁸ Other pro-cycling factors described for other European countries such as “comprehensive traffic education and training of both cyclists and motorists, and a wide range of promotional events intended to generate enthusiasm and wide public support for cycling”⁹ appear to also apply to France.

  The road code in France even states that vehicle drivers need to leave a distance of at least 1m within cities and 1.5m outside cities when overtaking a cyclist.¹⁰ The high parking costs and higher fuel prices (relative to New Zealand) are also likely to encourage active transport in France.
Tobacco retail outlets—In general, New Zealand appears to lead in the key domains of tobacco control—i.e. the ones discussed in a recent review. Nevertheless, France appears to have a lower density of retail outlets as only licensed “tabacs” sell tobacco (and not supermarkets or petrol stations). We estimate that the density of outlets is around 1160 per million population in New Zealand compared to 520 per million population in France (for outlet numbers see refs 12,13). Furthermore, licensing provides opportunities for future developments in tobacco control such as tighter restrictions on how tobacco is sold and the removal of retail displays.

When considering these three areas, it would seem reasonable for New Zealand to seriously explore all of these public health lessons from France. However, we realise that highly efficient public transport systems may not be particularly cost-effective until New Zealand cities become much more compact and better designed.

Improvements in nutrition also face many obstacles, including vested commercial interests in the food production and marketing sectors. Yet the small and innovative nature of New Zealand society may make it relatively well placed to tackle these challenges in order to continue to better protect and also improve public health.

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References:


Transmission dynamics of the 1918 influenza pandemic in New Zealand: analyses of national and city data

Understanding the detailed transmission dynamics of previous influenza pandemics is crucial for planning an appropriate response to future pandemics. Although the Southern Hemisphere is fairly unique in that the countries in this hemisphere experienced the so-called “autumn wave” of the 1918 influenza pandemic (caused by influenza A virus [H1N1]) in the spring season, the transmission potential has been empirically explored only in a confined (military camp) setting in New Zealand and by using coarsely reported data in a city in Brazil.

To quantify the transmissibility of the 1918 influenza pandemic in a community setting, we investigated more detailed historical data in New Zealand and estimated the reproduction number, $R$, the average number of secondary cases generated by a single primary case. This estimate is in a country that did not successfully apply widespread public health control measures, and where the disease was possibly exacerbated by mass celebrations for the end of World War I.

We analysed influenza-attributed mortality in five large population groups: daily number of deaths in the three largest cities (Auckland, Wellington and Christchurch, all based on individual records) and the daily mortality report (per 100,000) for the entire North and South Islands (see Table 1). The data were for European populations only; unfortunately, the impact of the disease in the Maori population was not as well documented at this time (though Maori were nearly all residing outside of the main cities in 1918).

Figure 1 shows the observed temporal distributions from October-December, 1918. To estimate $R$, we investigated the initial growth phase (i.e. first 15 days). The historical data based on individual death certificates enabled us to ignore reporting delays and to assume exponential growth as seen in the onset of disease. During the initial growth phase, Malthusian (exponential) growth of death $i(t)$ at time $t$ with daily growth rate $r$ is expected, and we estimated $r$ using the following likelihood, which was based on an explicit stochastic birth process:

$$L(r, i_0) = \prod_{i=1}^{15} \left[ \frac{i(t) - 1}{i_0 - 1} \right] \exp(-i_0 rt)(1 - \exp(-rt))^{i(t) - i_0}$$

for $i_0 > 1$, where $i_0$ is the initial number of cases (which was jointly estimated).

Based on the detailed historical investigations by Geoffrey Rice, epidemic time $t = 1$ was counted from 17th October in Auckland and 1st November for other data. The generation time was assumed to be gamma-distributed with mean $\mu = 2.92$ days and variance $\sigma^2 = 5.57$ days, respectively. Solving an estimator of $R$ given $\mu$ and $\sigma$, $R$ was estimated by replacing $r$ in equation (1) by the right-hand side of
Since the generation time of influenza has yet to be fully clarified, we investigated the sensitivity of $R$ to different $\mu$. Moreover, since the proportion of symptomatic infections among the total number of infected individuals still remains unknown, we estimated the proportion using $R$ in three cities and examined the sensitivity to different case fatality proportions.

Table 1. The reproduction number of the 1918 influenza pandemic in New Zealand

<table>
<thead>
<tr>
<th>Main island / city</th>
<th>$R$ (95% CI)</th>
<th>AIC</th>
<th>Data source (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North Island</td>
<td>1.60 (1.47, 1.78)</td>
<td>77.1</td>
<td>5</td>
</tr>
<tr>
<td>South Island</td>
<td>1.47 (1.33, 1.68)</td>
<td>62.7</td>
<td>5</td>
</tr>
<tr>
<td>Auckland (North Island)</td>
<td>1.44 (1.33, 1.61)</td>
<td>68.7</td>
<td>4</td>
</tr>
<tr>
<td>Wellington (North Island)</td>
<td>1.55 (1.42, 1.76)</td>
<td>67.9</td>
<td>(Unpublished)*</td>
</tr>
<tr>
<td>Christchurch (South Island)</td>
<td>1.33 (1.22, 1.50)</td>
<td>50.5</td>
<td>(Unpublished)*</td>
</tr>
</tbody>
</table>

$^{1}R$, reproduction number; $^{2}$CI, confidence interval; $^{3}$AIC, Akaike information criterion ($= -2 \times \text{LogLikelihood} + 2 \times \text{parameters}$); $^{*}$Daily unpublished individual level mortality data supplied by Geoffrey Rice, the author of a large historical study. The 95% confidence intervals were derived from profile likelihood.

Figures 2A-C show the observed and predicted number of influenza deaths during the initial growth phase. The goodness-of-fit was assessed by Akaike Information Criterion, and the deviation did not significantly differ between the datasets (Table 1). Table 1 summarises the maximum likelihood estimates of $R$ for five populations. The expected values ranged from 1.3 to 1.6. Among the two cities in the North Island, Wellington yielded higher estimate (1.6) than that in Auckland (1.4), though the difference was not statistically significant.

The estimate for the South Island city of Christchurch was the lowest (1.3). The comparative size-relationship of $R$ was consistent with the crude mortality by the end of pandemic (795, 761 and 494 per 100,000 for Wellington, Auckland and Christchurch, respectively). It should be noted that $R$ for Auckland and Wellington was smaller than that for the entire North Island (1.6), indicating the importance of spatial spread at a local level.

Figure 2D shows the sensitivity of $R$ to different mean generation times in the plausible range. Given that the mean generation time $\mu$ ranges from 2 to 4 days, $R$ may lie in the range of 1.2 to 1.8. This brief work is the first to report $R$ for community transmission in the Southern Hemisphere for the 1918 pandemic with
detailed daily data. The estimates were consistent with those in the Northern Hemisphere and were close to the lower bound among previous published estimates.12-14

Figure 1. Epidemic curves of the 1918 influenza pandemic in New Zealand

(A) Reported daily mortality (per 100,000 inhabitants) in North and South Islands and (B-D) the absolute number of influenza deaths in the 3 largest cities: Auckland, Wellington and Christchurch (see Table 1 for data sources).

The tendency to be smaller than the estimates in the Northern Hemisphere may be related to virus-fitness to spring weather and social contact patterns in New Zealand. Within-country variations in $R$ indicated the importance of the detailed spatial and other heterogeneous patterns of spread. In particular, given that $R$ for the entire North and South Islands were greater than those for their major cities alone, detailed contact patterns (rather than crude measures such as urbanization and population density) have to be explored to elucidate the mechanism to yield different $R$ estimates.

Figure 2E shows the proportion of symptomatic infections as a function of the case fatality proportion. According to the available literature, we assumed that the case
fatality proportion of the 1918 influenza pandemic ranged from 0.5-10.0% with 2.0% as the most plausible community estimate.\textsuperscript{6,15} If the case fatality proportion is 1.5%, then 73.2-93.3% of infected individuals will develop symptoms. If 2.0%, then 54.9-70.0% of infected individuals are symptomatic. The probability of asymptomatic infection being up to 30.0-45.1% is consistent with a published estimate (at 33.3%) based on an analysis of meta-data of experimental infection with seasonal influenza viruses and also with the common epidemiological assumption in other studies.\textsuperscript{8,9}

**Figure 2. Transmission dynamics of the 1918 influenza pandemic in New Zealand**

(A-C) Observed (markers) and predicted (lines) numbers of influenza deaths during the early stage of the 1918 influenza pandemic in New Zealand. (A) Auckland; (B) Wellington (triangles and dashed line) and Christchurch (circles and dotted line); (C) North (X and thick continuous line) and South (Y and thick dashed line) Islands. (D) Sensitivity of the reproduction number to the different mean generation times; (E) Sensitivity of the proportion of symptomatic infections to the different case fatality proportion estimates.

Our estimates of $R$ for the 1918 pandemic in New Zealand appeared to be broadly consistent with previously suggested estimates for Northern Hemisphere settings\textsuperscript{12-14} and were close to the reported lower bound. Although $R$ for the 1918 pandemic is therefore not exceptionally large, it should be noted that the generation time is as short as 3 days and the proportion of asymptomatic infection is as large as 45%. The former characterises the rapidity of spread, and so pandemic plans have to involve the rapid and effective implementation of both non-pharmaceutical (e.g. social distancing measures) and pharmaceutical interventions (e.g. antivirals and possibly pandemic
vaccines). The issue of asymptomatic transmission further complicates control and so pandemic plans may need to consider this issue (e.g. media messages that encourage social distancing for all people; and stockpiles of rapid diagnostic tests to assist with case finding). But more research to clarify the relevance of asymptomatic infection in pandemic influenza is critical as although it might be common, its public health relevance (in terms of transmission) is far from clear.

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Interpretation of vitamin D status may be affected by alternative supplementation

Low vitamin D is considered a major public health issue and has been shown to be implicated in diseases such as type 1 diabetes mellitus, colorectal, breast and prostate cancer, hypertension and multiple sclerosis. Low vitamin D levels are common in New Zealand and consequently there is an increasing demand for plasma vitamin D analysis and vitamin D supplementation.

Imмуnoassay, either using manual kits or newer automated platforms, has been the main method of analysis for plasma vitamin D. Individual immunoassays have varying activity towards vitamin D3 (cholecalciferol) and plant or yeast derived vitamin D2 (ergocalciferol) indeed Roche have recently released an immunoassay which measures only vitamin D3.

An alternative method of analysis utilising tandem mass spectrometry allows separate determination of both vitamin D2 and D3 to derive the total plasma vitamin D status. Initially it was thought that vitamin D2 had a lower potency and half life than that of vitamin D3, but recent investigation suggests this may not be the case. While prescribed vitamin D supplementation in New Zealand is vitamin D3, vitamin D2 is also available for prescription and can be obtained widely from alternative sources.

Therefore, it is important to use techniques that are able to accurately quantitate vitamin D2 and vitamin D3 to avoid inadvertent overdosing or toxicity induced by either form of vitamin D supplementation. Practitioners who measure vitamin D should ensure that the laboratory they use measures vitamin D by the preferred mass spectrometry method.

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Time to implement the polypill approach

Two recently published landmark studies have added considerable support to the concept of a preventative cardiovascular polypill.

The first ever polypill study, The Indian Polycap Study (TIPS), showed that when low-dose cardiovascular medicines were combined into a single capsule, the physiological effects were approximately as would have been expected. Importantly, there was no unexpected increase in side effects resulting from having the medicines combined into one capsule, with less than 4% of the study participants who took the polycap leaving the study because of drug-related side effects.

The second study, from the authors who first proposed the polypill concept in 2003, was a meta-analysis of around 150 randomised trials of blood pressure lowering drugs recording CHD events and strokes, involving 464,000 participants. With few exceptions, “all classes of blood pressure lowering drugs were found to have a similar effect in reducing CHD events and stroke for a given reduction in blood pressure and the proportional reduction was the same or similar regardless of pretreatment blood pressure and the presence or absence of existing cardiovascular disease”.

Analyses showed that one drug at the usual dose decreased the incidence of CHD by a quarter and of stroke by a third, but three drugs at half the usual dose doubled these effects. The authors concluded that “…our results indicate the importance of lowering blood pressure in everyone over a certain age, rather than measuring it in everyone and treating it in some.”

These studies provide strong evidence that the benefits of the polypill approach to cardiovascular disease prevention are likely to greatly outweigh the risks. Some commentators still maintain that long-term primary prevention studies are needed, but is there really any doubt that reducing clotting, blood pressure and cholesterol will not reduce heart attacks and strokes? Surely the more relevant question is: what are the risks of not implementing the polypill approach now?

Commentators have made the point that a safe pill that reduced cancer by 50–80% would not face some of the resistance and the lack of progress encountered by the polypill, which has been described as an approach that could have a greater impact on the prevention of cardiovascular disease in the Western world than any other single intervention.

Disclosure: SH has recently launched a cardiovascular medicine packing service Polypack
www.polypack.co.nz

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Permitting sex selection

In a recent article in this *Journal*,^1^ Gareth Jones, Mike King, and Maja Whitaker criticise the Bioethics Council’s 2008 report *Who Gets Born*. The Bioethics Council no longer exists, swept away by the new government in the economic storm. Nonetheless, I want to respond, as former Chair of the former Council, because the topics the report dealt with, and the deliberative democratic approach the Council adopted, have not gone away for good.

The criticisms were mainly aimed at a recommendation about not prohibiting sex selection through PGD for non-therapeutic reasons. The authors said (1) the Council was not clear why it made the recommendation; (2) the reasoning for the recommendation should have been more transparent; and (3) the recommendation appeared predetermined, and participants in the deliberation may consequently feel misled in some way.

The sex-selection recommendation was one among many, and hardly the most important. (Much more important were the recommendations on securing genuine free and supported consent in all antenatal screening.) It did attract the most media interest, but that is a fact about the media’s interest. The participants in the deliberations were generally not especially interested in sex selection. Moreover, the Council was told that after the media interest, our then-Minister (Nanaia Mahuta) received the princely sum of 12 letters on the subject, half in favour and half against.

In essence, the reasoning behind the recommendation was this. On the whole, participants favoured parental decision. Even some disability activists, when pressed, could not say that parents should be prevented from screening for disability and deciding what to do, within the law, after getting the results. So there was a widely-shared background principle of parental decision-making, which, in the absence of other considerations, would require permitting sex selection too.

As I said, when it came to selecting sex, most people who deliberated did not have strong views. (The authors cited only the data from our on-line choicebook, which did not involve people deliberating with each other. They did not cite the face to face and on-line deliberations.) So there was a widely- and firmly-held background principle in favour and no widespread strong opposition.

There were some specific objections to sex selection, to do with skewing the sex ratio, expressing a discriminatory preference for one sex, or interfering with nature. But there is no evidence permitting sex selection would skew the sex ratio in New Zealand; someone with four children of one sex can quite reasonably want another child to be of the opposite sex without thinking males or females are intrinsically inferior; and those who objected to interfering with nature did not explain why choosing sex is more of an interference than the other uses of PGD they did not oppose. Hence the overall conclusion: there is insufficient reason to prohibit sex selection.
Perhaps the reasoning should have been more transparent. However, committees have to balance explaining their decisions with the need to make a report accessible. And the report is not the only explanation of the reasoning. The points in the previous paragraph were (transparently) made in the media after the Report’s release; and if the recommendation were to be pursued, it would require a law change and so more opportunity to explain the reasoning.

Was the Council’s recommendation predetermined? Not at all. If the participants in our deliberation had not tended to think parents should be the ultimate deciders, or if they had strongly opposed sex selection after deliberating, the Council would probably never have made its recommendation.

It is true that the Council, in making it, went beyond what many participants had said. But, as our terms of reference required and as we made clear throughout the deliberative process, the Council would not only report public opinion, but also advise its minister; and while the advice would be informed by what it heard, the Council may well go beyond it. The independent evaluation we commissioned showed that the vast majority of participants were happy with the process. It is also striking and gratifying that some of the most vocal supporters of the Council at the time of its extinction were the church and other religious groups who participated in our deliberation.

As the authors point out, it is hard to decide at a policy level on the ethics of reproductive technologies, as it is with much biotechnology. People should have their say, and not only the usual suspects (the lobby groups, activists, and ‘stakeholders’). People’s views often change when exposed to rival opinions, so they should deliberate with each other rather than give an isolated view. What they say has to help with hard choices. And policy has to be made, in some way based on the diverse collection of people’s views. None of this is easy, and more can be learnt all the time.

I hope that, although the Bioethics Council is no more, what it has learned will not be wasted.

Martin Wilkinson
Ex-Chair
Toi te Taiao: the Bioethics Council
Wellington

Reference:
   http://www.nzmj.com/journal/122-1294/3585
John Heywood Taylor

John Taylor died as he would have wished—on the golf course—on 30 December 2008, aged 80 years. John was one of the rare individuals from his generation to have achieved a seemingly perfect balance between family, busy specialist obstetric and gynaecological practice, and a wide range of sporting and business interests. He was one of the early obstetricians and gynaecologists to develop a special interest in family planning.

John was educated at Auckland Grammar School where he was head prefect, senior athletic champion, and captain of hockey.

He represented Otago University in hockey and tennis. He graduated MB ChB, from Otago in 1953. The following year he married Marie Lindberg.

Following house surgeon years in Wanganui he commenced specialist training in obstetrics and gynaecology at St Helen’s Hospital in Christchurch. For the first 6 months he was on continuous duty. He continued his postgraduate training at the young National Women’s Hospital (NWH) which was at that time beginning to establish an international reputation in research and teaching.

He proceeded to England, completing his training in the King’s College Hospital group in London, passing his MRCOG in 1959. The following year he returned to Auckland entering private practice with Bernie Kyle. He joined the Part-Time Visiting Staff at NWH in 1961 and remained on C Team until his retirement in 1993. He was a member of the surgical staff of Rawhiti and Brightside Hospitals.

Early in his career he developed a special interest in family planning, later in termination of unwanted pregnancy. His desire to extend his knowledge and improve his technical skills—for the benefit of New Zealand women—stimulated periods of overseas study, including at the University College of Los Angeles. He introduced day case vaginal tubal ligation and mid-trimester surgical termination of pregnancy.

John and Marie have demonstrated their commitment to the provision of contraception for the underprivileged by their generous support of the Family Planning Association. John was at the forefront of leadership following the legalisation of abortion in NZ in 1977. From 1978 he was medical co-ordinator at St Margaret’s Hospital and later at the Epsom Day Unit at Greenlane. He demonstrated tolerance and respect to those with views contrary to his own, even those who picketed his surgery and home.
One of John’s defining qualities was his ability to focus undivided attention—whether during a medical consultation, administrative issue or golf club meeting—carefully considering the question or issue and rationally synthesizing the best solution. His advice was widely sought. Another of his great assets was his ability to discuss any topic, no matter how contentious, without prejudice.

John Taylor’s attention to detail, together with his boundless energy, wasn't confined to obstetrics and gynaecology. He was a very good golfer, who played his best golf when under the pressure of competition. While recovering from a coronary bi-pass, and conscious of his divided sternum shifting when he played a full shot, and having had minimal practice, he won his second intermediate championship of the Auckland Golf Club over 36 holes. His lowest handicap was 2, and on several occasions, he completed rounds below 70. He contributed hugely to the AGC, and was duly recognised when the club elected him life member.

He knew the Auckland Harbour, its outlying islands, and the Northland coastline like the back of his hand. As a consequence of his interest in boating, he discovered that the Auckland Coastguard was facing imminent bankruptcy. This occurred at a time when he was still building up his obstetric practice. Somehow he found the time and energy to restructure the Coastguard finances and its services, and was later recognised with life membership of the Auckland Regional Coastguard. Later, in 2007, he was further honoured when the Coastguard made him its first Patron.

His passion for power boating induced him, at the age of 65, to establish a record for the circumnavigation of New Zealand in 4 days 16 hours in a 32-foot boat propelled by two 225-horsepower outboard motors. Following the passage from Akaroa to Napier, in appalling sea conditions, one of his very experienced crew described the voyage as “by far the single worst experience of my life”.

Despite his involvement in golf and boating, he made every one of his children, their spouses, and his and Marie’s 11 grandchildren, feel that they are the most special people on the planet.

To Marie, Richard, Susan, Jennifer, and Alison and their families we extend our deepest sympathy.

Ron Jones and Michael Cooper wrote this obituary.
Norman Derek Walker
6 May 1921–14 May 2009

Norman Derek Walker died aged 88 at his home in Christchurch.

Near the end of his working life, he returned to the modern Lyttelton Group Practice, working part time with his original partner Dr Noel Chambers’ daughter Dr Rose Chalmers.

During 1955 the family lived in London where Norman obtained his Child Health Diploma. Subsequently while his wife, Noeline, completed her medical degree in Dunedin, he became a Public Health Doctor, getting blisters with all the jabs that he had to give to school children.

As well as being a Port Doctor for Lyttelton for many years, he was a Port Doctor for Heathrow Airport, London for several years in the early 1970s (while Noeline gained her Diploma of Psychological Medicine, UK).

Back in New Zealand he ran the Sunnyside Mahu Clinic for treatment of alcoholics, including a stint at the Hanmer Clinic. He published a number of research papers on the treatment of Alcoholism. At an addiction conference at the US Navel College he had dealings with Buzz Aldrin, the moon astronaut.

As Member (1974) and Fellow (1987) of the Royal College of General Practitioners (NZ) he helped to set up the ACC scheme. Later Norman developed the NZ-wide Doctors Health Advisory Service, whose purpose is to help doctors with addiction and mental health issues.

As the Founding or Charter President of the Lyttelton Lions Club he co-coordinated all the Lions Clubs in Christchurch to fund-raise and make the initial and significant donation to buy mountain radios and to set up the Mountain Radio Scheme. Geoff Harrows, Norman Kirk, and Edmund Hilary were present at the cheque presentation.
The current Lyttelton Lions Club President told us that Norman generously donated land for the Lyttelton Ambulance while the Lions Club raised funds for the building. He was one of the early members of the Christchurch Ski Club at Temple Basin. About 5 years ago Norman and Noeline, along with several others were helicoptered up to Temple Basin for the Temple Basin’s 75th anniversary.

During the war he steam-bent planks of wood to make his own skis and with Noel Chambers, his fellow medical student, converted a car to burn coal so they could go skiing at Coronet Peak. Unfortunately one ski had the wood going against the grain: it left a trail of splinters in the snow.

For many years he was a Councillor and Deputy Mayor for Lyttelton. With his medical knowledge he promoted the fluoridation of Lyttelton’s water supply.

In his 80s he wrote and published two books *Stories for my Grandchildren*, and *Port Doctor*. The second was sold publicly and had strong demand. Last year in recognition of his services he became the patron of the Cashmere Croquet Club.

At 82 he was still skiing with his family and group of friends at Mount Hutt. At 84 he was biking the Otago Rail trail with his daughter Heather and his son David. At 86 he gave an hour-long lecture to the Diamond Harbour Historical Society. At the same age he was still fishing and playing croquet. At 87 for his birthday he was taken on a sightseeing flight. (Using his private pilot’s flying skills he took the plane’s controls for some of the return trip.)

He and his wife Noeline were key members of a private choir, which has run for about 25 years. The choir sang at his funeral on Monday 18 May 2009.

Above all he was a family man. He made everyone feel special; he really cared and really listened to people. He had lots of energy, needing a 40-hour day to fit in everything he wanted to do. Two years after his wife died, he developed the chronic heart disease that eventually killed him. He is survived by his children—Heather Macleod, Stephen and David Walker; his 5 grandchildren—Jennifer, Susan (also a GP), Peter, Luke and Alan; and two great grandchildren—Emma and Hamish Grindlay.

Heather Macleod (Norman’s daughter) wrote this obituary.
University of Otago Faculty of Medicine
Freemasons Postgraduate Fellowships in Paediatrics and Child Health for 2010

The above Fellowships or Scholarships are open to University graduates who intend long term to pursue work in Paediatrics or Child Health within New Zealand. The Fellowships include full-time salary for one year with provision for a further year.

Applications close on 19 June 2009 with the Department Manager, Department of Women’s & Children’s Health, Dunedin School of Medicine, PO Box 913, Dunedin 9054, from whom further details may be obtained (wch.admin@otago.ac.nz)
Speaking for the Dead: The Human Body in Biology and Medicine (2nd edition)

D Gareth Jones and Maja I Whitaker. Published by Ashgate, 2009.

Should cadavers be used in car crash safety tests? Are there situations where it is justifiable to use data from unethical human experiments? Should skeletal remains be repatriated from museum collections around the world?

What are the current ethical and regulatory constraints on embryo research? These are just some of the challenging questions explored in the second edition of Speaking for the Dead. But do not be fooled by the title.

Although the book is primarily concerned with the uses and abuses of the dead body, much of the content relates to the living body and the conduct of modern medical research.

With a background in human anatomy, neuroscience and bioethics the authors offer a unique and valuable insight into the medical, ethical and legal aspects of a broad range of issues surrounding the use of human body parts and tissues.

The book contains a wealth of material, much of it new since the first edition in 2000. As the authors state “... the manner in which we respond to the dead, the use we make of their skeletal remains and their tissues, and the ways in which we learn about ourselves by studying them, raises ethical queries that go to the heart of what it means to be human.”

The book begins by exploring the ethical significance of the dead body and the origins of human dissection, highlighting the organ retention scandals in the UK, USA and Australasia. A chapter on the abused body follows, which inevitably touches on many of the profoundly disturbing human experiments carried out during the twentieth century.

In the section on the plastinated body, the resin impregnated human cadavers on public display in the Body Worlds exhibition are discussed. Somewhat prophetically the authors state that Gunther von Hagens, the German anatomist who pioneered this technology and style of exhibition, has yet to stoop to the level of tastelessness shown by some of the cadaver poses created by the 18th Century French anatomist, Honoré Fragonard. However, just recently, von Hagens has become embroiled in further controversy following his display of plastinated cadavers posed in sexual intercourse.
The numerous ethical issues surrounding organ transplantation including opt-in versus opt-out policies, the use of organs from executed prisoners and anencephalic babies, and xenotransplants are reviewed in the chapter on the transplanted body. The indigenous body addresses the issues surrounding skeletal remains in physical anthropology. Finally, there are chapters on embryo research, brain death (including an excellent account of the persistent vegetative state), Alzheimer’s disease, and surgical and pharmacological methods of enhancing the body.

Each section is well referenced and written in a clear and engaging style. Numerous themes are revisited throughout: the issue of moral complicity (those who use material or data obtained unethically implicate themselves in unethical practices); parallels between society’s treatment of the dead and the living; and the difficulties created for contemporary practices by changing ethical standards.

The authors deliberately and reasonably do not attempt to address in detail ethical issues surrounding genetic material. However, I was surprised to find no mention of cryonics, a multimillion dollar industry in the United States that feeds the desire of those who wish their dead body to be frozen in the hope of future resurrection.

I can thoroughly recommended this book as an extremely readable, scholarly and balanced account of ethical issues surrounding the use of human body parts and tissues. All health care professionals and researchers from students to retired practitioners would find it a fascinating and informative read.

Mark Stringer  
Professor of Anatomy  
Otago School of Medical Sciences  
University of Otago, Dunedin
Law, Mind and Brain

Michael Freeman and Oliver R Goodenough, eds. Published by Ashgate, 2009.
ISBN 9780754670131. Contains 430 pages. Price £70.00

As Freeman and Goodenough point out in their introduction to this book, the collaboration between neuroscience and law, and the “fountain” of new knowledge flowing from the emergence of “neurolaw”, threatens to become a flood.

While, as the editors note, discourse has moved rapidly from early medicolegal debates centred on attempts to formulate an alternative definition of death, ethical questions are still firmly at the centre of discussion as to how neuroscience might impact criminal law and justice. This is the principal area of attention in the book. However, the collected essays are more than a treatise on criminal blame and responsibility.

The book is an interdisciplinary collection of essays by writers with a particular interest in issues of blaming and responsibility but also with wider perspectives informed by biology and particular understanding of human behaviour. In fact, the range of subjects addressed in this volume is very broad.

In addition to contributions on how neuroscience might assist understanding on responsibility and blaming issues in relation to juveniles and in the presentation of courtroom evidence, separate chapters address such diverse concerns as the distinction between mental and physical illness in involuntary treatment law, the legal implications of memory “damping”, the potential of psychedelics in palliative care, and words and pictures and law amongst others.

It is undoubtedly true that the law and neuroscience debate is rapidly expanding. Recent well-publicised debates have addressed issues around the law and ethics of brain scanning and emerging neurotechnologies for lie detection. Scientists claim to be close to being able to diagnose Post Traumatic Stress Disorder through brain scanning. Work continues apace in behavioural genetics and in neuroanatomical quests to understand the brains of particular target groups. Law, Mind and Brain enhances this academic and scientific enterprise.

Law, Mind and Brain emerged from an international interdisciplinary colloquium held at The Law Faculty of University College London in 2006. The list of international contributors are drawn principally from the professions of law, psychological medicine, and neuroscience. The clear “flavour” of the contributions is towards the implications of neuroscientific inquiry for criminal law, in particular how the insights of neuroscience might be brought to both the study and practice of criminal law.
The book does not follow any particular structure. The individual chapters are simply presented as a body of writing which, it is hoped, demonstrates that legal scholarship and practice will increasingly be enriched by an interdisciplinary study of law, mind and brain. A number of the chapters have been previously published as journal articles and are republished with the consent of the original publishers.

This book, as already noted, contains a fairly eclectic mix of topics, not all of which have a direct bearing on issues of neuroscience and law. To that extent it might be claimed that the title of the book Law, Mind and Brain offers more than it delivers, at least for those looking for a compilation of more focussed discussions on issues around the complex relationship between neuroscience and the law. This is so if the title of the book is compared with Professor Goodenough’s earlier book of essays entitled Law and the Brain (2006), which is uniformly concerned with issues around the relationship between the law and ongoing neuroscientific research. However, in the present volume, the chapters that do address those concerns—namely chapters 2, 3, 4, 8, 9 & 11—add usefully to the literature and tend to support the editors’ claim in the opening chapter that the study of law has begun to draw insights from this body of new knowledge.

The remaining chapters, though not directly relevant to developments in neuroscience and law, nevertheless contain many interdisciplinary matters that will be of interest to both lawyers and medical professionals and are worthy of consideration in their own right. But for those not interested in the broader range of issues discussed, those chapters concerned more directly with law and neuroscience reward careful study and contain insights and observations which significantly further the dialogue between law and science in this important area of debate.

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