THE NEW ZEALAND MEDICAL JOURNAL
Journal of the New Zealand Medical Association

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This Issue in the Journal

"I wouldn't want to become a nuisance under any circumstances"—a qualitative study of the reasons some healthy older individuals support medical practices that hasten death
Phillipa J Malpas, Kay Mitchell, Malcolm H Johnson

In this study we explored the reasons older healthy New Zealanders held for supporting medical practices that hasten death. We undertook this study because we know (from two surveys) that a large percentage of the population support medical assistance to die in certain circumstances. This mirrors support in several other countries, including Australia. However we do not know their reasons for supporting such practices. This may have important implications for medical practice at the end of life, particularly where patients request that medical treatment be withheld of withdrawn.

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George Cowie, Anita Bell

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Deborah Walkden, Krishna Badami

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Annemarei Ranta, Calvin Chan, Dorothea Rump, Pietro Cariga

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Nicholas Child, John Fink, Shelley Jones, Kevin Voges, Mark Vivian, P Alan Barber

The clinical care of 832 patients, representing 1 in 5 stroke patients admitted to hospital in New Zealand over a 6-month period, was audited. It is clear that the implementation of best practice guidelines for stroke care has been patchy and there is significant regional variation across New Zealand. Not all people have access to stroke unit care, and clot-busting "thrombolysis" treatment rates remain low and should be seen as the top priorities for improving patient care.

New Zealand Malayan war veterans' exposure to dibutylphthalate is associated with an increased incidence of cryptorchidism, hypospadias and breast cancer in their children
Matthew Carran, Ian Shaw

Dibutylphthalate (DBP) was used to prevent New Zealand soldiers contracting diseases (e.g. bush typhus) transmitted by ticks and lice during their service in the Malayan Emergency (1948–1960) by applying it to the seams of their clothes (the point of access of disease vectors) before they went into the jungle. DBT is known to inhibit the synthesis of the male hormone, testosterone (it is an endocrine disruptor). The article reports the results of a questionnaire study that shows an increased incidence of diseases/disorders associated with exposure to endocrine disruptors (cryptorchidism [undescended testes], hypospadias [deformed penis] and breast cancer) in the children of DBP-exposed soldiers compared to the general population. It is proposed that DBP interferes with the function of genes (epigenetics) associated with testosterone synthesis and thus results in cellular feminisation and that this explains the increased incidence of the diseases seen in the children of the Malayan Emergency veterans.

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Debates on euthanasia

Sinéad Donnelly

Recently I attended the Paediatric Palliative Care Conference in Wellington and was impressed by the compassion and dignity afforded to children who are dying in Starship Children's Hospital, Auckland. The negatively phrased tick box "Do Not Resuscitate" (DNR) order while in hospital has been replaced by "Allow Natural Death" (AND). Even more dignified and compassionate is the Maori translation of AND: *Te Wa Aroha*.

Families are presented with the reality of their child dying and agree to engage with the palliative care team in "a time of love, a way of communication to prevent suffering, to promote comfort and dignity." I was heartened and inspired to hear about *Te Wa Aroha* and the poignant stories of children dying and raw family grief.

In contrast I was deeply saddened on reading Malpas et al paper in this month's *NZMJ* that healthy older people advocating euthanasia felt a burden, useless and an inconvenience in contemplating their future. I felt burdened by their distress. It read like a lament.[1]

As a palliative medicine physician I find debates on euthanasia disturbing. Care of the person who is dying is not an issue for debate. It is not a dual, nor a contest to win or lose. It is more than that for me.

I have worked for 20 years caring for 400 people each year who die. That experience has taught me how complex each person is, how individual is their life and death, how again and again people respond to holistic care and attention. In Malpas et al's paper I hear an urgent call for better medicine and care of the elderly, not for euthanasia.

The study participants' fear seems to be of "institutionalised aging". An aging person it is assumed will not be loved and will not receive care. I groan to read a study participant's comment, "when I'm useless and have nothing to contribute". Does fear of growing old justify euthanasia? Does fear of being a burden justify euthanasia? If so, what a cruel society we have created.

The inconvenient truth is that "being a burden" can happen at any age—infancy, childhood, teenagers included. This is the very reason not to legislate in favour of euthanasia. In the Court of Usefulness, who presides? How do we ensure that older people feel useful? What right have we to make older people feel useless?

Quotes from interviewees in this study are challenging, e.g. "old people are a drain on resources". Is this the reason to legislate for euthanasia? There is no limit to the drains on resources—e.g alcoholics, drug addicts, depressed people. They see older people

"getting little sympathy from caregivers frequently". Is this the impression we are giving to older people? This is the challenging area.

The problem does not reside with the older people who request euthanasia. The real problem is that people in our midst feel they are a burden and feel or know we will not care enough. They are right.

The easy answer for us is to bury the problem. The more uncomfortable reality is to look at ourselves the carers, the able bodied and say "they are right, we do not care enough". We must show our older people and our younger people that we know how to care for each other.

At times throughout our lives we are a burden to people. That is because we are human. Because we are all a trial or a burden, we create a community where there is give and take. But have we created community? Have some groups, e.g. Maori, Pacific People, held onto community? They are not in this self-selected pro euthanasia group. Why not? What have they got?

Agrich et al's comment that "long-term care has become associated with images of frailty and despair, loneliness and destitution" rings true. People are afraid of getting old. One clear response to this fear is to create an excellent, integrated care of the elderly service. Our best and brightest young doctors should be vying with each other for advanced training positions to learn how to care for our specific needs when we are old.

Prior experiences with health care as a family member or friend was dying is an interesting influential factor in favouring legalisation of euthanasia. It highlights the needs of grieving family and friends—they, as much as the dying person, need great care and attention. Attention paid to them will help in their bereavement and future contact with dying and death. This is well recognised for bereaved children so why would it not also apply to bereaved vulnerable adults.

Euthanasia or assisted suicide, and sometimes both, have been legalised in a small number of countries and states. The Netherlands, Belgium and Luxembourg have legalised euthanasia.

In the United States, Oregon and Washington states legalised physician-assisted suicide (PAS) but euthanasia remains illegal. Switzerland allows non-physicians to assist suicide.

Legislators in several countries and jurisdictions have in the last year voted against legalising euthanasia and PAS. Those jurisdictions include France, Scotland, England, South Australia and New Hampshire. They have opted to improve palliative care services and to educate health professionals and the public.[2]

The World Medical Association[3–5] and the New Zealand Medical Association[6] are opposed to both the concept and practice of euthanasia and doctor-assisted suicide. Moreover, The Australian & New Zealand Society of Palliative Medicine[7] believes that the discipline of palliative medicine does not include the practice of euthanasia or assisted suicide.

I disagree with Malpas et al saying euthanasia is legalised in "carefully qualified situations". The Netherlands' 30-year experience shows clearly the rapid expansion of what are seen as acceptable justifications for euthanasia—e.g. babies and children; non-consenting and depressed adults; an old man who wants to avoid a nursing home; suicidal middle-aged men.

According to Margaret Somerville—founding director of the McGill Centre for Medicine, Ethics and Law research—dying people request euthanasia far more frequently because of fear of social isolation and of being a burden on others.[8]

The medical authority of Oregon (where physician-assisted suicide is legal) seems to have accepted cost-saving as a justification: it has acknowledged that when it turns down an application to cover the cost of an expensive new drug, it simultaneously sends out a reminder that the state's assisted-suicide programme is available at an affordable cost.

Somerville cites increasingly lax conditions around who can request assisted suicide in the Netherlands as proof of a "slippery slope" toward abuse. "When first allowed through a judicial decision, the conditions were that the person was an adult, terminally ill, in terrible pain and suffering … competent, had given their informed consent and had asked for euthanasia over a considerable period of time," she explains. "Not one of those conditions now applies".

If the basic principle is autonomy and that's always the over-riding value, which is what they argue in the report, then if you've got a broken-hearted 18-year-old who wants euthanasia, how can you reject what she's asking for?" Somerville contends.

She adds that legalising euthanasia causes death and dying to lose their moral context. Maintaining a moral context is crucial in light of an aging population and scarce, expensive healthcare resources, which will face us with many difficult decisions about who lives and who dies.

Concerns were expressed in Canada about abuses that might occur if decriminalisation of assisted suicide and voluntary euthanasia was implemented.

"What about people who already feel like they're a burden? If it's very difficult for their families, it's a failure of our social services and health care system," argued Rhonda Wiebe, Co-Chair of the Council of Canadians with Disabilities' End-of-Life Ethics Committee. "They shouldn't be paying with their lives because health and social services can't step up to the plate".

Legalisation of euthanasia creates societal pressure on vulnerable populations, such as people with disabilities, to end their lives. Wiebe adds "There's this continual apology for your own existence and when you start internalizing that, what happens when you go to a doctor who is supposed to be helping you negotiate life with a disability, and they're saying death is always an option?"[8]

There is the burden some people (e.g. Malpas et al's study participants) feel at the thought of being disabled. And there is the burden disabled people already feel in

struggling to live in the society we have created. The latter will be compounded by legislating in favour of euthanasia.

People are asking not to be considered a burden. They are asking us "are we a burden?" We say yes when we legislate for euthanasia.

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"I wouldn't want to become a nuisance under any circumstances"—a qualitative study of the reasons some healthy older individuals support medical practices that hasten death

Phillipa J Malpas, Kay Mitchell, Malcolm H Johnson

Abstract

Aim To explore the reasons some healthy older New Zealanders support medical practices that hasten death.

Methods Recruitment was from the Voluntary Euthanasia Society of New Zealand (VESNZ), an organisation that supports legal medical assistance in dying. All participants were members of VESNZ. 106 individuals returned signed consent forms. All interviews took place in the participant's home. After 11 interviews, saturation of information was reached and interviewing was stopped.

Results An important finding of this study indicates that healthy, older individuals who support medical practices that hasten death have serious concerns about their (perceived) future incapacities and dependency on others, as well as their fears around becoming a burden. The study also found that fear of future pain was not a dominant reason to support medical assistance to die.

Conclusion Our study provides confirmation that the fear of being a burden on others is not only felt by those facing their imminent mortality, but also by older individuals who are currently healthy and living independently in the community. We also conclude that for some older people their prior experiences with health care and dying may be a strong factor in influencing and supporting medical practices that hasten death at the end of life. We believe it is crucial to understand the reasons why people support medical practices that hasten death well in advance of such practices ever becoming legally available.

Support for medical assistance in hastening death appears to be growing both around the world and in New Zealand. This is evidenced by the fact that in the past decade a number of countries and states have legislated for euthanasia and/or physician-assisted suicide to be made available to patients in carefully qualified situations (the Netherlands, Belgium, and Luxembourg).[1]

Presently, the states of Oregon, Washington and Montana in the USA allow for physician-assisted suicide. Laws in Switzerland accommodate assisted suicide that does not necessarily involve assistance by a physician.

Over the past 2 decades a number of studies have examined the attitudes of terminally ill patients[2-5] and physicians[6-8] towards medical practices that hasten death (euthanasia and physician-assisted suicide). For instance, Wilson et al[9] found that psychological

aspects may be as important as physical symptoms for cancer patients who would actually make a request for their death to be hastened by a physician.

Johansen and colleagues[10] also investigated attitudes towards physician-assisted dying with cancer patients who had a life expectancy of less than 9 months. They found that whilst some patients held positive attitudes towards euthanasia and physician-assisted suicide, the wish to die was ambivalent and fluctuating: a mental 'solution' for the future. Further studies have explored physicians' experiences of end of life decision-making[11-15].

Furthermore in New Zealand, two surveys of the general population concluded that around 70% of New Zealanders support medical assistance in hastening death when someone is terminally ill and their suffering is intractable and unbearable.[16,17] Some general practitioners in New Zealand consider it justifiable[18] and some do intentionally end the life of a patient who is incurably ill.[19] Despite this, practices that hasten a patient's dying are neither lawful[20] nor openly practised in New Zealand.

To date no study has explored the reasons healthy, older people might have for supporting medical practices that hasten death. Examining the reasons some individuals have for supporting these practices is important in understanding how individual circumstances may influence personal decisions concerning medical care and treatment at the end of life. For instance, in understanding the factors involved when requests are made to withdraw or withhold medical treatment, or in the preferences expressed in advance care directives.

Furthermore, exploring the preferences an individual has regarding end of life decision-making may help health practitioners develop more patient-centred care plans at the end of life.[21]

The present study set out to explore these reasons in the New Zealand context.

Methods

Study design and ethics—A qualitative approach was used to explore the reasons some older healthy individuals support medical practices that hasten death at the end of life.

University of Auckland Human Participants Ethics Committee approval was obtained for the study (UAHPEC Reference number 2010/055).

Sample selection—Recruitment was from the Voluntary Euthanasia Society of New Zealand (VESNZ), an organisation that supports legal medical assistance in dying. All participants were members of VESNZ; some participants were also members of EXIT International. VESNZ Head Office forwarded 330 letters (from the researchers) advertising the study to Auckland members of the society inviting them to participate in the study. 138 people contacted PJM via phone, email or letter enquiring about the study.

All individuals who self-identified as healthy and were 65 years or older were sent information packs: these contained a participant information sheet explaining the study and what it entailed, a consent form, and a self-addressed envelope. 106 individuals returned signed consent forms which were numbered as they were opened. Every tenth participant was chosen for interviewing, with the exception of one spouse who was also interviewed (convenience sampling).Participants were then phoned by KM to ask about a convenient time to meet.

All interviews took place in the participant's home. After 11 interviews, saturation of information was reached and interviewing was stopped.

All participants lived in their own homes (one woman lived with her daughter), and all identified as healthy. None of the respondents had long term disabilities and were in fact remarkably healthy, except for an 89 year old woman who had mobility issues related to age-onset illness. This was not long-term, although she did not expect it to improve.

Participant numbers 4 and 4a were husband and wife.

Table 1. Demographic details of participants.

ID	Age	Gender	Religious affiliation	Living situation
1	79	female	No religious affiliation	Lives alone
2	78	male	Atheist	Lives alone
3	80	female	Baptist	Lives alone
4	82	male	No religious affiliation	Lives with wife
4a	86	female	No religious affiliation	Lives with husband
5	80	male	No religious affiliation	Lives with wife
6	88	female	No religious affiliation	Lives alone
7	89	female	Quaker	Lives with daughter
8	81	male	Atheist	Lives alone
9	69	male	Agnostic Christian	Lives with wife
10	75	male	No religious affiliation	Lives with partner

Data collection—Semi-structured interviews were conducted based on open questions concerning past experiences with death and dying, planning for end of life, concerns or fears about dying, reasons for joining VESNZ and/or EXIT. Interviews were conducted by one of the authors (KM) in respondent's homes, and took approximately 1 hour.

The phrase 'medical practices that hasten dying' referred to interventions by a doctor that either assisted a patient to die (as in giving the patient the means to end their own life at their explicit request—physician-assisted suicide), or directly ended a patient's life (as in a lethal medication administered by a doctor at the explicit request of the patient—euthanasia).

Interviews were recorded and transcribed. Each respondent was sent two copies of their transcript and asked to read and delete or alter any information they believed was inaccurate or did not represent their views. Once the transcripts were forwarded to the researchers they were used for purposes of analysis.

Analytical strategy—Our aim was to derive themes and meaning from the interviews. To do this we employed the grounded theory approach whereby responses in each previous interview were incorporated into the interview structure for subsequent interviews[22]. Interviews were imported into QSR NVivo 8 and subjected to multiple close readings by KM in a general inductive approach to identify broad categories of subject beneath which were identified themes that were coded for further analysis[23]. All three authors then separately read the interview sections and the final identification of themes and selection of representative quotations was by agreement.

Results

Participants' demographics–All participants were aged 65 years or older at the time of interview. Compared to the over 65s in the 2006 New Zealand Census, our sample were more likely to be European (100% cf 80.56%) and to have no religious affiliation (73% including atheists cf 11.8%).

Participants' responses—It became clear during the analysis that participants' reasons for supporting medical practices that hasten death were deeply intertwined and not easily captured in separate categories.

This can be seen in the interview with the first participant. She began by reflecting on caring for her mother more than 50 years ago when she was in her mid-20s and appears to incorporate this memory into her fears of being a burden on her own children:

> Although I didn't know it at the time she had cancer throughout her body [...]. I was the last one to get married so she lived with me. [...] It was a family responsibility
>
> I just feel that I don't want to be a burden on my children. And when I get old I don't want them to have to look after me. Um, it's just too hard for them, I don't want to do that to them

While the genesis of this fear of being a burden may have been in her memories of caring for her mother, it appears to have been awakened by a recent experience of visiting a friend with Parkinson's disease, in a rest home (nursing home):

> I have been to see them and those people; they are just waiting around to die. It's awful, it's just awful

Participants' reasons for supporting medical practices that hasten death at the end of life were clustered around four main categories: concern for self at the end of life, concern for others, prior observed experiences with health care, and suicide issues. The first three categories are the subject of this paper. Themes identified under these categories are reported in italics.

Concerns for self at the end of life—*The desire to remain independent* and active for as long as possible was raised by several participants in our study:

> Yeah. It's got to be an independent life, I mean I really don't think I want to live in a wheelchair in an institution you know (8)
>
> Oh God, I can't imagine not being independent (6)

A fear of pain and suffering at some future point in time was given as a reason for supporting assisted death, as was the need to maintain one's dignity at the end of life:

> My fear is pain and not being able to you know, live an independent life …I certainly don't want to be incontinent lying in a hospital bed with no hope of ever getting better. Even if the pain could be dulled, it'd still be (8)
>
> That's the, that's the insidiousness of aging. I worked this out. I might have a small pain and I think oh, that's okay, I can live with it. And a week later it might be slightly worse and I think, oh, I can live with it. And a week later it will be slightly worse and then you go on and realise about a year later, you know, that life hasn't got much value because of the physical pain. And you just keep going on. Well I don't want to do that (1)

Autonomy was important to several participants who spoke strongly about their right to make their own decisions about what they wanted at the end of life, and less about the actual reality of what they could or could not accept:

> I cannot understand as I said right to start off with, why other people think they have got the right to tell me that I can't die when I want to and I don't see why I have to be desperately ill and talk to lord knows how many doctors to convince these people because I might not be in a state where I could convince anybody. All I know is that I know myself… Being in that sort of position and everybody's thinking that they're doing – they know better than we do and *'you shouldn't think like that dear'*, and all the rest of it. What the hell? I mean we've both gone 80, [...] we've got the right to clear off when we want to (4)
>
> I want to be aware enough to say 'no'. And I'd like to be able to do something about it while I have sufficient power (1)

Being useful appeared to be a bridge between concern for self and concern for others and was mentioned by several participants as a reason to go on living:

> Yes, I think it comes down to what I can contribute, how useful I am. And when I'm useless and have nothing to contribute and can't look after myself. I think that's when I would wish to do something about it (1)

One woman questioned whether she would be missed by her family if she suicided and then recalled how much her daily phone calls meant to her granddaughter and great granddaughter who lived overseas:

> ....my calls every day, I know she looks forward to them. I know she doesn't always speak [to me for long] but that's the only thing I might be, I feel, of some use. But then I'm not going to try to hang onto a life where there's nothing there. I mean that would be terrible (6)

Concerns for others—A negative alteration in mental and physical abilities and body image can lead to a negative concept of self.[24,25] Arguably in age, this is occurring at a time when a positive self-concept particularly in relation to loved ones becomes increasingly relevant to quality of life.

For many participants, the desire to be remembered 'in a good way' by loved ones is important. It was clear that individuals wanted others to remember them as someone who was both physically and psychologically healthy, and not as one who was now a shadow of their former self:

> And I feel that when I get to that stage, I won't be like I am now. I won't be as they know me now, I will be somebody else who they, well they're sort of stuck with really (1)

> I wouldn't want my grandchildren or daughters to see me at a stage when I am not the person that they always remember me as (5)

A desire not to be a drain on health care resources and society was articulated by several participants:

> And I rather annoy I suppose a lot of my contemporaries because I really feel that, the old people around are a drain on resources. Well we are, it's a fact (6)

Being a burden or nuisance on others was a concern for a number of participants. It is a concern found in other studies:[26–28]

> Knowing that you are a nuisance to everybody and getting little sympathy from caregivers frequently, um, even from family. You know you are a nuisance, a drag on them. I wouldn't want to become a nuisance under any circumstances (3)

> Well if I was so physically handicapped that I couldn't do anything myself, if I needed attention all the time I would hate that. And um, and also if my mind was so unclear that I was just a trial. [...] Yes. Oh yes, I would hate to be a trial to people (7)

Becoming dependent on others for personal care and hygiene appeared related to being a burden, and troubled some individuals:

> ....if you couldn't do your basic care, couldn't wash yourself or go to the loo (toilet) by yourself, I don't want to go on after that. Thank you. And I don't expect (husband) wants me to go on like that either, or my family (4a)

One man spoke of his horror at the thought of having to be toileted:

> When I can't wipe my own bum I want to be gone (2)

Prior observed experiences with health care—A number of participants began their interview discussing the decline and (in some cases) death of a family member or

friend and how those experiences had influenced their views around the dying process.

The experience of seeing family members or friends in long term care also profoundly affected some participants. For some the experience happened several decades before.

One man said of his experience of visiting a long term care facility:

> I've visited one of these old age peoples' places and oh what depressing places they are. I love organ music so I play the church organ. And I got dragged into going there one night and playing hymns for them and arrggh (expression of disgust). God, most of them had gone, you know (8)

The experience of witnessing the decline of friends and family involved issues around how pain and suffering was (mis)managed, the prolonged duration of an illness (such as Alzheimer's disease) and its effects on the family, having to do everything for another person, and concern about lack of dignity in dying. Some participants were adamant that as a result of their experiences, they did not want to move into long-term residential care.

Agich[29] notes that "in our culture it is less death than long-term care that strikes us as so repugnant". He argues that long term care has become associated with images of frailty and despair, loneliness and destitution. For some individuals in our study their prior experiences with long term care reinforced both their need to be self-reliant and independent for as long as possible, and their aversion to dependency and need.

> My wife had an uncle who was just a couple of years older than her and he had a heart attack when he was about 40-something after we were married and he lost the power to move his arms and legs and would speak a little bit and effectively my wife looked after him for years and years and years and years.... and I used to go around there twice a week for half a day and do everything that he needed. And I just thought how horrible it would be in that state (5)
>
> And my mother died at 90 and she had Alzheimer's [disease] for 20 years, and I'd go and see her every fortnight and my last remaining brother would do alternate weeks and we did that and it is very distressing to see that happen. And I'd hate to see me in similar circumstances (9)
>
> I'm one of six brothers, four of whom have died. Three from cancer related illnesses and they died in their mid-50s, quite a short lifespan in my opinion and their passing, well their illness was quite devastating you know to witness what they had to go through and I thought well, if there was something I could have administered to stop their pain and suffering, I thought I would or I'd probably do it (9)

Discussion

Like many industrialised countries, New Zealand faces the challenge of an aging population. As expenditure in health care increases with age, understanding the issues and preferences that influence the health care decisions made by older individuals would seem to be an important aspect of providing good medical care. This is especially so when older individuals may be considering their choices and making decisions about the kind of medical treatment and care that is appropriate for them at the end of life.

Our participant group comprised individuals who are members of an organisation that supports legal medical practices that hasten dying at the end of life. We chose to focus on this group of individuals because they had made a conscious decision to become

members of VESNZ and therefore had (presumably) given some thought to why they supported medical assistance to hasten death.

An important finding of this study indicates that some healthy, older individuals who support medical practices that hasten death have serious concerns about their (perceived) future incapacities and dependency on others, as well as their fears around becoming a burden. We also found that fear of future pain was not a dominant reason to support medical assistance to die. These findings also suggest that for some older people, their prior experience with health care and dying may be a strong factor in supporting medical practices that hasten death at the end of life.

The fear of becoming a burden on others is well documented within the end of life literature[30–33] although the majority of studies explore the concept of being a burden in persons with a terminal illness.[26–28, 34,35] Our study adds to the current body of research that fear of being a burden on others is not only felt by those who are terminally ill and facing their imminent mortality, but also by older individuals who are currently healthy and living independently in the community.

It is important to note that as individuals move through various stages throughout their lives their views on, and support of, many things may change. The person who fears disability or increasing dependence on others may reason that a future that includes these would be unacceptable to them.

Our research shows that for some individuals, support for medical assistance to hasten death may be in response to concerns such as these.

There is evidence from the Netherlands, and Oregon and Washington States (USA) that many individuals whose requests for an assisted death are approved by doctors, are not actively assisted to die at the end of life, or do not choose to use the lethal medication they have been prescribed[36-38]. For instance, in Washington in 2010[37], 87 individuals were prescribed lethal medication under the Death with Dignity Act.

Of the 67 individuals who died (for whom an After Death report was received by the Washington State Department of Health), 15 did not use the lethal medication to end their lives. While some of those individuals may have died of the underlying disease, some may have changed their mind about the manner of their death.

In their study examining the practices that surround euthanasia, Dutch and American researchers found that euthanasia discussions with patients, "in part serve a palliative effect, affirming social bonds and social identity at the end of life, and putting the onus on patients to continue discussions towards a euthanasia death"[38]. This open approach to discussions on dying and a willingness to engage with the patient may also contribute to a personal sense of control in the dying process.

Whilst it can be plausibly claimed that some of our participants may change their mind (about wanting a medically assisted death) as their future fears are not realised, or are successfully managed by other means, we cannot assume their current reasons for supporting medical assistance to hasten death will not have implications for their future medical treatment and care. This is an area of end of life decision-making that requires further research.

Whilst the findings of our study are not intended to be generalisable, they contribute to a wider body of knowledge around the influences and attitudes of personal preferences in regards to medical treatment and care at the end of life.

These findings highlight the need for health care practitioners to be aware of, and attentive to, the multifaceted reasons some healthy older individuals may have towards medical treatment and care at the end of life, especially where an individual expresses a desire to withdraw or withhold certain medical treatments.

Fear of losing one's independence and becoming dependent on others as one ages appears instrumental in influencing and shaping preferences made near the end of life. Although dependence on others is an essential feature of human development, and an essential condition of what it is to be a human person[29] some participants seemed to view dependency as deficiency; almost as though the loss of independence was a failure on their part.

Seale and Addington-Hall[39] found in their study which described the circumstances in which a representative sample of adults died, that certain forms of distress and dependency are more likely to lead to desires to die sooner, and to requests for euthanasia than others.

Prior experiences with health care that have involved the dying and death of a family member or friend may also deeply influence an individual's expectations of medical treatment and care available at the end of life and what they may want at the end of life. It was clear from several participants that the health practices they witnessed and often experienced (sometimes decades ago) would not be practiced today.

Informing older patients about advances in certain medical treatments and life expectancy outcomes may assist in alleviating concerns and fears around end of life issues. Inviting older patients to discuss such experiences may encourage dialogue around issues of dependency, the management of pain, and fears of becoming a burden on others.

As for study limitations it is important to note that all our participants identified as being of European descent. Thus we were unable to explore some of the particular issues of significance that may have arisen in the context of end of life decision-making for people who may have very different outlooks around dying and death. For instance, in communities where members have a more collectivist approach towards how decisions are made across the life span (as opposed to more individualistic approaches), support for medical hastening of death may be viewed very differently.

In an American study, Cahill and colleagues found that White older adults were more likely than Black older adults to discuss burden[40]. They concluded that the expression and meaning of burden differed according to ethnicity; "burden is expressed in different ways and meanings that sometimes correspond to the experiences of particular ethnic groups".

Exploring the reasons other groups of individuals have for supporting medical assistance in hastening death will add to a more nuanced picture of how end of life decision-making is approached and shaped. This should include individuals who live with chronic conditions, diverse ethnic groups, those who are disabled, younger

individuals, and those who hold spiritual or religious beliefs that inform their decision-making.

We are currently undertaking a qualitative study that is exploring the reasons some healthy, older individuals oppose medical practices that hasten death. There is a scarcity of research exploring and understanding the issues arising for different groups of individuals near the end of life within the context of hastening death.

Furthermore the problem of dependency needs to be addressed at a deeper level than we were able to go in this study. Seale et al,[39] note that "*the issue of dependency in the elderly is a broad one, and may not be as amenable to remedy as certain symptoms have proved to be*".

Although surveys from many different countries indicate that increasing numbers of the public support medical assistance in hastening death, we still know very little about their reasons for doing so. We believe it is crucial to understand the reasons why people support medical practices that hasten death well in advance of such practices ever becoming legally available.

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Competing interests: PJM is a member of Voluntary Euthanasia Society of New Zealand (VESNZ), an organisation that supports legal medical assistance in dying. The rest of the research team (KM and MJ) are not. PJM did not interview any of the participants and only had access to anonymised transcripts.

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A retrospective review of notified human leptospirosis cases in the Waikato region of New Zealand, 2004 to 2010

George Cowie, Anita Bell

Abstract

Aim To retrospectively review notified human leptospirosis cases in the Waikato region of New Zealand between 2004 and 2010 and to identify risk factors for human leptospirosis infection.

Method Waikato leptospirosis notification data for the period 1 January 2004 to 31 December 2010 were analysed to identify any trends in the rates and distribution of key variables.

Results Annual Waikato leptospirosis notification rates were consistently higher than national rates. Infection was associated with males (93%) of working age (97%) who had exposure to animals through their occupation. Most cases were employed in dry stock farming, dairy farming or in the meat processing industry.

Conclusion Those who work with cattle continue to be at risk of infection from *Leptospira*. The data suggests that dry stock cattle farmers are at the highest risk. It is speculated that the immunisation of all cattle herds may further reduce the incidence of leptospirosis, although more accurate collection of work exposure data and further analysis is needed to determine this.

Leptospirosis is an infectious disease caused by bacteria of the *Leptospira* genus. Typically, it is hosted by both wild and domesticated animals and transmitted to humans by contact with infected urine, either directly or via water or soil. Worldwide it is considered a significant zoonotic disease, although incidence rates in the developing world are significantly higher than in the developed world.[1] Human to human transmission is rare worldwide and has never been recorded in New Zealand.[2]

Leptospirosis has a wide range of symptoms, in people, including jaundice, diarrhoea, abdominal pain, fever, headache, myalgia, arthralgia, haemoptysis, conjunctival suffusion, chills, rash, nausea, vomiting, cough and sore throat.[3] It can also be asymptomatic. The incubation period is usually 10 days but ranges from 2 to 30 days.

In New Zealand, leptospirosis is notifiable and the most common occupationally acquired zoonotic disease with incidence rates higher than other comparable industrial countries.[3] The most common species identified in cases are *L. interrogans* and *L. borgpetersenii* and each has several serovars prevalent in New Zealand, all of which have a variety of animal vectors.[4]

Until the early 1980s most human cases within New Zealand were dairy farmers infected with *L. borgpetersenii* serover hardjo-bovis. However after a campaign to immunise dairy herds, leptospirosis rates in humans fell significantly.[5,6]

The Waikato region of New Zealand has one large urban centre but has a significant rural population with approximately 42% of the population living in rural or small independent urban areas compared to 25% for the whole of New Zealand. It has higher than national rates of notified leptospirosis and significant numbers of both dairy and dry stock farming.

The aim of this study was to retrospectively review and describe notified leptospirosis cases in the Waikato region of New Zealand between 2004 and 2010 and to identify risk factors for leptospirosis infection.

Methods

All cases of leptospirosis notified to Waikato District Health Board between January 2004 to December 2010, were retrospectively reviewed. Data was obtained from the EpiSurv database, which contains information on individual cases collected from general practitioners, hospital staff and public health staff, and includes information on a range of possible risks factors. The questionnaires originally used by public health staff during the original case investigation to collect data for EpiSurv were also reviewed.

A confirmed case of leptospirosis was defined as an individual with clinical symptoms compatible with leptospirosis and either a ≥400 serological titre on a MAT or a fourfold or greater increase in titre between two consecutive samples.[7] A probable case was defined as an individual with clinical symptoms compatible with leptospirosis and a single raised agglutination titre of >400. Individuals that did not meet these case definitions were not considered to be a case.

All positive samples are now directly notified to Population Health by the laboratory in question. All notified cases were investigated by Population Health staff, using a standardised questionnaire, to try to identify possible sources of infection including: demographic information such as age, gender, occupation and information on activities regarding exposure to animals and fresh water sources for 10 days prior to the onset of symptoms.

The data was entered into the EpiSurv database along with information from general practitioners and hospital staff. The original questionnaires for all of the leptospirosis cases notified to Waikato District Health Board between 2004 and 2010 were also reviewed.

Incidence rates were calculated using population data for the Waikato District Health Board region from the 2006 New Zealand Census. Group specific population data was used to calculate demographic specific incidence rates. Information on herd numbers and types of herds in the different territorial authorities, within the Waikato DHB area, was obtained from the Animal Health Board.

Correlations between number of cases and a variety of exposure factors were examined using EpiInfo® version 3.3.2 and Microsoft Excel® software. These correlations included comparisons between risk factors and identified serovar to determine occupational risk of infection for the three occupational groups identified as being most at risk of leptospirosis in the Waikato.

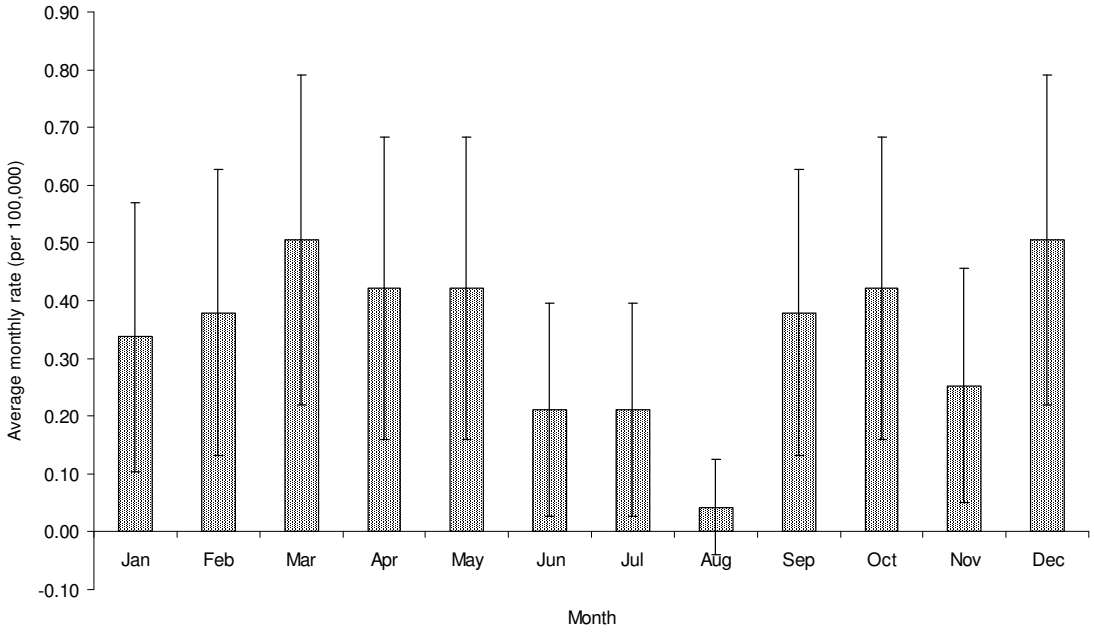
Results

A total of 97 cases of leptospirosis were notified within the Waikato DHB region between 1 January 2004 and 31 December 2010 and all are included in the analysis; 86 (89%) were confirmed cases, 8 were probable and 3 were described as under investigation.

Notified rates within the Waikato were typically higher than national notified incidence rates for the same period. The average Waikato annual rate was 4.1 cases per 100,000 population compared to 2.3 cases per 100,00 population for the whole of New Zealand.

No apparent annual trend in rate was observed during the study period but monthly rates were lower during the winter months of June, July and August (Figure 1) and a significant difference ($p<0.05$) was observed between the rate of cases during the winter and non-winter months.

Figure 1. Average monthly leptospirosis notification rates, Waikato District Health Board, 2004 to 2010



The rate of disease in males (7.4 per 100,000) was approximately 12 times higher than in females. The median age of cases was 41 years (range 17 to 72 years) and 70% of cases were aged between 25 to 64 years. There were no cases aged 15 years or under. Approximately 80% of notified cases were European (4.8 per 100,000) (Table 1).

Forty-seven of the 97 cases (48%) were hospitalised as a result of the illness with 72 of the cases (74%) receiving antibiotic treatment.

Two outbreaks were observed during the period studied both involved only two cases. The linked cases were infected by the same serovar and had similar occupational exposure through working on the same farm.

The rates of disease were generally higher in the southern rural districts of the Waikato DHB area, in particular the proportion of cases (21%) and rates (30.3 per 100,000) were highest in Waitomo District (Table 2).

The most common classified occupation recorded for the notified cases was `farmer and farm manager (35.1%)' followed by `dairy farmer' (25.8%) and `meat process worker' (17.5%). There was a considerable number of different occupations recorded, but few were occupations outside of the farming or meat processing industry.

Table 1. Notified leptospirosis cases by key variable, Waikato District Health Board, 2004 to 2010

Variable	Average annual number of cases	Average annual rate (per 100,000)	95% CI
Ethnicity			
European	10.9 (78.4%)	4.8	1.9–7.6
Māori	2.4 (17.5%)	3.6	-0.9–8.1
Pacific People	0.1 (1.0%)	1.3	-5.6–8.3
Unspecified	0.4 (3.1%)	2.6	-5.3–10.5
Gender			
Male	12.9 (92.8%)	7.4	3.4–11.5
Female	1.0 (7.2%)	0.6	-0.6–1.8
Age group (years)			
15 to 24	2.3 (16.5%)	4.7	-1.4–10.7
25 to 44	6.4 (46.4%)	7.1	1.6–12.6
45 to 64	4.9 (35.0%)	6.1	0.7–11.5
65+	0.3 (2.1%)	0.7	-1.8–3.1

Table 2. Notified leptospirosis cases by territorial authority, Waikato District Health Board, 2004 to 2010

Location	Average annual number of cases	Average annual rate (per 100,000)	95% CI
Hamilton City	0.6 (4.1%)	0.4	-0.7–1.6
Thames Coromandel District	0.4 (3.1%)	1.7	-3.3–6.6
South Waikato District*	0.6 (4.1%)	2.5	-4.0–9.1
Waikato District	1.3 (9.3%)	2.9	-2.1–8.0
Hauraki District	0.6 (4.1%)	3.3	-5.3–11.9
Waipa District	1.7 (12.4%)	4.0	-2.0–10.1
Matamata Piako District	2.1 (15.5%)	7.0	-2.4–16.4
Otorohanga District*	1.7 (12.4%)	18.9	-9.4–47.2
Ruapehu District (part)*	2.0 (14.4%)	23.0	-8.9–54.8
Waitomo District*	2.9 (20.6%)	30.3	-4.8–65.4
Waikato District Health Board Area	13.9 (100%)	4.1	1.9–6.2

* Southern TA

In total seven different serovars of leptospira were associated with notified cases, with hardjo-bovis (24.7%) as the most common followed by pomona (23.7%), ballum (16.5%) and tarassovi (14.4%) (Table 3). In 15 cases the serovar was not identified.

Table 3. Notified leptospirosis cases by serovar, Waikato District Health Board, 2004 to 2010

Serovar	Number of cases (%)
Australis	1 (1%)
Canicola	1 (1%)
Copenhageni	3 (3.1%)

Tarassovi	14 (14.4%)
Ballum	16 (16.5%)
Pomona	23 (23.7%)
Hardjo-bovis	24 (24.7%)
Not identified	15 (15.5%)

Of the 97 notified cases, 90 (93%) had direct exposure to animals and 19 (20%) had exposure to water. Eighty five of the cases (87.6%) had potential exposure to leptospirosis through their occupation and five through overseas travel.

The distribution of serovars for the three most common occupations varied (Table 4). All three occupations had similar proportions of cases infected with the hardjo-bovis serovar, but dairy farmers had a higher proportion infected with tarassovi and fewer infected with pomona than those with occupations described as `farmer and farm manager' and `meat processor'.

Table 4. Number of cases (%) for each serovars for the three largest represented occupation groups, Waikato District Health Board, 2004 to 2010

Occupational group	Serovar case numbers (%)						
	Ballum	Copenhageni	Hardjo-bovis	Pomona	Tarassovi	Unspecified	Total
Dairy farmer	5 (20)	1 (4)	5 (20)	0 (0)	11 (44)	3 (12)	25 (100%)
Farmer and farm manager	6 (17.6)	1 (2.9)	7 (20.6)	9 (26.5)	2 (5.9)	9 (26.5)	34 (100%)
Meat processor	0 (0)	0 (0)	5 (29.4)	10 (58.8)	1 (5.9)	1(5.9)	17 (100%)

Typically in those cases associated with dairy herds, the herd immunisation status was known and was higher than other occupational groups with most herds either fully or partially immunised. For the farmer and farm manager occupational group the immunisation status of half of the herds was unknown. Where this was known most herds were either only partially immunised or not immunised with only three herds identified as fully immunised, For cases employed in the meat industry the immunisation status of the herds was always 'unknown'.

Examination of the residential territorial authority (TA) of cases, within the three main occupational groups, also shows variation between the groups. The 'dairy farmer' cases were evenly spread with a concentration within the Matamata Piako District. The 'meat processing' and `farmer and farm manager' groups had higher number of case residing within the Waitomo and Ruapehu Districts.

Data received from the Animal Health Board on herd numbers showed higher numbers of herds within the areas covered by Waipa and Waikato District councils

but higher ratio of dry stock herds to dairy herds within the Ruapehu and Waitomo District areas (17.7 and 11.3 respectively, compared to 0.73 for South Waikato District and 0.80 for Matamata Piako District, which had the two lowest ratios within this study).

Discussion

In the Waikato, the rate of notified leptospirosis has remained constant over the study period, with an annual average rate of 4.1 per 100,000, compared to the 2010 national average of 1.9 cases per 100,000.[8] This is higher than rates in other developed countries [9–11] but lower than most developing countries.[12–14]

Leptospirosis cases in Waikato were more likely to be associated with working age, European males who had close contact with animals in their working environment, either through work on a farm or in the meat processing industry. This is consistent with leptospirosis studies in other parts of the world.[15–18]

The largest single identified occupational group at risk was farmer or farm worker. This group included those who specified their occupation as livestock farmer, beef farmer, sheep farmer, or mixed livestock farmer, but did not include those who worked on a dairy farm as this was listed as a separate occupation group.

Typically within NZ, dairy herds are immunised against three leptospira serovars; hardjo-bovis, pomona and copenhageni. Dry stock herds are typically not immunised. Immunisation of dairy herds started in the 1980s resulting in a major reduction in the incidence of the disease within dairy farm workers.[6] Before immunisation of dairy herds became widespread, dairy farmers formed the occupational group with the highest incidence of the disease.

Within the period of this study dry stock farmers were the occupational group with the highest rates and dairy farmers formed the second largest occupational group. This is reflected in the differences seen between different TAs. The highest case numbers and incidence rates are found within those TAs where dry stock farming dominates.

Studies have shown that the MAT can be unreliable in identifying the infecting serovar, because of cross reactions between serovars. In a study of leptospirosis cases in the Caribbean the MAT only correctly identified the infecting serovar in less than 50% of cases.[19] However, antigens from more than 20 serovars were included in the MATs in that study.

In New Zealand MAT only includes antigens from the eight serovars which are known to circulate within New Zealand. This reduces the likelihood of cross reactivity and increases the confidence in the test. Further confidence is achieved, within New Zealand, as the MAT is done on two blood samples, one during the acute phase of the illness and the second during the convalescent period, three to four weeks later. This second blood test provides greater specificity than the first (D. Harte, ESR, personal communication, 2012).

The distribution of identified serovars for cases whose occupation is in the meat processing industry is similar to the farmer and farmer manager group and different from those within the dairy farming group. Cases who worked within the meat processing industry were typically infected with serovars hardo-bovis and pomona and dry stock farmer cases were typically infected with serovars hardo-bovis, pomona and ballum. These three serovars are all strongly associated with cattle.

Over 40% (11 cases) of dairy farmer cases were infected with serovar tarassovi. This cluster of tarassovi (2009) was specific to the Waikato and not reflected across the rest of New Zealand. The distribution of infecting serovars within the three main occupational groups suggests that dry stock farmers and meat process workers risk could possibly be minimised by the immunisation of all cattle herds against leptospira.

In conclusion, notified leptospirosis infection in the Waikato continues to be higher than the New Zealand average and that of other developed countries. Occupational exposure is the most significant risk factor with very few cases not having some contact with agricultural animals.

A lack of data within the EpiSurv database makes it difficult to determine incidence rates between different farming systems although it does suggest that beef and dry stock farmers, whose herds are less frequently immunised against leptospirosis, have higher rates than dairy farmers. More accurate data collection and reporting on occupational and non occupational exposure, farming type and herd immunisation is required to determine this with confidence.

The significant reduction in leptospirosis rates in dairy farmers, achieved during the 1980s, because of herd immunisation, demonstrates the effectiveness of the immunisation programme.[5,6] Similar reductions may perhaps be achieved within dry stock farming and the meat processing industry if the immunisation programme were extended to cover all cattle herds.

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Phlebotomy patterns in haemochromatosis patients and their contribution to the blood supply

Deborah Walkden, Krishna Badami

Abstract

Aims To determine venesection patterns in hereditary haemochromatosis (HC) patients in Christchurch, New Zealand, their contribution to the blood supply, and reasons for deferral.

Methods Review of clinical records of 412 HC patients venesected by the NZ Blood Service at least once during 2009.

Results Of 275 males and 137 females, 384 had been tested for HFE gene mutations—76% were C282Y homozygotes, 12.8%, C282Y/H63D compound heterozygous, 8.6%, either H63D homozygotes, C282Y heterozygotes or H63D heterozygotes. Small numbers had no detectable mutations, were not iron overloaded but had been venesected for isolated hyperferritiniaemia. 53% were donors. C282Y homozygotes required significantly more venesections than patients of other genotypes. Eligible HC patients donated 3 units/donor/year compared to 1.63/person/year by healthy donors ($p<0.001$). HC patients contributed 3.4% of whole blood collections in 2009. There were 212 permanent or temporary donation deferrals—common reasons were abnormal liver functions, chronic or malignant disease, or immigration from vCJD risk countries.

Conclusions HC donors donate at nearly twice the rate of healthy donors but contribute only a small amount to the blood pool. Revision of selection criteria may increase this contribution without compromising blood safety.

Hereditary haemochromatosis (HC) is an autosomal recessive disorder characterised by excessive iron absorption from the diet. In populations of northern European origin, as in Christchurch, New Zealand, most HC is due to mutations in the HFE gene on chromosome 6. In such populations, more than 85% of clinical HC cases are caused by the C282Y mutation. Most of the remainder are compound heterozygotes who have another HFE mutation such as H63D or S65C in addition to the C282Y mutation.[1]

Roughly 1 in 250 Caucasians are believed to be C282Y homozygotes and a 1998 study showed homozygosity for C282Y in 1 in 200 of 1064 New Zealanders.[2] Though the prevalence of these mutations in certain populations is high, biochemical evidence of iron overload is seen in only 70% of C282Y homozygotes and clinical manifestations in an even smaller proportion. Penetrance is even less marked in those with non-C282Y HFE mutations.

Factors influencing phenotypic expression are not well understood but probably involve other genetic components, blood loss, diet, and excessive alcohol consumption. Common symptoms in untreated HC cases are lethargy, arthralgias, loss of libido, and impotence. Complications of untreated iron overload include cardiac arrythmias, diabetes mellitus, skin bronzing, cirrhosis, and hepatic carcinoma.[1]

Venesections are a well-established, safe and effective treatment for HC. 'De-ironing' and maintenance of normal iron levels often requires venesections on an ongoing basis. An average of 33.9 venesections was required during the de-ironing phase in a study of over 2000 American HC patients.[3]

It is now accepted that HC patients can safely donate blood if they are otherwise healthy.[4,5] Since they tend to donate more frequently than their non-affected counterparts, they could make a substantial contribution to the blood pool.

The New Zealand Blood Service (NZBS) provides therapeutic venesection services free of charge. Thus, there is no incentive for HC patients to obtain venesections free-of-charge by becoming blood donors, possibly concealing relevant medical information, and endangering the health of transfusion recipients in the process.

Though triggers and targets for therapeutic venesections in HC are in a state of flux, at our centre, essentially the same criteria were, and are, applied to all patients irrespective of sex, age, or genotype. Generally, we have tended to start venesections when serum ferritin levels (SF) exceed 500 mcg/L and continue treatment to keep this at less than 100 mcg/L.

NZBS allows HC patients to be blood donors provided all donor acceptability criteria are met and their liver function tests (LFT) are normal. Blood from HC patients who are not donors is either discarded or used for research purposes.

The aims of the audit were to investigate:

- To what extent HC donors contribute to the blood donor pool.
- Whether there is a difference between males and females with respect to venesection frequency, and age at initiation of venesection.
- The percentages of common genetic mutations, and venesection frequencies between genetic groups.
- The reasons for deferral from donation.

Methods

All HC patients, venesected at least once between 1 January 2009 and 31 December 2009 at the Christchurch centre, were included in the audit. Data—age, sex, HFE genotype, number of units venesected, the number of whole blood donations obtained, and the reasons for permanent or temporary deferral—for the 12-month period were obtained from the clinical records.

Summary statistics for sex, age, genotype, venesections, donations and deferrals were calculated. The 2 sample t-test with pooled variance was used to compare the means of continuous variables

such as age, and the χ^2 test to compare the means of categorical variables such as the numbers of males and females, and number of venesections and donations.

Results

We audited 412 patients (137 females and 275 males).

Data are summarised in Table 1.

Table 1. HC patients in Christchurch, 2009: demographic, venesection and blood donation characteristics

Sex Number (donors)	Age mean ± SD (range)	Venesections (mean/patient/year)	Donations (mean/eligible patient/year)
Females 137 (67) Males 275 (152)	51.7 ± 12.7 (20–75) 50.1 ± 11.7 (18–74)	449 (3.3) 1111(4.0)	186 (2.8) 470 (3.1)
All 412 (219)	**50.6 ± 12.1 (18–75)**	**1560 (3.8)**	**656 (3.0)**

There were significantly more males than females, and males needed significantly more venesections than females (P<0.001). However, the mean age of males and females was similar (P = 0.21) and the number of donations from males was not significantly greater than that from females (P= 0.2129).

Of 412 patients, 219 (53%) were registered as donors and they donated 656 whole blood units over the twelve month audit period averaging 3 units/eligible HC patient/year. In contrast 18,764 units were obtained from 11,485 healthy donors at our centre during the same period averaging 1.6 units/person/year (P<0.001). HC donors contributed 3.4% of the whole blood units collected in Christchurch in 2009.

Of 412 patients, 384 (93%) had been tested for HFE mutations. As expected, the majority (293, 76%) were homozygous for the C282Y mutation. Forty nine (12.8%) were C282Y/H63D compound heterozygotes, 8.6%, in total, were either heterozygous for C282Y (21), or H63D (9), or homozygous for H63D (3). A small minority (7, 1.8%) had been tested but had no detectable HFE mutation.

The average venesection rate for all HC patients combined was 3.8 units/patient/year. C282Y homozygotes required significantly more venesections than patients of other genotypes (P<0.001). There were no significant differences between the venesection rates of patients who were C282Y/H63D compound heterozygotes, C282Y or H63D heterozygotes, or H63D homozygotes (table 2).

Table 2. HC patients in Christchurch, 2009: HFE gene status and venesections

Genetic status number (%)	Venesections number (mean/patient/year)*
C282Y homozygote 293 (71.1)	1173 (4)
Compound heterozygote 49 (11.9)	161(3.3)
C282Y heterozygote 21 (5.1)	73 (3.5)
H63D heterozygote 9 (2.2)	38 (4.2)
H63D homozygote 3 (0.7)	20 (6.7)
Negative for C282Y and H63D 7 (1.7)	15 (2.1)
Not stated 30 (7.3)	80 (2.9)
All 412	**1560 (3.8)**

*Average venesection rates were calculated using figures for both initial iron reducing, and maintenance phases.

178 donation deferrals were permanent (Table 3).

Table 3. HC patients in Christchurch, 2009: reasons for permanent deferral from donating

Reason	Number (%)
Abnormal LFT	55 (30.9)
vCJD-risk[#]	40 (22.5)
Historic or current malignant disease	23 (12.9)
Chronic medical conditions	40 (22.5)
Blood borne infection risk	12 (6.7)
Other*	8 (4.5)
Total	**178**

[#] Residence in the UK/France/Ireland for ≥ 6 months cumulatively between 1980 and 1996

* 4 unsuitable veins, 1 faint, 1 old age, 2 personal choice.

HC patients deferred for abnormal LFT can be reinstated as donors when these normalise. Those over 75 years of age, those with cerebrovascular disease, ischaemic heart disease, or predisposition to fainting, are required to attend designated, medically-supervised clinics. Blood is not collected for donation at these clinics. Twenty one deferrals were temporary—16 on account of potential infection risk, 4 because of recent trauma or surgery, and in 1 case, due to insufficient blood collected. In 50 instances, the reason for deferral was not documented.

Discussion

The audit shows that, in our setting, 53% of HC patients were eligible to donate and they donated more frequently than non-HC donors. However they contributed only a small proportion (3.4%) of the whole blood units collected in 2009 at this centre. Leitman et al reported that 76% of their HC patients were eligible to donate blood and contributed 14% of units to the inventory. Their donors were permitted to donate with ALT levels up to 100U/L.[4] In contrast, in another report on 16 US blood centres, only

0.4% of red cell units came from HC donors. The author attributed the low rate to the complexity of paperwork and testing associated with such donors.[6]

Our audit included significantly more males than females, and showed that males required significantly more venesections than females. These likely reflect the natural history of HC and demonstrates the lower iron content of the female diet, and menstruation, pregnancy and lactation during the premenopausal years. Interestingly, the age range and mean age of females did not differ significantly from that of males (Table 1). This, which has also been noted in other studies,[7,8] may be due to clinically mild HC being detected early in females who were tested to rule out iron deficiency as a cause of non-specific symptoms or as part of a family study following the initial diagnosis of HC in a male relative.

The proportions of subjects of each genotype in our audit was similar to that found by Leitman et al.[4] As expected, C282Y homozygotes required more venesections than patients with other genotypes with the exception of patients homozygous for H63D but numbers were small in the latter category. Seven patients with no detectable HFE gene mutations had been diagnosed with HC based solely on high SF without documented transferrin saturation (tfs) exceeding 50%. In these patients the average venesection rate was 2.1/patient/year–considerably less than the overall rate of 3.8/patient/year. It is important to remember that a raised fasting tfs is generally regarded an important diagnostic criterion for HFE-related HC at presentation though non-HFE HC, and some HFE-related HC may not present this way.[1]

High SF with normal tfs is a common finding suggestive of conditions other than HC such as inflammation, excessive alcohol consumption and the dysmetabolic syndrome.[9] With the current obesity epidemic, this is becoming common and may account for a number of venesection referrals which may not benefit, and indeed harm some patients.[9]

178 HC patients (43.2%) were permanently deferred from donating. Some of these deferrals (e.g. on account of abnormal LFT) are permanent only in the sense of being open-ended. Such patients can be reinstated as donors when these parameters return to normal. However, significant proportions of permanent deferrals are indeed truly permanent (Table 3).

About 20% (40/199) of all deferrals amongst HC patients were because of prior residence in vCJD-risk countries compared to 0.8 % among blood donors in general.10 This reflects the number of people of north-western European origin in Christchurch.[11] In addition, it has been and continues to be, common for young New Zealanders to spend extended periods of time overseas—especially in the UK.

As expected, homozygous C282Y HC patients had higher venesection rates than those of other genotypes. The average age of male and female HC patients was similar though males were venesected significantly more often than females. HC donors donated at almost twice the rate of those without HC emphasising their value to the blood service.

Many HC donors are deferred on account of the vCJD risk and abnormal LFT. Non-HC donors do not routinely have iron status or LFT checked and may, in fact, have abnormal results on account of undiagnosed HC, dysmetabolic syndrome, etc. The significance, to transfusion recipients, of high SF and liver enzymes in blood donors, in the absence of other abnormalities, is unclear.

A re-evaluation of current donor deferral criteria applied to HC patients is warranted. This has the potential to increase their contribution to the whole blood pool without compromising patient or blood safety.

Competing interests: None known.

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Safety and efficacy of stroke thrombolysis at a secondary provincial hospital in New Zealand

Annemarei Ranta, Calvin Chan, Dorothea Rump, Pietro Cariga

Abstract

Aims Stroke thrombolysis with alteplase is the most effective therapy for acute ischaemic stroke. Most trial data comes from tertiary centres. This study set out to assess safety and efficacy of thrombolysis at a secondary provincial centre in New Zealand.

Methods A retrospective 3-year audit was performed to assess efficacy and safety of altepase at a secondary provincial hospital in New Zealand.

Results Out of 27 patients receiving treatment 17 (62.3%) improved and 10 (37.0%) enjoyed essentially complete symptom resolution (mRS=0 or 1). There was one symptomatic intracranial haemorrhage (3.7%).

Conclusion Administration of intravenous alteplase for ischaemic stroke patients is effective and safe in the secondary provincial setting if local protocols are used, patient selection is stringent, and care is supervised by neurologists with training/experience in stroke care and thrombolysis. Aspects of thrombolysis-related management issues in this study population are discussed.

Thrombolysis with alteplase is the most effective medical therapy for acute ischaemic stroke. Its application has been increasingly permeating medical practice around the globe ever since the publication of the NINDS trial data in 1995 establishing safety and efficacy if the medication is administered within 3 hours of symptom onset adhering to strict in- and exclusion criteria.[1]

Subsequent trials and meta-analyses have confirmed the utility of this medication in the tertiary setting under expert guidance.[2,3] In 2008, the window was extended from 3 to 4.5 hours after publication of ECASS III using slightly more stringent criteria[4].

Most international data come from tertiary centres equipped with stroke units and 24 hour/7days a week (24/7) on-call stroke neurologists casting some doubts on the transferability of this data to community hospitals and countries such as New Zealand where even tertiary centers struggle to provide an on-call roster of stroke neurologists.

Fink et al published their Christchurch audit data in 2009 indicating that this therapy can be administered safely and efficaciously within New Zealand with general neurology oversight.[5]

A similar paper comes from Australia.[6] However, these studies once more come from tertiary centres that enjoy a sufficient number of neurologists/stroke physicians on staff to provide such a service.

A recent population-based study from South Australia once confirmed that the vast majority of stroke thrombolysis occurs in the tertiary setting and that distance to a tertiary hospital inversely correlates with access to thrombolysis.[7] A few smaller studies report thrombolysis use at community hospitals[8–10] and associated ethical dilemmas are discussed.[9,11,12]

Other papers addressing thrombolysis at non-tertiary or rural/provincial centers focus primarily on telemedicine utilising two way videoconferencing systems to provide tertiary centre back-up[9,13,14] rather than the provision of on-site expert support. In New Zealand, stroke thrombolysis is offered at a number of non-tertiary, provincial, and/or rural centres (data unpublished, Ranta, 2011) although data to support this practice in New Zealand is lacking.

Since March 2008 stroke thrombolysis has been offered at Palmerston North Hospital, a 350-bed secondary teaching hospital located on New Zealand's North Island serving a population of 167,000. The acute stroke service, established in July 2007, operates a 5-bed stroke unit and comprises a multi-disciplinary team lead by two full-time neurologists providing routine Monday through Friday 8am to 5pm coverage and an informal after hour (24 hours, 7 days per week) thrombolysis roster on a goodwill basis (i.e. without remuneration) with only rare occasions of no coverage being provided. All thrombolysis cases are attended in person and directly supervised by either one of the two staff neurologists both during regular and after hours.

This paper presents a complete retrospective audit spanning three years from mid-March 2008 through mid-March 2011 capturing all stroke patients thrombolysed at Palmerston North Hospital starting from the local introduction of this therapy through completion of this audit. This audit was intended to assess safety and efficacy of stroke thrombolysis at a secondary centre in New Zealand.

Methods

Since initiation of stroke thrombolysis at Palmerston North Hospital in March 2008 all patients receiving or being considered for stroke thrombolysis have been entered into a registry for later audit purposes.

Registered patient files were reviewed retrospectively to extract the following: time of symptom onset, ambulance times (dispatch, arrival at the scene, departure of scene, and arrival at the hospital), triage category in ambulance and emergency department (ED), time of computed tomography (CT), time of laboratory value availability, time of neurologist notification/arrival in the emergency department, any reason if treatment was deferred, protocol violations, needle time, complications including haemorrhage on CT, neurological deterioration, death of any cause, modified Rankin Scale (mRS) score at time of neurologic assessment, at 24 hours, at discharge, and at outpatient follow-up 6–12 weeks after discharge if available.

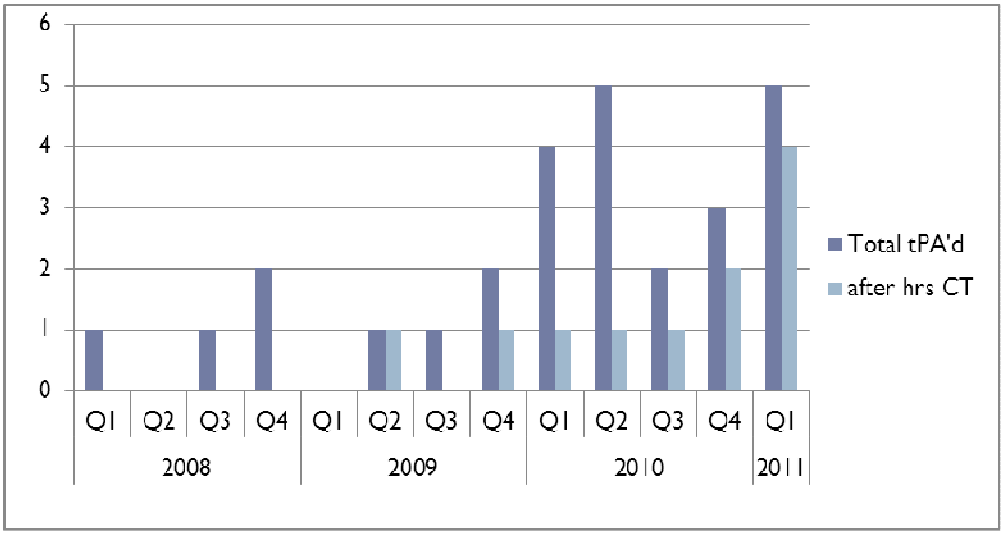
Generally, mRS was determined by two independent investigators, neither of whom was involved in the care of the patients. In cases where there was a discrepancy between reviewers the primary investigator was consulted to make a final assessment. Data was collated and analysed using Microsoft Excel. As there was no comparison group and overall numbers were small statistical significance was not assessed.

Results

Between March 2008 and 13 April 2011, Alteplase was considered in 58 patients, 27 of whom received the treatment (45.6%). The total number of ischaemic strokes

admitted to Palmerston North Hospital over the same period was 552 indicating a low thrombolysis rate of only 4.9%. However, case frequency has progressively increased over time (Figure 1) and the thrombolysis rate rose to 7.3% during the final 12 months of this audit (16 thrombolysed; 220 total ischaemic strokes). Eleven patients (40.7%) were treated outside of regular hours and one of these was treated after midnight.

Figure 1. Number of patients treated per quarter and proportion out of hours



Average ± standard deviation (SD) onset to needle time was 170 ± 40 minutes, with a significant proportion spent after completion of CT (average of 52 ± 30.1 minutes) in comparison to a relatively short time span from door to CT (48 ± 32.2 minutes).

The average time of the ambulance crew spent on the scene was 21 ± 6.4 minutes. Priority scores during the ambulance and ED phase ranged from 1–3 with 65% (in ambulance) and 57% (in ED) receiving a priority of ≤2 (i.e. high acuity transported with sirens activated).

Patients with a lower acuity score experienced on average a non-significantly longer time on location (1.8 minutes), but an average 12-minute longer door to needle time in ED. Ambulance transport times could not adequately be compared as patient distance from location to hospital varies widely given the size of the district.

Patient demographics, time delays, and a comparison to tertiary hospital data are summarised in Tables 1 and 2.

Table 1. Patient demographics and presenting times and location

	Palmerston North (36-month data) n*	Christchurch[5] (12-month data) n
Patients thrombolysed	27	16
Mean age (years)	67	65
Age range (years)	38–90	33–84
Male	11	8
Female	18	8
Regular hours (Mon–Fri 08:00–17:00)**	16	
After hours (Sat/Sun or Mon–Fri 17:01–07:59)**	11	
Emergency Department (ED)	24	
Inpatient	3	

*Except when specified e.g '(years)'; ** Regular hours = Monday through Friday 8am–5pm; After hours = Saturday, Sunday, and Monday–Friday 5:01pm–7:69am.

Table 2. Time delays in minutes

	Palmerston North Mean (± SD)	Christchurch Mean (Range)
Symptoms to needle	170 (±39.9)	150 (60–177)
Dispatch to scene	11 (±6.5)	–
Scene to departure	21 (±6.4)	–
Departure to ED	27 (±22.9)	–
Dispatch to ED	61 (±25.8)	–
Door to needle	90 (±23/3)	99 (47–160)
CT to needle*	48 (±32.2)	–
Door to CT*	52 (±30.1)	60 (30–106)

*These figures exclude three patients in whom CT time was not documented; coincidentally these three individuals received tPA faster than the total average, which explains why average 'CT to needle' and 'Door to CT' figures do not exactly add up to total average door to needle time.

Overall, 17 (62.3%) patients improved after receiving alteplase, 10 (37%) of whom had a very favourable outcome (mRS = 0–1), six (22.2%) patients remained unchanged, and four (14.8%) patients worsened. The symptomatic intracranial haemorrhage (ICH) rate was 3.7% (Table 3).

The average degree of improvement observed in responders was 2.41 ± 1.33 points on the mRS. Overall change in mRS including the patients who worsened, died (including non-alteplase related deaths), or did not respond still showed an average net improvement of 1.26 ± 1.95 points (Table 4 and Figure 2).

Table 3. Patient outcomes

Variables	Palmerston North n = 27		Christchurch n = 16	Meta-analysis n = 2239[3]
	n	%	%	%
Improved mRS	17	62.3	50*	
Very favourable outcome (mRS 0–1)	10	37	31*	37
Unchanged mRS	6	22.2	31	
Poorer mRS	4	14.8	6.3	
ICH	4	14.8	12.5	
Symptomatic ICH	1	3.7	6.3	5.2
Deaths	4	14.8	6.3	13
rtPA-related deaths	1	3.7		
Discharged to rehabilitation	13	48.1		
Discharged home	8	29.6		
Other**	2	7.4		

* In the Christchurch study improvement was reported as a drop in NIHSS of 4 or more points (NIHSS ranges 0–41) and very favourable outcome as mRS of 0–2.

** Wellington Hospital for CEA (1); Whangarei Hospital (1); both were subsequently discharged home.

mRS= modified Rankin Scale; ICH=intracerebral haemorrhage; rtPA=recombinant tissue Plasminogen Activator.

Table 4: mRS scores in thrombolysed patients

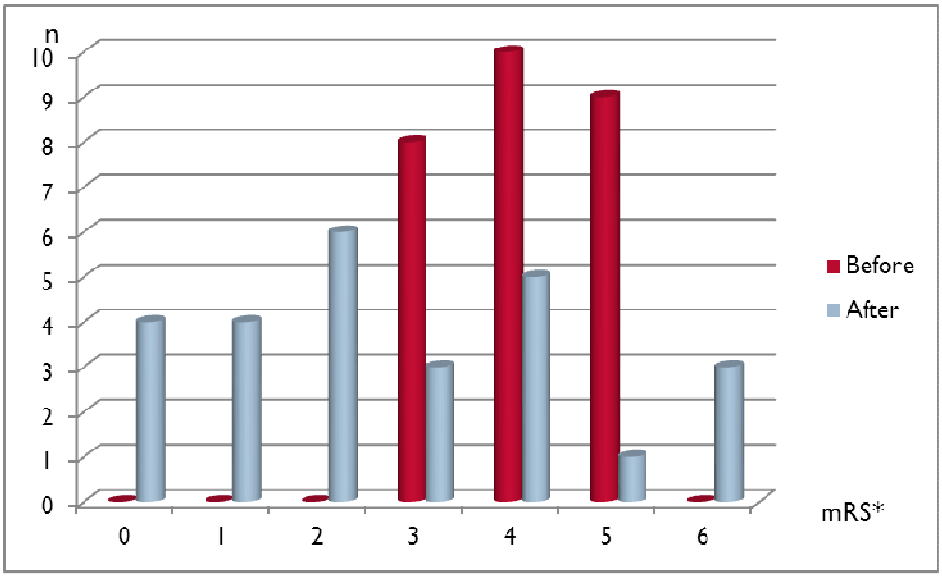
Variables	Average	SD
At presentation	4.04	0.81
At 24 hours	3.11	1.76
At d/c or f/u*	2.63	2.06
Overall change	1.26	1.95
Change in responders	2.41	1.33
Change in non-responders	0.5	1.09

* d/c=discharge; f/u=follow-up when available and within 3 months of rtPA.

Six patients were thrombolysed within the extended 3–4.5 hour window. One of these died of a subsequent myocardial infarction, one patient did not improve, and four improved by an average mRS of 3.25 ± 2.06.

All four patients who worsened died. Three of these deaths were unrelated to Alteplase use. Two patients died from ischaemic stroke complications (i.e. aspiration pneumonia) without change in neurologic function after receiving Alteplase and follow-up head CTs did not show any evidence of bleeding. The third patient's infusion was prematurely stopped after just a third of the dose had been administered because the nurse thought she had made an error in administering the drug. Shortly after stopping the infusion the patient suffered a cardiac arrest. Autopsy demonstrated no evidence of an alteplase-related complication (including no evidence of ICH) and root cause analysis revealed that no medication administration error had taken place. The cause of death was determined to be a myocardial infarction.

Figure 2. mRS before and after treatment



*0=No symptoms; 1=Mild symptoms, full ADL; 2=Mild symptoms, some decrease in ADL, but fully independent; 3=Moderate symptoms, requires some help with ADL, but ambulatory; 4=moderately severe disability, non-ambulatory, unable to attend to own bodily needs; 5=severe disability, requires constant nursing care; 6=dead.

The one patient who suffered a symptomatic ICH had a severe ischaemic stroke on presentation with National Institute of Health Stroke Scale (NIHSS) of 27; given the severity of the stroke bleeding risk was considered relatively high, but after consultation with patient's family it was deemed in the patient's best interest to provide the treatment, the patient was within the 3 hour window and all NINDS inclusion criteria were met.

One other patient showed evidence of a significant haemorrhage on post-thrombolysis CT, but this did not lead to clinical worsening and is thus not classed as a "symptomatic" ICH.[1,4] This patient also met all inclusion/exclusion criteria although the patient had a borderline platelet count of 99,000/ml^3, which rose to 102,000/ml^3 on rapid re-check prior to giving alteplase (cut off is 100,000/ml^3).

Two further patients demonstrated mild "streaking" on CT suggesting a very minor haemorrhage. Both patients were asymptomatic from these minor haemorrhages and experienced significant and rapid recovery from their presenting stroke symptoms. Aside from the debatable deviation from inclusion criteria in the above patient with a borderline platelet count there were no identified violations of the local thrombolysis protocol, which is largely based on the NINDS criteria.

Reasons for deferring thrombolysis in the 31 patients who were referred for thrombolysis but not treated included ICH on CT, rapidly improving or resolved symptoms, current warfarin therapy/elevated INR, persistently elevated blood pressure, increased systemic bleeding risk (e.g. recent bleeding ulcer), and presentation inconsistent with stroke.

The majority of the remaining 492 ischaemic stroke patients admitted to Palmerston North Hospital during the study period were not 'considered' for tPA because they arrived outside the treatment window. However, some patients also missed out because of inefficiencies and unawareness of thrombolysis availability by emergency room staff. This was predominantly a problem shortly after introduction of stroke thrombolysis at our centre and since these rates started to be monitored 12 months ago we are aware of only a single patient who missed out due to a poor triage process. This patient was a cancer patient and was initially referred to the oncologists instead of the thrombolysis team and by the time neurology was notified too much time had elapsed.

Discussion

This is a retrospective audit and is thus limited by its observational, non-randomised, and open label design. Observer bias was limited by recruiting independent chart auditors and adhering to international definitions for determining mRS and classifications such as "symptomatic haemorrhage."

Keeping the limitations of a retrospective audit and small sample size in mind this study is reassuring as regards safety of stroke thrombolysis with intravenous Alteplase in the secondary setting in New Zealand given that our results closely mimic both tertiary data from a New Zealand centre as well as data from a large international meta-analysis.

Efficacy is more difficult to evaluate from an unblinded series with no control group. However, it is encouraging that our efficacy data not only closely mimics the Christchurch and meta-analysis results, but also the results of the pivotal NINDS placebo-controlled trial. This trial demonstrated at 39% rate of very favourable outcome (compared with our 37%), which compared with placebo indicated a 30% greater likelihood of recovery.[1] It is furthermore reassuring that the extension to the 4.5 hours window, based on the ECASS III trial,[4] has not adversely affected the overall outcome in our series.

Despite significant benefit in the responder group, as anticipated there are associated risks. While three of the four patients who died suffered unrelated deaths one died as a direct result of treatment. It is noteworthy that under the ECASS III protocol[4] this patient would have been excluded due to his high NIHSS score. While some patients and families may prefer to accept the higher bleeding risk and still choose thrombolysis as it may offer the only hope of a meaningful recovery in this situation we no longer routinely offer thrombolysis to patients with an NIHSS of >25.

The patient with the borderline platelet count did not come to harm and whether the ICH was related to the borderline platelet count remains unclear. Several consultant haematolgists have indicated that the link seems unlikely. Nonetheless, despite a lack of similar cases in the literature one might conclude that treating in the setting of a borderline platelet count should perhaps be avoided.

Delays in accomplishing a head CT in a centre with a single available CT scanner and no after-hours on-site CT technicians is understandable and results are in fact quite

encouraging. However, the observed delays by ambulance staff at the scene and in ED after the CT is obtained are more difficult to understand and justify. These delays are most likely related to limited awareness of the urgency with which these patients need to be assessed and lack of familiarity with local protocols. This may, in part, be due to a combination of frequent staff turn-over and relative infrequency of these cases.

Some of the delays may also be attributable to poorly written protocols and much effort has gone into collaborating with ED staff to maximise user-friendliness. Similar efforts have gone into ongoing education of ED staff and should go into education of ambulance staff. The latter can be challenging as ambulance crews are typically trained off site and are thus not under the direct influence of the local stroke team. Similarly difficult to reach is the public who often continues to take the attitude of attempting to "sleep off" the symptoms and thereby missing out on the opportunity of treatment.

While this audit is very reassuring, it has to be emphasized that supervision occurred by on site experienced neurologists, in the setting of an organised stroke service with a formalised local thrombolysis protocol and essentially no protocol violations. Thus it is not possible to draw conclusions about the safety and efficacy of thrombolysis provided by less experienced clinicians at even smaller centres around the country.

Even with neurologists on site a one-in-two roster is difficult to maintain and alternative options, such as tele-medicine through regional networks, ought to be explored by district health boards to further increase patient access to this very effective therapy without exposing patients to excessive risks.

Competing interests: None known.

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New Zealand National Acute Stroke Services Audit: acute stroke care delivery in New Zealand

Nicholas Child, John Fink, Shelley Jones, Kevin Voges, Mark Vivian, P Alan Barber

Abstract

Aims To audit the care of a consecutive group of acute stroke patients admitted to all District Health Boards (DHBs) in New Zealand.

Methods A clinical audit involving a review of up to 40 consecutive stroke patients treated and discharged from each DHB between 1st of June 2008 and 31st of December 2008.

Results The clinical care of 832 patients [400 men; median age 77 (interquartile range 67–84) years] admitted to 20 of 21 DHBs was audited. This represents approximately 20% of all stroke patients admitted to hospital in New Zealand over this 6 month period. Most of the audited patients were independent (66%, mRS ≤ 2) and 90% lived at home prior to their strokes. At stroke onset, 40% had a known diagnosis of atrial fibrillation (AF), of whom only 24% were taking anticoagulants. Thirty-eight percent of patients arrived in hospital within 4.5 hours of stroke onset but only 3% were treated with stroke thrombolysis. Only 28% of patients were managed in a stroke unit but these patients had higher rates of thrombolysis, more rapid access to multidisciplinary team assessments and a lower rate of stroke progression (8% vs 15%, $p<0.01$). Only 21% of ischaemic stroke patients received aspirin within 48 hours and 35% of patients had a speech-language therapist assessment within 48 hours of admission.

Conclusion Access to stroke unit care and thrombolysis rates remain low in New Zealand and should be seen as the top priorities for acute stroke care improvement along with anticoagulation for stroke prevention in AF, acute aspirin use and increased speech language therapy assessments.

Stroke is the third most common cause of death after heart disease and all cancers combined and a the major cause of long term adult disability. There were approximately 6 000 first ever and 2 000 recurrent strokes in New Zealand in 2009 of whom 90% were admitted to hospital.[1] The annual life-time cost of stroke to New Zealand is estimated to be $450 million per year.[2]

The Diabetes and Cardiovascular Disease Quality Improvement Plan 2008 (QIP) identified improvement of stroke services as a healthcare priority.[3] However, there has been little information on the provision of stroke services and this hampers the evaluation and benchmarking of District Health Board (DHB) service provision. The National Acute Stroke Services Audit was an initiative of the Stroke Foundation of New Zealand (SFNZ) to audit stroke care in all DHBs and was supported by the

Ministry of Health. We report the results of an audit of the clinical care provided to 40 consecutive patients in each DHB.[4]

Methods

The National Acute Stroke Services Audit was carried out in collaboration with the Australian National Stroke Foundation (NSF). The audit determined the resources available to support the delivery of evidence-based care and examined conformance of clinical practice with evidence-based best practice recommendations. Audit questions were developed by the Australian National Stroke Foundation Audit Advisory Committee, on which there were New Zealand representatives, and question terminology was revised to reflect the New Zealand situation.

The audit was comprised of two parts: an organisational survey of structural and process elements of acute stroke care service provision, which is reported separately; and a clinical audit involving retrospective review of patient records of 40 consecutive stroke patients admitted, treated and discharged from acute care in each DHB.[5]

All 21 DHBs were contacted inviting them to participate in the audit. All 21 DHBs participated in the organisational component of the audit and 20 participated in the clinical audit of acute stroke care delivery, with one small DHB opting not to take part. A stroke unit was defined as a discrete ward, or beds within a ward, with a dedicated specialised multi-disciplinary team (MDT) and could include acute stroke units that discharge patients to a rehabilitation service, or an integrated acute and rehabilitation unit.

An audit team was established within each DHB and consisted of medical, nursing, and allied health professionals. An hour of on-line training was provided via teleconference by the NSF National Audit program manager and project officer. Responses could only be recorded where there was documented evidence for process of care indicators.

The audit was carried out online and the person reviewing the notes entered the data. The clinical audit period in which patients must have been admitted, treated and discharged from acute care occurred between 1 June 2008 and 31 December 2008.

DHBs were split into three groups on the basis of population served and the predicted number of stroke admissions per year. These groups were: Large, with a population catchment > 200 000 people, Medium with a population of 120 000 – 200 000 and Small with a population of < 120 000. Where data was reported from more than one acute hospital within a DHB it was aggregated and reported for the whole DHB.

The audit was conducted in Australia at the same time and was identical with the exception that patients admitted to individual hospitals and not DHBs were audited with the results reported by hospital size.

DHB datasets were de-identified and analysed using PASW Statistics Version 18.0. Organisation data from DHBs was aggregated to provide national estimates with results divided into DHB category (large, medium or small) and stroke unit status. The median (50th percentile) and interquartile (25th percentile) ranges were reported for continuous data. Data collection was carried out from April to August 2009

Results

The clinical care of 832 patients [400 men (48%); 108 (13%) Maori, median (interquartile age) 77 (67-84) years] was audited**.** Equal numbers of patients were audited from large (33%), medium (33%) and small (34%) DHBs.

791 of 832 (95%) patients had brain imaging; 90% had computed tomography (CT), 18% magnetic resonance imaging (MRI) and 8% had both imaging modalities.

Of the patients with brain imaging, 657 (83%) had an ischaemic stroke and 134 (17%) had intracerebral haemorrhage. Stroke subtype was documented by the Oxford Stroke

Classification in 401 of 608 ischaemic stroke patients; of whom 32% had partial anterior circulation infarcts, 25% had posterior circulation infarcts, 24% had lacunar infarcts and 19% total anterior circulation infarcts.

751 of 832 (90%) patients had lived at home prior to the stroke and 549 of 832 (66%) had a pre-stroke modified Rankin scale score of 0-2. Pre-stroke risk factors were recorded in 69–90% of patients (depending on the risk factor) (Table 1), with zero, one, two and multiple risk factors seen in 9%, 18%, 23% and 50% of patients, respectively.

Prior to the stroke, 463 of 536 (87%, where this data was recorded) of hypertensive patients were taking anti-hypertensive therapy, 171 of 244 (71%) of patients with elevated cholesterol were taking lipid lowering therapy and 66 of 272 (24%) of patients with atrial fibrillation were taking anti-coagulant therapy.

Table 1. Known risk factors prior to stroke where recorded

Risk factor	N / total N*
Previous stroke / Transient ischaemic attack (TIA)	308 / 685 (45%)
Atrial fibrillation	272 / 682 (40%)
Hypertension	536 / 747 (72%)
Hypercholesterolaemia	244 / 606 (40%)
Current / past smoker	320 / 666 (48%)
Ischaemic heart disease	232 / 678 (34%)
Diabetes	158 / 696 (23%)
High alcohol consumption	58 / 547 (11%)
Valvular heart disease	71 / 572 (12%)
Myocardial infarction within 6 months	/ 656 (6%)

* Where this information was recorded.

Where this information was recorded 578 (69%) patients were transported to hospital by ambulance, 176 (21%) arrived by private vehicles and 20 (3%) patients had strokes while in hospital.

290 of 772 (38%) patients, where this information was recorded, arrived in hospital within 4.5 hours of symptom onset. Only 28% of patients were managed in a stroke unit, which was less than the 49% of Australian patients managed in stroke units. Even in the eight DHBs with stroke units, only 52% of patients actually received stroke unit care.

Aspirin was given acutely (<48 hours) to 126 of 602 (21%) ischaemic stroke patients where this data was recorded. Patients presenting to the 8 DHBs with stroke units were more likely to be treated with stroke thrombolysis than those without stroke units (13% versus 4% of patients arriving within the 3-hour treatment window; p=0.04, Fisher's exact test).

Patients in large DHBs and in those DHBs with stroke units were more likely to have a physiotherapy, speech language and social work assessment within 48 hours (Table

2). Patients treated in a DHB with a stroke unit were less likely to suffer complications of stroke progression and pulmonary embolism than those treated in a DHB outside of a stroke unit (Table 3).

Carotid imaging was obtained in 182 of 832 (22%: SU 19%, no SU 24%) of patients compared with 50% of all Australian patients.

Table 2. Multi-disciplinary team assessment

Assessment	Total (N=832)	Large (N=277)	Medium (N=273)	Small (N=282)	Stroke unit (N=336)	No stroke unit (N=496)
PT assessment – within 48 hrs	639 (82%) 316 (41%)	240 (91%) 143 (54%)	205 (79%) 104 (40%)	194 (76%) 69 (27%)	276 (86%) 162 (51%)	363 (79%) 154 (34%)
OT assessment – within 48 hrs	515 (68%) 134 (18%)	197 (77%) 53 (21%)	171 (67%) 58 (23%)	147 (60%) 23 (9%)	223 (71%) 75 (24%)	292 (66%) 59 (13%)
SLT assessment – within 48 hrs	447 (61%) 259 (35%)	167 (70%) 99 (41%)	144 (59%) 88 (36%)	136 (55%) 72 (29%)	198 (66%) 131 (43%)	249 (58%) 128 (30%)
Swallow assessment*	280 (61%)	85 (54%)	99 (70%)	96 (61%)	123 (63%)	157 (61%)
SW assessment – within 48 hrs	331 (44%) 69 (9%)	152 (60%) 43 (17%)	99 (41%) 20 (8%)	80 (32%) 6 (2%)	161 (53%) 49 (16%)	170 (38%) 20 (4%)

* Swallow screened within 24 hours; PT=physiotherapy; OT=occupational therapy; SLT=speech language therapist; SW=social worker.

Table 3. Complications during hospital stay

Complication	Total (N=832)	A/large (N=277)	B/medium (N=273)	C/small (N=282)	Stroke Unit (N=336)	No Unit (N=496)
Stroke progression	100 (12%)	32 (12%)	23 (8%)	45 (16%)	27 (8%)	73 (15%)
New stroke	32 (4%)	13 (5%)	7 (3%)	12 (4%)	13 (4%)	19 (4%)
Fever	98 (12%)	43 (15%)	30 (11%)	25 (9%)	37 (11%)	61 (12%)
Pneumonia	83 (10%)	32 (12%)	31 (11%)	20 (7%)	29 (9%)	54 (11%)
UTI	60 (7%)	18 (6%)	21 (8%)	21 (7%)	20 (6%)	40 (8%)
New AF	41 (5%)	12 (4%)	15 (5%)	14 (5%)	15 (4%)	26 (5%)
Pressure sores	14 (2%)	5 (2%)	3 (1%)	6 (2%)	5 (1%)	9 (2%)
MI	19 (2%)	10 (4%)	4 (1%)	5 (2%)	6 (2%)	13 (3%)
DVT	6 (1%)	3 (1%)	0 (0%)	3 (1%)	2 (1%)	4 (1%)
PE	4 (<1%)	1 (<1%)	0 (0%)	3 (1%)	0 (0%)	4 (1%)

* UTI=urinary tract infection; AF=atrial fibrillation; MI=myocardial infarction; DVT=deep vein thrombosis; PE=pulmonary embolus.

Of the 832 patients, 120 (14%) died while still in hospital, 224 (27%) were transferred from acute services to inpatient rehabilitation, 333 (40%) were discharged to their own or a relative's home and 90 (11%) were discharged to residential care.

Prior to discharge, 297 of 712 (42%) had a discharge care plan provided where this information was recorded, 268 of 832 (32%) received patient education and 53 of 408 (13 %) had a home visit performed.

The median Modified Rankin Score of patients discharged from acute care services was 3 (IQR 2-4).

At discharge, prescriptions were given for anti-hypertensive therapy in 71% of patients, lipid lowering therapy in 73% and anti-thrombotic therapy in 94% of ischemic stroke patients. There was no difference in rate of secondary prevention medication use in DHBs with and without a stroke unit and rates were also comparable between New Zealand and Australia.

Discussion

The clinical care of 832 patients, representing approximately 20% of all stroke patients admitted to hospital in New Zealand over this 6 month period, has been audited. All but one small DHB participated so that the results presented are nationally representative of the state of acute stroke care.

There is overwhelming evidence that stroke unit care significantly reduces death, disability and need for institutional care compared with care in general wards.[6-8] Only 18 patients need to receive organised inpatient stroke care to prevent one from dying or being dependent at one year.[9]

New Zealand stroke guidelines have stated that "the most important intervention that can improve outcomes for all people with stroke is the provision of organised stroke services, an important component of which is a stroke unit. Without an organised stroke service, adherence to recommendations about specific interventions is likely to have little impact on outcomes for people with stroke."[10,11] It is clear from an earlier survey that New Zealand clinicians recognise the benefits of stroke units.[12]

It is therefore of concern that only just over one quarter of stroke in-patients in New Zealand were being managed in a stroke unit on the day of the audit and only half of all patients admitted to a DHB with a stroke unit were being managed in the stroke unit.

Access to stroke unit care remains a key deficiency in stroke patient management in New Zealand and requires urgent action. The 2010 New Zealand stroke guideline specifies the level of service provision expected from small, medium and large DHB's for stroke patients.[11] Further work is required in many DHBs to meet these obligations, including improved access for patients to the stroke unit where one is provided.

This audit has confirmed that patients admitted to a stroke unit have better access to thrombolytic therapy. However, very few stroke patients are actually treated with thrombolysis in either New Zealand or Australia. Improving the rate of stroke thrombolysis should be a top priority for all stroke service providers.

The treatment window for stroke thrombolysis at the time of this audit was 3 hours. This window has subsequently been extended out to 4.5 hours,[11, 13] and this will likely lead to an increase in stroke thrombolysis rates. However, it is still of concern that only 38% of patients with a known time of symptom onset arrived in hospital within

4.5 hours of symptom onset. This may in part be due to the finding that only two thirds of people with stroke are transported to hospital by ambulance.

Public awareness of stroke, including recognition of acute stroke in the community and the need to call emergency services for rapid transport to hospital must also be improved if stroke thrombolysis rates are to be improved.

Although patients with hypertension and hypercholesterolaemia were generally on primary prevention treatment for these conditions, a surprisingly low number of patients identified as having AF in both New Zealand and Australia were taking anti-coagulant therapy to prevent stroke and systemic embolism.

While half of New Zealand ischemic stroke patients with AF may have contraindications to anti-coagulant therapy,[14] this audit still suggests the benefit that could be achieved from increased use of anticoagulant therapy for stroke prevention in AF would be great.[15, 16]

The recent introduction of dabigatran, an oral direct thrombin inhibitor, may improve anticoagulant therapy rates as this agent does not require regular blood-test monitoring or dose adjustment and has fewer food and drug interactions than warfarin.[17]

The use of aspirin within the first 48 hours of stroke onset appeared to be very low (21%) compared with the 94% uptake of antithrombotic treatment at discharge. Early use of aspirin is shown to reduce early stroke recurrence.[18] Greater use of rectal administration of aspirin or sub-lingual use of dispersible formulations of aspirin could ensure that patients who are made 'nil by mouth' due to dysphagia are not denied access to this medication.

Urgent access to swallowing screening by trained personnel is another area in need of improvement. New Zealand stroke guidelines specify that "All stroke patients should have their swallowing screened as soon as possible, but at least within 24 hours of admission."[11] Rates of SLT assessment in New Zealand are significantly lower than in Australia with 61% of patients receiving documented SLT assessment during acute hospital admission here, compared with 81% in Australia, and only 35% of New Zealand patients assessed within 48 hours of admission compared to 60% in Australia. The SLT assessment rates in DHB's without a SU are lower than those with a SU.

Access to brain imaging is satisfactory and similar to that seen in Australia. However, early brain imaging was reduced in medium DHB's with 76% of patients having scans within 24 hours compared with 93% in large DHB's, 94% at small DHB's and 91% in Australia.

Carotid ultrasound rates were reasonably consistent among NZ centres, regardless of DHB size but were lower than in Australia. It is of note that carotid ultrasounds were less likely to be ordered in DHBs with stroke units. This finding suggests that the difference in trans-Tasman practice is not primarily related to availability of ultrasound but rather a more conservative approach to investigation of carotid disease.

We speculate that carotid ultrasound in New Zealand is being reserved for good potential carotid surgery candidates. Utilisation of secondary prevention therapies at hospital discharge appeared reasonably good and was a consistent finding across New Zealand DHBs with similar rates as those seen in Australian centres.

This audit allows comparison between stroke services provided in New Zealand and Australia. More Australian patients are admitted to stroke units (49 % vs 28 %) than New Zealand however the proportion of patients thrombolysed is similarly low across the two countries.

New Zealand compares favourably with Australia in other areas with similar proportions of patients seen by physiotherapy, occupational therapy and social workers. Hospital mortality, length of acute hospital stay and discharge destination of patients after acute stroke were also similar in New Zealand and Australia.

This audit has some limitations. The data collection was retrospective and only aspects of stroke management that were clearly documented in the patient notes were captured. Although large DHBs admit 60% of all stroke patients, there were equal numbers of patients audited between large, medium and small DHBs, given the requirement to audit 40 consecutive patients in each of the DHBs. The reasons why a DHB may not have a stroke unit were not explored and this should be addressed in future studies.

This audit provides a comprehensive overview of the clinical care of people presenting to hospital with stroke in New Zealand and it is reasonable to assume that the responses reflect the current state of stroke management. It provides a benchmark with which to measure improvements over time and against our international peers. It is clear that the implementation of best practice guidelines for stroke care has been patchy and there is significant regional variation.

The full audit report is freely available at http://www.stroke.org.nz/stroke-health-professionals

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New Zealand Malayan war veterans' exposure to dibutylphthalate is associated with an increased incidence of cryptorchidism, hypospadias and breast cancer in their children

Matthew Carran, Ian C Shaw

Abstract

It is well known that the endocrine-disrupting chemical (EDC) dibutylphthalate (DBP) inhibits testosterone synthesis and can lead to feminisation in male laboratory animals. Moreover, it has long been speculated that human exposure would result in the similar effects, but this is difficult to study because specific human exposure cohorts are rare.

We report increases in the incidences of hypospadias ($p < 0.05$), cryptorchidism ($p<0.05$) and breast cancer ($p<0.05$) in the children of New Zealand soldiers who served in Malaya (1948–1960) and were exposed to DBP applied daily to their clothing as an acaricide to prevent tick-transmitted bush typhus. In addition, we modelled absorption of DBP from the soldiers' clothing and using published data for skin absorption, and calculated a large theoretical absorbed dose of 64 mg/kg body weight/day which is similar to DBP's lowest observed adverse effect level (LOAEL) of 50 mg/kg body weight/day and thus indicates a biological effect is possible.

This is the first report of a multigenerational developmental effect following DBP exposure in human males.

Endocrine-disrupting chemicals (EDCs) either have structural analogies to hormones and can occupy and activate hormone receptors (e.g. human estrogen receptors hERα and hERβ) or interfere with the metabolic production or destruction of hormones.[1–3]

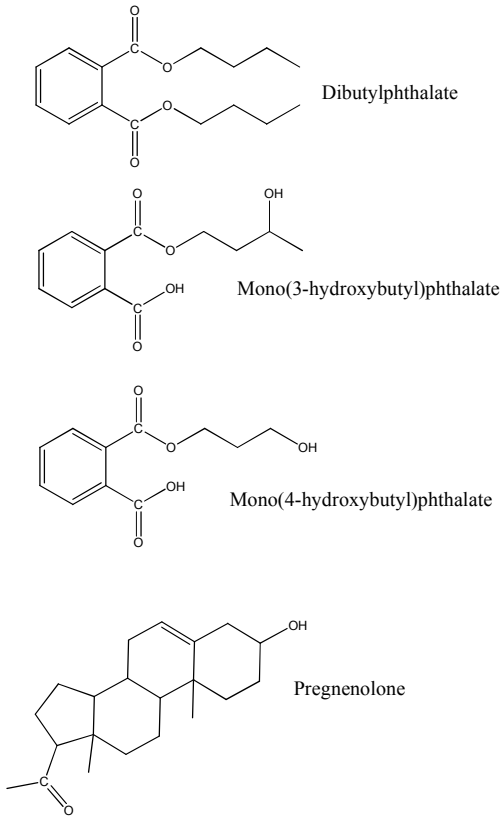
Dibutylphthalate (DBP) and/or its metabolites reduce the activity of enzymes of the testosterone synthesis pathway[4] possibly because of their structural analogy to testosterone's steroid precursors (e.g. pregnenolone; Figures 1 and 2).

The decrease in testosterone concentration upsets the androgen:estrogen ratio and introduces significant cellular feminising pressure and therefore could result in effects on growth and development in males. Indeed, at the lower end of the evolutionary spectrum, namely amphibia, studies in frogs (*Rana rugosa*) have shown that exposure to DBP affects testicular differentiation during metamorphosis[5]. The effects of DBP in mammals are very similar; the offspring of DBP-exposed female rats mated with unexposed males results in a dose-related decrease in testis weight in the offspring.[4]

Thus, DBP exposure affects gonad growth and development across the evolutionary spectrum and such changes are likely to have far reaching effects on fecundity. It is

likely that DBP will have the same or very similar effects on growth, development and reproduction in humans.

Figure 1. Molecular structures of dibutylphthalate (DBP), its major metabolites (mono(3-hydroxybutyl)phthalate and mono(4-hydroxybutyl)phthalate) and the testosterone precursor pregnenelone



Note: The structural analogy of the DBT metabolites to testosterone precursors is likely to explain their inhibition of testosterone synthesis enzymes.

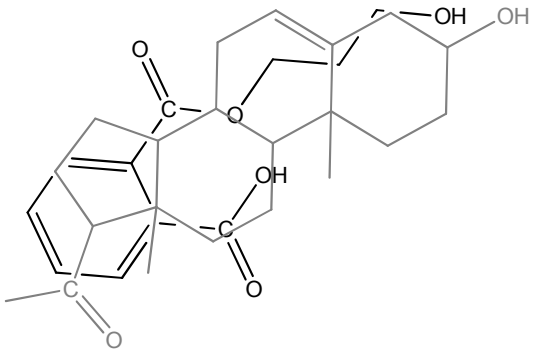
It is widely believed that there is a link between exposure to EDCs and their effects, but there are few human exposure/effect data to substantiate this, particularly in relation to individual compounds. For example, it is known that the human sperm count is in decline[6,7] worldwide; similarly, the age of onset of puberty in girls is declining[8] and both have been associated with exposure to EDCs in some studies (e.g. bisphenol A [BPA][9]), but it is difficult to prove cause and effect without definitive exposure data. In addition, increasing rates of cryptorchidism and hypospadias have also been linked to EDC exposure in some studies.[10]

It is widely accepted that increasing exposure to myriad EDCs is having effects on sexual development and function in humans, but the complexity of the exposure

profile and the large number of individual EDCs to which we are all exposed makes unravelling cause and effect relationships almost impossible.

There is still some controversy about the cause of the observed changes in sexual development; EDCs might not be the sole cause and it is possible that, for example, changes in dietary status might also influence sexual development. This is particularly the case for precocious puberty where better diet might, at least in part, explain the phenomenon. It is, however, difficult to explain how dietary changes have caused declining sperm count in countries in the developed world. It is likely that the effects are multifactorial with multiple risk factors (e.g. diet and exposure to EDCs) leading to a common sexual development endpoint.

Figure 2. Molecular structures of mono(4-hydroxybutyl)phthalate (a metabolite of DBP) (black) and pregnenelone (grey) superimposed to show their structural analogies



Note: They have aliphatic hydroxyl groups in similar spatial arrangements; keto groups in similar positions and a significant central region of hydrophobicity.

Considering EDCs as one risk factor, they can either have direct effects (e.g. bind to and activate ERs) on the individual receiving the EDC dose or they might have multigenerational effects. The latter could involve exposure of a pregnant female to EDCs in which case the foetus might also receive a dose of the EDC if it, or its active metabolites, cross the placental barrier or are absorbed by the foetus from amniotic fluid.

In addition, it is possible that exposure of males to EDCs could cause genetic or epigenetic effects on sperm DNA that could, in theory, affect the offspring produced from the modified sperm—this is a different mechanism to the direct EDC interaction with ERs following direct exposure of adults to EDCs or indirect exposure of the foetus following maternal exposure to EDCs.

The possibility that sperm effects, following paternal exposure to EDCs, might lead to effects in offspring is, to some extent, theoretical; however, a recent review[11] has explored this and presents compelling evidence that paternal exposure effects on offspring is a distinct possibility.

In this paper we present data on the incidence of cryptorchidism, hypospadias and breast cancer in the children of New Zealand veterans of the Malayan (now Malaysia) Emergency (1948–1960) who were exposed to DBP during their military service. DBP is an insecticide and acaricide and was used by the military to reduce insect and mite infestation in troops.[12,13]

New Zealand troops deployed in Malaya during the 1950s and 1960s painted the seams of their uniforms with a proprietary liquid DBP concentrate preparation before undertaking operations in the jungle to prevent them being bitten by trombiculid mites (chiggers, e.g. *Eutrombicula hirstii*) which carry the scrub typhus pathogen (*Orientia tsutsugamushi*).[14]

The New Zealand/Malaysia veterans present an interesting DBP exposure cohort in which to investigate cause and effect relationships following known exposure to this potent EDC. Our findings provide further evidence that paternal exposure to EDCs can lead to developmental changes in offspring.

Materials and Methods

New Zealand Malaysian veteran questionnaire study

Setting & study design—This is a retrospective cohort questionnaire study of NZ Malaysia veterans of the Malayan Emergency (1948–1960) known to have been exposed to DBP who currently live in the Canterbury province of NZ.

Ethics committee approval—Approval for the study was given by the University of Canterbury Human Ethics Committee on 2nd December 2009 (approval reference HEC2009/165).

Data collection—Specially designed data collection forms were sent to 252 NZ Army veterans who were known (from military records) to have served in the Malayan Emergency between 1948 and 1960. They were contacted via their membership of the Canterbury branch of the Malayan Veterans' Association (Inc.), New Zealand. Data collection forms were sent out to the veterans in December 2009 and the recipients were asked to return the completed questionnaires within 2-weeks of receipt.

Data collection forms—Prior to designing the data collection forms we met with several members of the New Zealand Malayan Veterans Association Inc. to determine whether they, or their colleagues, were likely to remember events of some 50 years ago. We were particularly interested in their recollection of whether they had used DBP or not and how often they had applied it.

The discussion unequivocally demonstrated that the application of DBP was a memorable event since it involved painting the viscous liquid onto their uniforms in a pre-excursion military order setting and that it was applied whenever they were on military operations. The frequency of the latter was quite clearly a memorable event for the soldiers.

Specially designed data collection forms were used to collect data, including dates the veterans were stationed in Malaysia, whether or not they used DBP, whether they had children during their time in Malaysia or after returning to NZ, whether they, their children or grandchildren suffered from any of the following disorders:

- Cryptorchidism.
- Defects of the penis (respondents were asked to specify, e.g. hypospadias).
- Precocious puberty (female offspring only).
- Low sperm count.
- Reduced fertility.
- Disorders of the ovary or uterus.
- Breast cancer.

Some respondents who indicated that one of the above disorder criteria applied to them were followed up to ascertain the reliability of the diagnoses. In these cases, we talked to the respondent personally about the diagnosis, who had made the diagnosis and what the name of the disorder was. We used this process as a means of confirming the diagnosis and its reliability.

Data analysis—Data from veterans who had not used DBP (n=13; 14.3% of total) were discarded. Recipients whose answers to the data collection form questions were not clear were followed up by telephone to clarify the uncertainties.

The incidences of each of the disorders were calculated in the study cohort and were compared with incidence statistics for the general population. Published data for the New Zealand incidence of breast cancer are not available and therefore USA population data were obtained from the scientific literature. Binomial distribution statistics were used to compare the DBP-exposed veteran cohort data with the general population incidence of a particular disorder.

Statistics—A binomial distribution was used to determine the probability of the observed disorder incidence in the offspring of DBP-exposed veterans occurring in the general population. The Binomial Test was applied to the data to determine statistical significance. A particular disorder incidence was considered significantly different from its incidence in the control population if $p \leq 0.05$.

Absorption of DBP through clothing

An army uniform (trousers and shirt) used during the Malayan Emergency was obtained and its fabrics identified as 100% cotton by light microscopy. In these experiments, Cotton Drill cloth was used to represent the military uniform trousers and cotton Homespun Bedford cloth was used to represent the shirts (materials purchased from Haralds, Christchurch, New Zealand) in the DBP permeation studies as follows:

Cloth squares (5cm × 5cm) were positioned in contact with 3 layers of Whatman No 1 chromatography paper squares (5cm × 5cm) and 1mL DBP (density=1.04 g/mL; May & Baker, Dagenham, UK) was applied to the cloth with a 3cm 100% pure-bristle brush (i.e. the same method used by military personnel during the Malayan Emergency).

The cloth was left in contact with the chromatography paper for 5 hours to mimic the approximate period of time that the soldiers were exposed to DBP during their jungle activities.

Following the 5-hour diffusion period the chromatography paper was extracted with acetonitrile (10 mL × 3) in a centrifuge tube on a reciprocating shaker for 30 minutes. The extracts were combined and diluted 1/1,000 v/v with acetonitrile.

The diluted extracts were analysed for DBP by ultra violet (UV) absorption spectrophotometry (CARY®-100-Bio Spectrophotometer, Varian Inc.; 1cm quartz cuvette) at wavelength 222 nm using the molar absorption coefficient calculated from a linear calibration graph (calibration range=5–40 µg/mL; R2=0.9943) using Beer's Law (ε=7793/M/cm). DBP absorption from the cloth was calculated.

Results

Questionnaire study

Response rate—Of the 252 data collection forms sent out 85 (33.7%) completed forms were returned. The low response rate is likely to be due to the age (expected to be ≥80 years) of the veterans and the fact that men of this age are often reluctant to discuss matters of a personal sexual nature. In addition, despite remaining on the Malaya Veterans' Association (Inc.), New Zealand membership list, a considerable number of the veterans are likely to have died or be incapable of responding.

Cohort demography—Of the 71 veterans included in the study, 58 (81.7%) had children after serving in Malaysia, of these 155 offspring 79 (51%) were male and 76 (49%) were female. The number of children per family was 2.2±1.5 (mean ±SD). All of the children were born after their fathers had returned to New Zealand.

Findings from the questionnaire study—Table 1 shows the incidences of disorders in the children of the DBP-exposed veteran cohort compared with statistics for the general population.

Table 1. Comparison of incidences of diseases associated with exposure to estrogenic compounds in children of veterans of the Malayan Emergency who were exposed to dibutylphthalate and the incidence of the same disorders in the general population

Disorders	Incidence in children of DBP-exposed veterans (number of cases)	General population incidence	P value
Cryptorchidism	5.1% (4)†	2000: 1.09% [15]** 2005: 0.91% [15]**	<0.05* <0.05*
Hypospadias	2.5% (2)†	2000: 0.33% [15]** 2005: 0.30% [15]**	<0.05* <0.05*
Breast cancer	4.0% (3)‡	0.48% [16]***	<0.05*

Note: Data for hypospadias and cryptorchidism are given for 2 years to show that the incidence statistics vary little with time. Birth statistics used to calculate population incidence were taken from http://www.stats.govt.nz/browse_for_stats/population/births/births-tables.aspx The data for hypospadias also includes a small number of epispadias cases because they are not separated in the New Zealand Birth Defects Registry; * Denotes statistical significance; † n=79 men; ‡ n=76 women; ** New Zealand data; ***incidence for age group <39 years.

All of the other disorders included in the questionnaire showed either very low incidence or incidences that were not statistically different from the incidence in control populations. For these reasons these data are not included here.

Absorption of DBP through clothing

Absorption across the shirt material (Bedford Homespun) was 25±3.2% (mean±SD, n=5) of the DBP applied. The corresponding value for the trouser material (Cotton Drill) was 35±14.2 (mean±SD, n=6). These values correspond to 0.22–0.30 g DBP

and 0.22–0.56 g DBP absorbed across 25 cm^2 cloth following application of 1 mL DBP respectively.

Discussion

Response rate—The low response rate (33.7%) for this questionnaire study is likely to be due to the age of the New Zealand Malaysian veterans. Questionnaires were sent to all veterans on the Christchurch, New Zealand membership list of the New Zealand Malayan Veterans Association Inc. The Association updates its membership list when it is informed of members' deaths. However, if the Association is not informed, or is not informed immediately, of members' deaths, the members' names remain on the membership list.

The current members of the Association are in their mid-seventies to late eighties and therefore it is very likely that a considerable number of those to whom questionnaires were sent were deceased (life expectancy for New Zealand non-Maori males is 79.0 years and for Maori males is 70.4 years[17]). This is likely to explain the poor response rate.

Effects of DBP—Developmental abnormalities and sex hormone-related cancers have been linked to exposure to EDCs in some human studies and in animal studies, including breast cancer, cryptorchidism and hypospadias.[1,10]

Effects on the developing foetus as a result of passage of EDCs and their metabolites across the placenta into the embryo/foetus are thought to account, at least in part, for these developmental disorders.[14] In addition, epigenetic effects on ova and sperm might initiate gene regulatory changes (e.g. DNA methylation) that lead to developmental abnormalities that are not manifested until later in life.

In the present study, only males were exposed to DBP and therefore any multigenerational effects can only be explained by a sperm-based mechanism. In addition, all of the men in this study had returned to New Zealand before their children were born; therefore, they were not exposed to DBP immediately prior to conception. This suggests that any effects of DBP on their sperm were long lasting.

Much of the experimental work on DBP's developmental effects has been carried out in DBP-exposed female animals (e.g. rats[4]) and thus focuses on in utero exposure. The present study shows that occupational exposure to DBP in men might lead to abnormalities in their children. In addition, the abnormalities observed (cryptorchidism, hypospadias, breast cancer) have been associated with exposure to EDCs in animal and human studies[1,10] but not specifically via exposure of males. Recent studies have shown that exposure of human sperm to phthalate esters (including DBP) concentrations in the range found in semen of exposed individuals results in decreased motility and viability.[19] This suggests that phthalate esters can act directly on sperm.

If macrobiological changes (e.g. decreased motility and viability) occur, this must mean that there are underlying biochemical changes that, if exposures are low enough, might not preclude a sperm fertilising an ovum, but might have caused changes that will affect the make-up and development of the resulting zygote.

Our results suggest that DBP can affect sperm in such a way that leads to changes that, following fertilisation of ova, result in developmental changes that are manifested later in life. A possible explanation for this is epigenetic gene regulation. The mechanism of endocrine disruption is via an epigenetic mechanism; EDCs bind to the ER hormone binding domain, cause a conformational change in the receptor which leads to a sequence of events that results in the receptor-ligand complex migrating to DNA where binding to a specific site leads to DNA postsynthetic modifications (e.g. methylation) and concomitant gene regulation[20].

If testosterone levels are low the male hormone response will be concomitantly reduced while the estrogen response will remain constant. The overall effect of this activity ratio change leads to an over-expression of estrogenicity resulting in cellular feminisation. We speculate that DBP changes the balance of activity of specific genes in the sperm DNA and that this gene regulation is introduced to the zygote when the ovum is fertilised.

The outcome is a degree of biochemical feminisation of male offspring that leads to sex organ developmental abnormalities (e.g. hypospadias and cryptorchidism) or promotion of estrogen-mediated non-genotoxic carcinogenesis (e.g. breast cancer) later in life. Clearly, the DBP dose determines the magnitude of the effect; the higher the DBP dose the greater the inhibition of testosterone synthesis and therefore the greater the feminising effect.

Our study is unique because it investigates high DBP exposure individuals and thus establishes, without doubt, that the study cohort received a dermal DBP dose. It is, however, important to consider other possible exposures to EDCs that could, at least in part, explain our findings.

Dietary EDCs are important in this context because Asian diets are high in phytoestrogens (e.g. genistein in soy beans) and therefore it is possible that the NZ Malaysian veterans were exposed to higher doses of dietary estrogens than the control groups with which they were compared in this study and that this exposure accounted for the higher than control incidence of hypospadias, cryptorchidism and breast cancer.

Discussions with one of the New Zealand Malaysian veterans confirmed that the soldiers received British army rations. This suggests that the veterans did not receive a high phytoestrogen intake consistent with a typical Asian diet. It is therefore unlikely that dietary EDC intake explains our findings.

Studies on the passage of DBP across military uniforms gives an estimate of the skin exposure to DBP following its application during military operations. Combining these data with skin absorption data in animal model systems gives an indication of circulating levels of DBP (and its metabolites) resulting from its use as an acaricide in a military operations. Comparing the received dose with the Lowest Observable Adverse Effect Level (LOAEL) for DBP indicates whether there might be a biological effect in the exposed soldiers.

In our experiments the dose delivered via clothing following an application volume of DBP similar to that used in the military field was approximately 6.6 g per person (see

below). Dermal absorption of DBP in a hairless guinea pig model is 62±2% of dose[21] and in a rat dermal absorption model is 73.2% of dose.[22]

The similarity between these two absorption experiments in two different species suggests that absorption in humans is likely to be of the same order. Despite this, studies on fat-stripped post-mortem skin from human cadavers shows very much lower penetration than seen in ex vivo animal skin models.[23] However, in our view ex vivo animal skin is likely to more accurately reflect the in vivo human situation than dead human skin and, for this reason, 68% (mean of the two animal model results) was used in our calculations to estimate the absorbed dose of DBP in the soldiers.

Clearly, this is only an approximation and does not take account of important factors such as climatic conditions, skin surface temperature and perspiration; all of which will affect absorption. Nevertheless, the estimated human DBP dose thus obtained can be compared to the DBP LOAEL to determine whether there is likely to be a human biological effect following exposure. If the DBP dose and LOAEL are of the same order of magnitude it is possible that sufficient DBP was absorbed in the soldiers to cause a biological effect and, consequently, it is possible that the observed effects in the offspring of the soldiers might be explained by DBP exposure.

Frances et al 13 reported that the DBP application rates used in military operations were 23 mL for trousers and 7 mL for shirts. Using the lowest cloth absorptions determined in our experiments (i.e. 0.22 g/mL DBP applied for both Drill and Bedford Homespun cloths) this means that the lowest total skin DBP exposure is approximately 6.6 g. Assuming 68% skin absorption the absorbed DBP dose is approximately 4.5 g.

The LOAEL [rat] for a foetal testosterone reduction end point is 50 mg/kg body weight/day24. The mechanism of testosterone reduction following exposure of rats to DBP is thought to involve gene expression with changes in genes that code for enzymes of testosterone synthesis or carrier proteins for testosterone precursor (e.g. cholesterol) uptake by cells.[24]

The dose received by the New Zealand veterans (assuming an average body weight of 70 kg) was approximately 64 mg/kg body weight/day; this is close to the LOAEL and suggests that the dose received by the soldiers could have had a biological effect.

The results of our study show statistically significant effect in the incidence of hypospadias, breast cancer and cryptorchidism in the offspring of DBP-exposed soldiers (Table 1). These findings combined with the exposure estimate being close to the LOAEL point to DBP having an effect in exposed men that leads to effects in their children. It is, however, important to consider the potential for confounding effects.

It is possible that other factors could, at least in part, have contributed to our findings. The most likely is diet; however the New Zealand soldiers stationed in Malaysia received British army rations and thus they were not exposed to EDCs (e.g. genistein) associated with Asian diets. It is possible that military activity and its associated stress could have had an effect on spermatogenesis; this cannot be ruled out. It must, however be stressed that all of the veterans included in this study were exposed to high doses of DBP and that DBP has been shown to reduce testosterone synthesis

possibly via epigenetic mechanisms in rats.[24] This is a key point that must be considered with the fact that all of the children of the DBP-exposed fathers were born after their fathers returned to New Zealand from Malaysia.

Epigenetic changes (e.g. gene control by methylation) could last for a considerable time after exposure which offers a reasonable explanation for our findings; men were exposed to DBP for long periods and at high doses during their military service, this exposure led to epigenetic changes in sperm DNA which remained until conception. The epigenetically changed sperm DNA fertilised an ovum to generate a zygote with modified gene expression which led to developmental changes that resulted in higher incidences of hypospadias, cryptorchidism and breast cancer in the exposed men's offspring.

The gene expression-modified zygote might lead to an embryo that synthesised less testosterone which, in turn, could result in developmental errors in growth and development of the reproductive cleft. Reduced testosterone levels would lead to feminisation of the genitalia which might be manifested as hypospadias and cryptorchidism. The increased incidence of breast cancer is very much more difficult to explain, but it is possible that reduced testosterone levels in the developing embryo means that the estradiol:testosterone ratio is raised which might up regulate breast cancer genes and thus increase the risk of breast cancer in later life.

These are interesting hypothetical mechanisms that might explain our data. Clearly, much work is necessary to investigate the genetic phenomena that might be at play.

Competing interests: None known.

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Professionalism in its time and place—some implications for medical education

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Abstract

Professionalism is fundamental to good medical practice but is multifaceted so observing that a person is professional in some areas will not guarantee that person would be professional in others.

Most definitions of professionalism include a commitment to self-monitor and to improve; some personal virtues; and effective relationships with colleagues, patients and people who are important to those patients.

In addition, it is suggested that expectations of professionalism may alter depending on context, both of time and place. Societal expectations relating to professionalism are likely to change over time and our expectations of individuals may alter according to the stage of training. The environment (the workplace, one's colleagues, the work tasks) is also highly influential on the manifestation of professional behaviours.

The medical profession's social contract in relation to professionalism will always need to be updated. The effect of time and place means that searching for innate or stable elements of professionalism, in order to predict subsequent behaviours, is therefore difficult. This has implications for the selection, education and assessment of medical students.

The focus should be on how to build adaptability and resilience to contextual influences; to identify those elements of professionalism that can be learnt; and build systems of assessment that reflect professionalism's multifaceted and contextual aspects.

Professionalism is fundamental to good medical practice. Although it is well described as an expectation in medical education, training and practice, it is notoriously difficult to define and assess.[1,2]

Because "professionalisms" is a clumsy word, there is a risk that professionalism is viewed in the singular, and not as being multidimensional. The multidimensional nature of professionalism[1] means a student or practitioner can be professional in some aspects and not others. More importantly, noting that a person is professional in one aspect is not sufficient to know that he or she will be professional in all aspects, or in all circumstances, or at all times.[3]

Discussions on professionalism are hampered by a lack of an agreed definition. For some, professionalism in others is simply "being like me" while for others it may be "going beyond the call of duty" and putting in the extra hours. Some may even go so far as to say it's everything about being a doctor. There are numerous consensus statements on professional behaviour in medicine.[4–12]

A systematic review of consensus statements on meanings of professionalism placed all aspects under one of the following five headings:[1]

- Adherence to ethical practice principles.
- Effective interactions with patients and with people who are important to those patients.
- Effective interactions with other people working within the health system.
- Reliability.
- Commitment to maintenance, and continuous improvement, of competence in one's self, others and systems.

Whereas many discussions on professionalism focus on the individual [3], we suggest that the commitment to achieving and maintaining competence and to continuous improvement applies also to the profession as a whole. An individual's commitment to self-monitor and improve one's own competence includes taking steps to remedy any areas of weakness. The equivalent commitment on the part of the medical profession as a whole forms the basis of the social contract it has with the community.

This self-regulation incorporates the expectation that it will set standards, monitor its members and take appropriate steps where standards are not met. When the profession falls short in this responsibility it is rightly criticised by the public. The public expects and deserves no less – it needs to have confidence that the profession and the professionals within it are acting in the best interests of the health of individuals and their communities and that there are internal mechanisms to maintain standards that do not rely on constant vigilance from outside bodies.

The key regulatory body for qualified practitioners is the Medical Council of New Zealand but other parties, such as the Universities and Colleges also play a role, especially during training.

When considering professionalism, both in relation to individuals and to the profession as a whole, it is necessary to consider not only the characteristics of the individuals but also the context, in terms of both time and place. Time and place interact with the person to influence not only what professionalism means or looks like on a particular occasion but also in ways that can hinder or help an individual to "behave professionally."

Students and practitioners might be professional in some situations and not others, and on some occasions and not others. Just because an individual is professional at one point in time does not necessarily mean he or she will be so in the future.

Time

Definitions and meanings of professionalism have changed over time and will continue to do so.[13,14] Examples include the concepts of altruism[13] and confidentiality - both undoubtedly remain fundamental to our understanding of professionalism but both now have meanings that are more nuanced and bounded than previously. It is

now widely recognised that there are appropriate and desirable limits to each of these concepts.

Confidentiality as a guiding principle requires interpretation and application according to the particular circumstance and is no longer an absolute value to be upheld in every circumstance. For example, where breaching confidentiality is necessary to prevent harm to the patient or others it may be permissible to disclose limited information to appropriate others.[15]

Not only does society's expectations of professionalism change over time, so too can the expectations of a person change over his or her training and career. Expectations of a student just entering medical school are different from those of a recent graduate and different again from an experienced practitioner. This is at least in part because some aspects of professionalism are learnt during training and also because expectations change according to the circumstances of the job.

Consider reliability. Reliability in a student can be considered indicative of appropriate professional behaviour; however the expectations of reliability are different for a student and a senior clinician at least in part because of the different consequences.

Unreliable students impact largely on their peers and their own learning, whereas the consequences of an unreliable clinician are primarily experienced by patients (and also colleagues) and are not simply inconvenience but include potentially serious adverse health outcomes. It takes time and experience to fully learn and appreciate the consequences beyond the "classroom"; in particular the consequences for patients. A true appreciation of this requires an actual sense of responsibility and duty of care toward patients.

There are however some aspects where the expectations of professional behaviour do not change over time. For example, from the outset, students should demonstrate respect, honesty and trustworthiness.

Place

Professionalism also varies according to place. Just as time refers to two concepts (stage of training/practice and time of society), so too place can have more than one meaning. Place can be thought of as both the clinical situation and the work environment. What is considered professional, or not, can depend to some extent on the context as different situations can require different responses in order for the individual to behave professionally.

Different circumstances not only might require different responses but also might hide or reveal different professional and unprofessional behaviours. Additionally different work environments can make it more or less difficult to achieve and demonstrate professional standards and behaviours.

As an example, the same truly professional doctor interacting with a patient in an outpatient clinic discussing a risky elective procedure will behave differently when managing the consent process in an unstable trauma patient in the Emergency Department (ED). The guiding principles of respecting patient choice and prioritising

the patient's best interests are the same but in attempting to honour them the doctor will have to behave quite differently.

Any judgement made about whether or not the doctor behaved professionally should take account of the context. Likewise, a doctor interacting with a patient who is polite and readily compliant can appear to behave quite differently when interacting with another patient who is more challenging in some way - perhaps intoxicated and abusive—and yet still be behaving professionally on both occasions. The guiding principles of professionalism remain the same but the behaviours observed will look quite different and should be judged within that context.

It is also suggested that different places (different circumstances) can reveal or unmask underlying personal attitudes and characteristics which impact on professional behaviour and potentially produce either lapses of professionalism or examples of exemplary or meritorious professionalism. This interaction of the person with place is discussed later.

The second notion of place is as a work environment. There is increasing acknowledgement that an institutional climate can be highly influential on the professional behaviours of individuals—it may be harder for individuals to act professionally if they work within unprofessional environments. [13 16]

The powerful effects of role models and of the hidden curriculum are well documented— the importance of respect for patients and colleagues can be taught but if students do not see this modelled or if they see that employers do not show respect to employees, then much of this teaching will be powerfully undermined.

The influence of place needs to be considered in undergraduate education when both teaching and assessing the professionalism of students; for example students may have difficulty learning to respect patients and their peers if they witness qualified doctors making disrespectful comments about their patients and their colleagues.

Person

While time and place might alter behaviours and expectations, the third variable in the demonstration of professionalism is the individual and the personal resources and flaws each brings to their studies or work. The extent to which any characteristic or trait can be said to be innate, either in all people or in an individual, can be debated.

Furthermore, even those aspects that may be innate may not necessarily be stable. They could be eroded or developed, dependent on the environmental learning (and unlearning) opportunities. This is consistent with the notion, first proposed by Aristotle, that virtues are acquired by repetitive practice: an individual becomes virtuous by repeatedly doing what a virtuous person would do; a person develops courage by repeatedly practicing being courageous or compassion by repeatedly being compassionate.[17] This is congruent with the notions of deliberate practice[18] in the development of musical performance skills and in clinical skills,[19] and of cognitive load theory [20] which suggest that at least some professional behaviours can be learned and consolidated by feedback to students.

This has implications for selection processes because any assumption that professionalism is innate and/or stable could also be associated with the assumption that it could be predicted better. However, if we accept that some aspects may be learned and change over time, then one of the challenges is to determine those aspects (if any) that might be stable and not amenable or vulnerable to change. Arguably, it is only those aspects that are stable that could therefore be used to predict subsequent behaviours, and be included in selection criteria.

Time/place/person interactions

Examples of the interactions of time, place and person are not difficult to find. Recall the scenario of a doctor challenged by an abusive intoxicated patient, perhaps in a busy chaotic ED. The culture of the department and the resources available to the doctor, plus the doctor's personal attitudes, values and virtues, and the stage of training and experience will all combine to produce a response which could be considered more or less professional.

The response might be calm, non-judgemental and focused on managing the total situation including the clinical issues, or undisguised anger, disrespect and confrontation escalating the aggression of the patient and potentially jeopardising the care and safety not only of the patient but of others in the department.

As another example, consider the impact of culture. Different cultural groups have different expectations in relation to professional behaviours. This will be the case whether the cultural group is defined by ethnicity or country of residence or any of the many other ways in which groups share identities and understandings. There is almost certainly more cultural variation in the meanings and understanding of professionalism than acknowledged in the definitions produced within the dominant medical culture and literature.[21,22]

The understandings and expectations are often not made explicit and can pose problems when interactions between individuals cross cultures and when medical professionals do not recognise that their understanding of professionalism might not be shared by their patient, or indeed by colleagues. Furthermore, the expectations of most cultures change over time just as medicine has and does.

Another example is social networking though the internet (such as Facebook®[23]). This provides a new context in a new time and with some new attitudes amongst individuals to issues such as identity, privacy and ways of relating to each other. It has arisen relatively recently and so our current expectations of professionalism will need to be reviewed in relation to these developments. New "rules" and expectations are needed and are being developed locally as well as internationally. [24,25]

Finally, recent developments in health systems have highlighted the importance of the team, not just the individual. Health outcomes (including adverse outcomes) are considerably influenced by the health system and by the interactions amongst health professionals, as much as they are by the competencies of individuals. A focus on the professionalism of individuals alone therefore risks missing the other major factors, including the team context.

Implications for the profession

Observing that professionalism is dependent on context, time and place, as much as it is on the person has very important implications for how expectations are defined. Expectations will change according to context and over time and will change according to current society and culture.[14]

Professionalism is therefore not static but a dynamic entity such that definitions and expectations need to be reviewed and revisited. This cannot occur in isolation from either its membership or from society and needs to be a negotiated process. The profession's contract with society is neither fixed nor unconditional. The profession needs a means by which it engages with society, as well as with its own members, to review and renew its social contract, and to ensure definitions of professionalism remain relevant meaningful and valued.

Implications for medical education

The observation that professionalism is dependent on context, time and place, as well as person, also has implications for teaching and learning, and for selection and assessment. Moreover, such implications will vary depending on whether we are concentrating on elements of professionalism or on episodes of lapses in professionalism.

Formal teaching and learning about professionalism is now well established in medical school curricula, although role models, the institutional culture, and the hidden curriculum may overpower most traditional teaching approaches.[3] There is a need for a firm theoretical foundation in professionalism to be laid down so that it is not left to chance or to serendipitous workplace encounters to ensure our students acquire and continue to develop their professionalism.

Furthermore, formal teaching sessions, debriefing and discussion groups can assist in making sense of the powerful forces at work in our workplaces that may act to reinforce or undermine professionalism. These considerations suggest that professionalism belongs to everyone and therefore should be integrated into all that we do. However, it also suggests that the teaching and learning of professionalism have their own special attributes and theoretical underpinning and therefore need their own curriculum time.

Should the teaching and learning of professionalism therefore be integrated or standalone? The answer is clearly both so that learning occurs in multiple situations and at different stages during the course. Nevertheless, there needs to be vigilance to ensure that the integrated component reinforces and does not undermine the core elements, and that the standalone elements are valued and not ghettoised.

Most selection processes occur in one time and place. It is unclear which elements of professionalism are sufficiently stable to be useful in predicting future behaviour. There is therefore a limit to the degree that selection processes can be expected to predict subsequent professional behaviours.

Research into the increasing use of simulations in selection processes (such as through multiple mini interviews[26]) will provide useful data on how predictive these measures are for subsequent professional behaviours.

The emerging data suggest such processes are predictive of some elements of academic progress such as knowledge and communication.[26,27] If it is accepted that professional behaviours are dependent on time and place, then one-off selection procedures face considerable challenges if they are to predict future professional behaviours.

Assessment of professionalism during a medical course may pose slightly fewer problems than assessment of professionalism for selection. In medical courses there will be assessment related to the formal learning of professionalism in the course, which needs to be related to both the content and context of the learning. There is also the issue of assessment of general professional behaviour against specified criteria during the course, which many medical schools are attempting to put in place.

There is emerging evidence that some behaviours within a medical course might predict subsequent unprofessional behaviours after graduation.[28,29] However, while some key behaviours (such as failure to respond to feedback[28]) have a high relative risk of predicting subsequent unprofessional conduct, the absolute risk of these behaviours is very small. Any tool able to predict in advance when these unprofessional behaviours might emerge would be a very good tool indeed.

Assessment programmes that wish to include professionalism need to take a multifaceted approach[30] using multiple tools[1], multiple observers, in multiple places, over multiple times. Such approaches, almost by definition, suggest that most of this needs to be in the workplace. Within medical courses there need to be "workplace equivalents": situations and behaviours in learning environments that might be able to be used as surrogate markers of workplace professionalism.

The crucial element to such a programmatic approach however, is to ensure that all the pieces of information gathered by these multiple assessments are joined together to inform considered and defensible decisions[31]. These all need to be backed up by defining and publicising the clear expectations of the programme. Assessment of professionalism therefore also needs a system by which such information is collated and recorded.[31]

Given that some expectations of professionalism change over time, there needs to be a debate about how these accumulated assessments can and should influence student progression to graduation. Is it fair to carry over assessments from one stage to another or should the slate get wiped clear at each point of progression? It also needs to be considered what sources of information and kinds of behaviours can be legitimately and fairly added to the total assessment.

Are students, or qualified practitioners for that matter, ever "off duty" from the point of view of being assessed with respect to their professionalism? Are there some behaviours which should always be admissible as evidence and others in certain contexts which should be forgiven or excluded? This means any system of assessment of professionalism needs a mechanism by which behaviours are not just recorded and

reported, but also interpreted, in light of the context, stage of training, any mitigating factors, and any other misdemeanours; and then acted upon.

Remediation of unprofessional behaviour in medical students will depend on the behaviour of concern, the context and any relevant mitigating issues. Medical schools are developing processes to ensure that unprofessional behaviour of a serious nature is recorded and is formally brought to the attention of the student, often through Fitness to Practise committees. As yet there is little published work on the types and effects of remediation. The pressing research issue is to gain a better understanding of which aspects are remediable and which are not.

An analogy has been drawn between the teaching and learning of medicine and the launching of a rocket.[32] The old model suggested that you need to provide the rocket with enough fuel to last its whole journey. It will take off with enormous force and gradually return to earth just as the fuel runs out. The analogy in relation to professional competence suggests that we need to equip our students with all the knowledge and skills they need for their professional practice. They would then be launched into their professional careers and hopefully the parabolic curve they follow would mean they would run out of this knowledge just after they reached retirement age.

The new model makes use of refuelling stations. A successful launch needs to provide the rocket with enough fuel to get to the next refuelling stage, and with the equipment to engage with refuelling stations so that it can remain in orbit and functional for as long as is needed. Likewise, the analogy for the new model of medical education suggests a medical programme needs to equip students with enough core knowledge but more importantly with the skills by which they can constantly engage with new learning throughout their professional life. This “new” model analogy also applies to professionalism.

Conclusion

We suggest that professionalism is a dynamic and situated concept – an interaction of time, place and person. The concept itself and its manifestation in an individual will change over time, just as the health environment will change.

Students cannot therefore be either simply selected for professionalism or equipped with all that they need at the beginning of their journeys. Instead, they need to develop an understanding of the contributors to professionalism, including an awareness of their own personal characteristics and attributes, and be supported to learn and grow into their professional roles.

They will need the flexibility and ability to recognise when professional expectations are changing, to make sense of those expectations, and to recognise when the context, including colleagues, is not conducive to professional behaviours. Ultimately they will need to develop mechanisms to remain adaptable yet robust and resilient throughout.

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THE NEW ZEALAND MEDICAL JOURNAL
Journal of the New Zealand Medical Association

Asplenic fulminant sepsis secondary to a dog bite complicated by toxic epidermal necrolysis/Stevens-Johnson syndrome

Ken G Teo, Namrata S Anavekar, Anosha Yazdabadi, Sophie Ricketts

Abstract

We report a case of asplenic fulminant sepsis in Australia following a dog bite which was complicated by toxic epidermal necrolysis/Stevens-Johnson syndrome (TENS/SJS). *Capnocytophaga canimorsus*, the infective organism, is a rare cause of septicaemia: a high degree of suspicion of this unusual organism and its early aggressive management is paramount. The diagnostic and management difficulties of TENS/SJS in the context of a patient with fulminant sepsis, DIC and on inotropes are also highlighted.

Case report

A 60-year-old woman, with a history of splenectomy secondary to idiopathic thrombocytopenic purpura, presented to the emergency department in an Australian country hospital in septic shock 3 days following a minor dog bite to her left calf.

After fluid resuscitation, administration of antibiotics (cephazolin 2g, IV, metronidazole 500mg, IV, gentamicin 5mg/kg, IV) and metaraminol (2.5mg), she was transferred to a regional Intensive Care Unit (ICU), where she developed multi-organ failure and disseminated intravascular coagulation (DIC). She was intubated, commenced on haemofiltration, flucloxacillin (IV, 2g, 6-hourly) and ceftriaxone (IV, 2g, 12 hourly).

A progressive purpura was noted over her upper and lower limbs and she had cold extremities. After 24 hours, the Infectious Diseases Department was consulted, with commencement of meropenam (IV, 1g, 8-hourly) and lincomycin (IV, 600mg, 8-hourly) given the suspicion of *Capnocytophaga canimorsus* (*C. canimorsus*) as the causative organism. Activated protein C and intravenous immunoglobulin (IVIG) were administered.

Over the next 48 hours, there was haemodynamic improvement and inotropic support was ceased. However, dry gangrene developed at the finger tips and toes with ischaemic demarcation present on both soles of her feet. The purpuric rash on her limbs became more generalised with formation of flaccid bullae and desquamation.

With the clinical presentation, morphology/Gram stain of punch biopsies taken from the bite wound, and blood cultures being positive with anaerobic Gram-negative bacilli—*C. canimorsus* was determined as the causative organism.

On day 6, the bite wound was debrided (Figure 1) and the patient was extubated. A transfer was organised to a tertiary referral centre on day 11.

Figure 1. Debrided bite wound on left leg

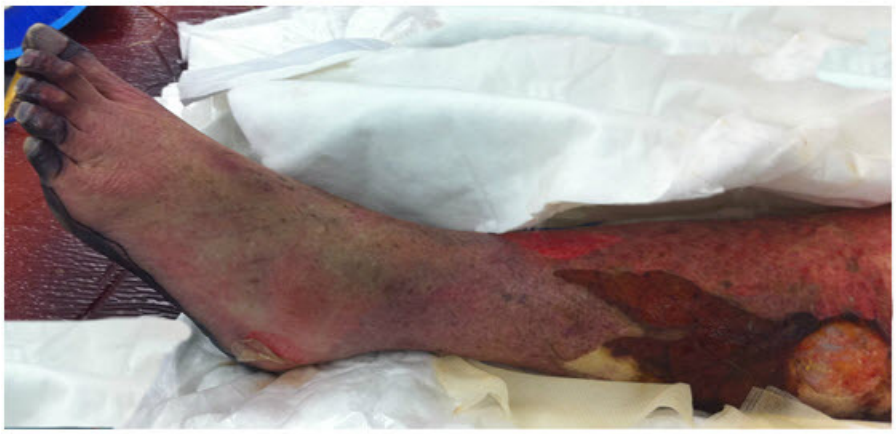


Figure 2. Right arm

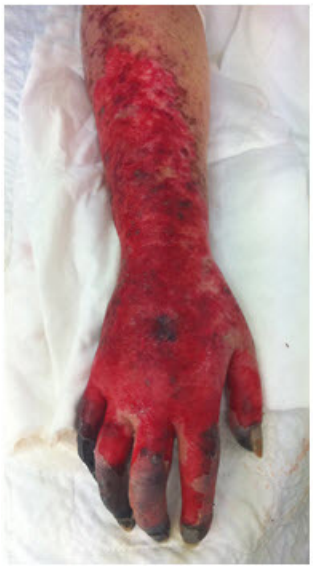
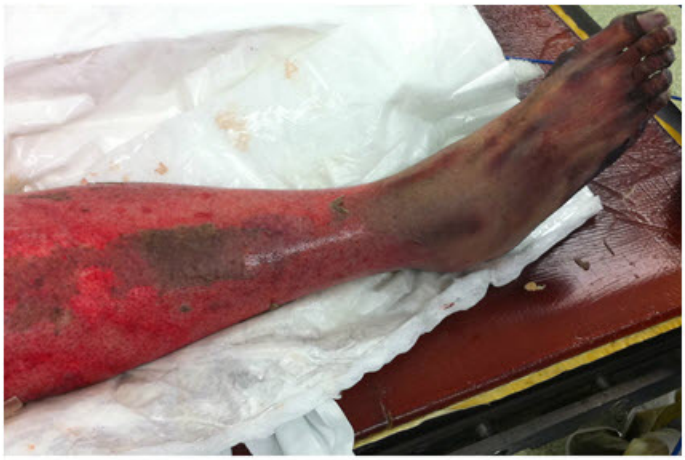


Figure 3. Right leg



On arrival, the patient presented with ongoing asplenic sepsis and necrosis of her fingers, toes and distal lower extremities. There were widespread areas of erythematous to violaceous macules and patches with flaccid bullae and erosions over the upper and lower limbs as well as the peri-areolar areas with positive Nikolsky's sign (Figures 2 and 3)—the total body surface area affected was 36%. Extensive mucositis and ulceration of the lips and oropharynx was noted with exposed hard palate. No other mucous membrane involvement was found.

Tracheostomy was performed and the wounds were cleaned and dressed with JelonetTM (paraffin gauze) in theatre. The diagnosis of toxic epidermal necrolysis/Stevens-Johnson syndrome (TENS/SJS) (later confirmed by skin biopsy), on a background of asplenic fulminant sepsis, was made. TENS/SJS was managed with IVIG (2mg per kg in three divided doses).

In view of meropenem and lincomycin being commenced 2 days prior to rash onset, they were thought to be the potential causative agents. They were subsequently ceased as were all other non-essential medications. Moxifloxacin (IV, 400mg, daily) and vancomycin (IV, 1g, BD) were commenced instead.

Over the next week there was systemic improvement of the patient as well as the desquamated areas of skin and mucositis. There was demarcation of necrotic distal extremities and of areas of full thickness skin loss more proximally on the thighs and buttocks.

There was concern that the patient's necrotic lower limbs posed an ongoing risk of further sepsis and so, lower limb amputations (right below knee and left above knee) were performed once the patient's condition had been optimised.

Two days post amputations, the patient suffered severe neurological injury following a cardiorespiratory arrest. The cause was presumed to be ongoing sepsis and the decision to palliate the patient was made by the treating units and family. The patient died 1 day later.

Discussion

Whilst *C. canimorsus* is an unusual cause of septicaemia (estimated incidence of 0.5 cases/million per year)[1], over 100 cases of human infections have been reported - predominantly in immunocompromised patients.[2] It usually causes systemic infections (94%) and seldom localised infections (6%).[2] Systemic infections range from mild to fulminating disease.

Rash (macular/maculopapular or purpuric) and gangrene are common. The organism is a commensal of saliva in dogs and cats, which can be transmitted to humans by bite (54%), scratch (8.5%) or mere exposure (27%).[2] It is a slow-growing (2–7 days), fastidious Gram-negative bacterium which is difficult to isolate, and including a clinical history of suspicion for the organism is imperative to aid microbiological diagnosis.[3,4]

Despite being susceptible to a wide range of antibiotics (including beta lactams, tetracycline and clindamycin), the mortality rate is 30%.[2] It is paramount that patients at high risk of *C. canimorsus* infection have prompt debridement and antimicrobial treatment.[5,6] Immediate treatment may favourably influence the potentially fulminant course of systemic infection and patients with an increased susceptibility should be well-educated about this.

It is challenging to diagnose TENS/SJS in the context of fulminant sepsis and associated DIC in a patient requiring inotropic support. These conditions may all result in skin changes.

DIC causes a purpuric rash and high doses of inotropes (such as metaraminol) can cause distal extremity ischaemia and necrosis secondary to peripheral vasoconstriction. Mucositis and epidermal sloughing, however, are hallmarks of TENS/SJS (which were present in the reported patient) and should strongly suggest this diagnosis.

Another point in differentiating the skin changes of TENS/SJS and DIC is skin lesions in TENS/SJS tend to appear first on the trunk, spreading to the neck, face and proximal upper extremities—the distal portions of the upper and lower limbs are relatively spared.[7,8]

In comparison, although the purpura and petechiae in DIC can spread in a centripetal fashion or become generalised, they are usually confined to the extremities.[9] TENS/SJS are severe idiosyncratic reactions most commonly triggered by medications and early identification and withdrawal of the offending agents improves prognosis significantly.[10]

This case emphasises the importance of a high degree of suspicion of this unusual organism (*C. canimorsus)* causing fulminant sepsis in asplenic and other immunocompromised patients, and the importance of its early aggressive management. In addition, it highlights the diagnostic challenge of TENS/SJS in the context of a patient with fulminant sepsis, DIC and on inotropes and the management difficulties that this poses.

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A rare tumour of the chest wall

Anirudh Aron, Alexander Hallock

A 66-year-old male with a 6 months h/o masses beneath both his arms pits presented with symptoms of gradually worsening shortness of breath for a week. He had significant orthopnoea and slight pleuritic chest pain but did not report any other symptoms and denied any work-up being done for these masses.

On examination, he was noted to be in moderate respiratory distress and his chest wall showed two hard masses on either side adjacent to the axillae. He had dullness to percussion over his lung fields and breath sounds were absent on both sides posteriorly. X-rays of his chest and abdomen confirmed pleural effusion and also demonstrated the calcified masses over the lower part of the chest wall (Figure 1 and Figure 2).

Figure 1. Posterior anterior chest X-ray revealed bilateral effusions and calcified masses over the chest wall

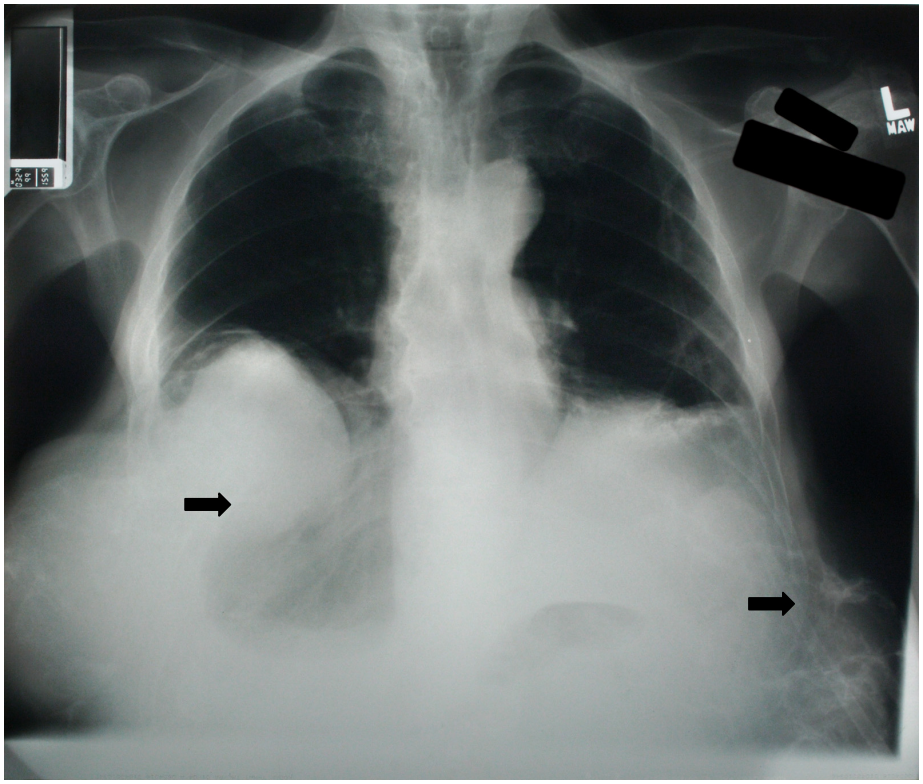
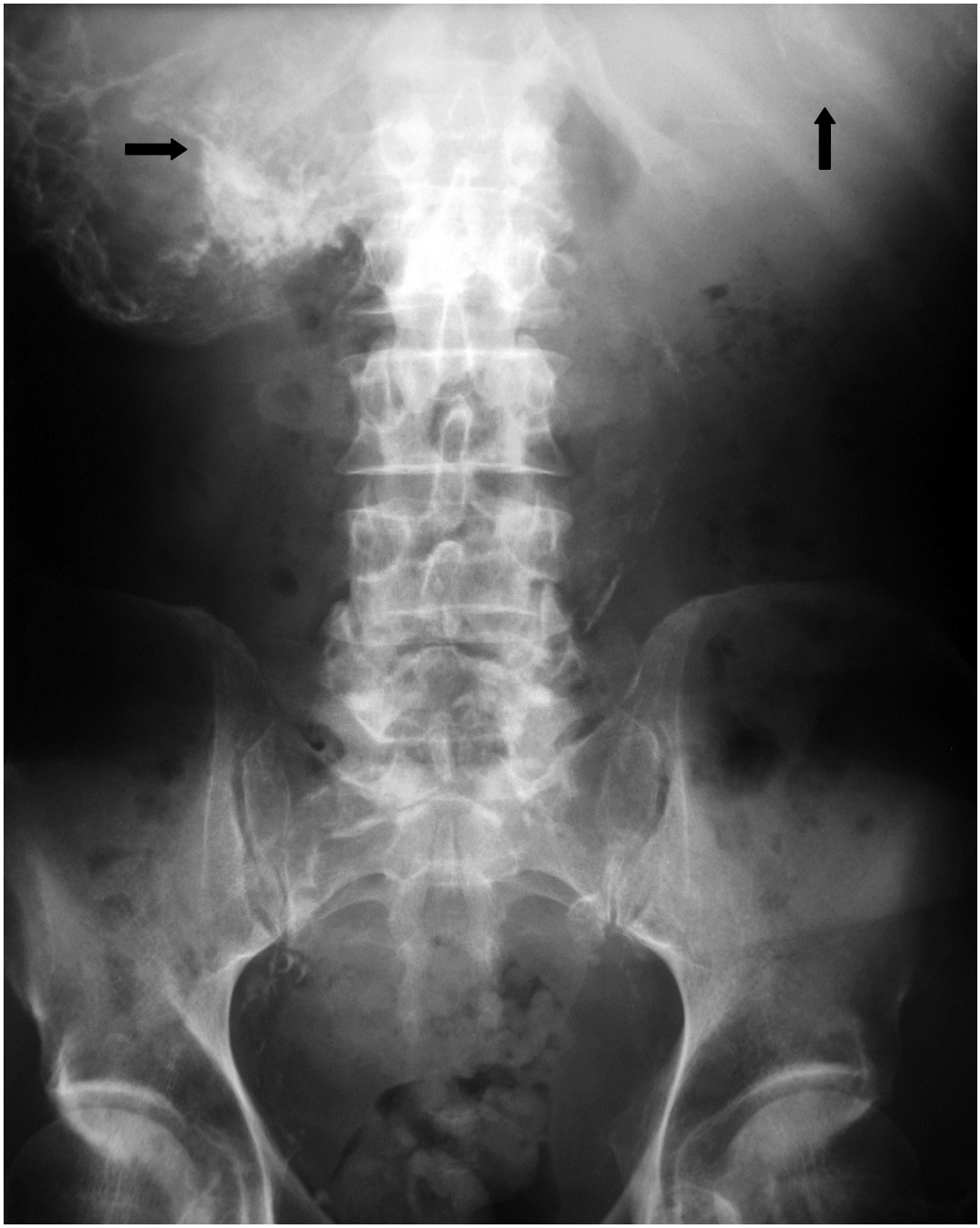
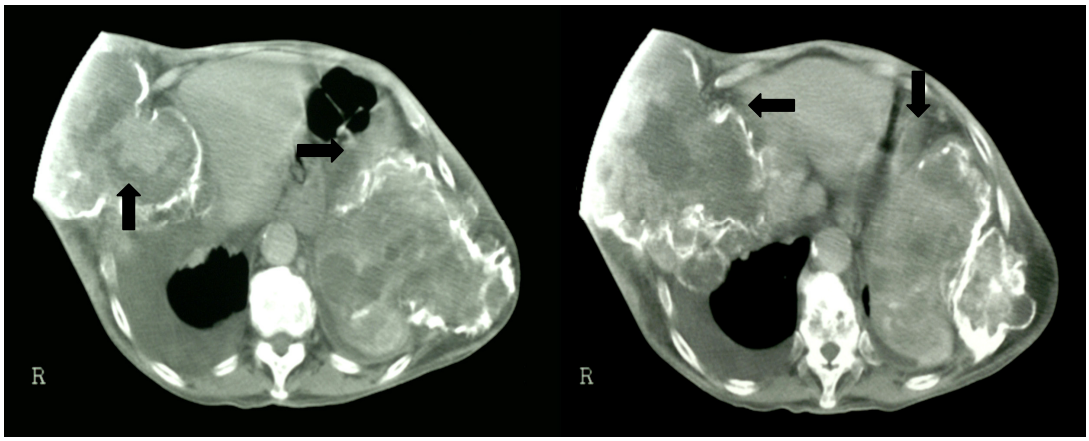


Figure 2. Abdominal radiograph demonstrated the calcified masses on either sides of the lower chest wall



A CT scan of his chest showed bilateral masses arising from the ribs measuring 10 × 15 cm in the coronal plane and 5–6 cm in the antero-posterior dimensions and extending into the mediastinum (Figure 3). The tumor on the left side even extended intra-abdominally, displacing the spleen.

Figure 3. Thoracic computerised tomography demonstrated 2 masses arising from the ribs bilaterally



There was no evidence on bone scan imaging to suggest continuity between these 2 masses and they were distinctive to each other in origin.

Thoracentesis was done and haemorrhagic fluid was aspirated which was otherwise unremarkable on analysis.

Are these tumors related and what is the diagnosis?—A core-biopsy from the mass on the right side revealed atypical spindle cells that were strongly positive for CD31, CD34, Ulex and Factor VIII (the latter only focally) on immunohistochemistry. The tumor was noted to surround the trabeculae of mature bone and because of this fact and it's location in the chest wall, it was suggested to be a primary Epithelioid Hemangioendothelioma (EH) of the bone with soft tissue extension. Later, a similar biopsy obtained from the mass on the left side was also diagnostic of EH. Patient declined any surgical or chemotherapeutic options for his management. However, he was repeatedly admitted with recurring hemothoraces that required therapeutic thoracentesis and blood transfusions until his death 2 months later.

Discussion–This is a case of multicentric EH of the bone originating synchronously from the ribs on either sides of the chest wall and invading into the mediastinum as well as causing hemothoraces. EH is a rare low-grade tumor of vascular origin that can arise from any site in the body and has a tendency to be multifocal[1]. It is unclear whether the separate lesions represent metastases or multicentric disease[1.] Diagnosis

requires immunohistochemistry and though it is a low-grade tumor, prognosis can be poor if left untreated.

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THE NEW ZEALAND MEDICAL JOURNAL
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PHARMAC looks great value for money—an Australian perspective

As an Australian Research Fellow currently visiting New Zealand, I have read with interest the media debate1 around the role of PHARMAC in securing access to pharmaceuticals in New Zealand.

When health budgets are limited, it is vital to identify those drugs that will achieve maximum population health at lowest cost; and organisations like PHARMAC are critical in ensuring that New Zealanders get the biggest bang for their health care bucks.

In the case of the cardiovascular statin drugs, PHARMAC has been very successful. In a recent study,[2] we found that Australians paid an average of $683 in 2008 for a one-year supply of the standard daily dose of statins, while New Zealanders could pay just $18 (one-year supply of 40mg/day simvastatin).

With a third of Australians aged over 55 currently eligible for statin drugs, the Australian Government effectively "wastes" more than $93 million annually in excessive prices; dollars that could be better spent on other pharmaceuticals or on public health initiatives to prevent disease.

This is a big cause for concern, given fiscal constraints on the Australian health system, but despite a Senate Inquiry on the matter and legislative reform on drug pricing in 2010, Australia continues to pay around five times the average price paid for statins in other OECD countries.[3] New Zealand, on the other hand, pays the least.[4]

So it is not surprising that the pharmaceutical industry may be keen to cast a shadow on organisations like PHARMAC that drive a hard bargain in securing cheaper prices on drugs, for fear that other countries, with even bigger markets, may follow suit.

Amidst the negative press around PHARMAC, let us not forget the successes of this agency in getting good value for money on pharmaceuticals like statins, and remember the importance of publically-funded organisations in putting population health ahead of politics and profits.

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No need to ban smoking in cars with children present—it's almost snuffed out

Smokefree environments are widespread in New Zealand with legislation banning smoking in workplaces, bars, casinos and restaurants, school grounds and on public transport. Many local government councils are expanding smokefree environments to include parks, playgrounds, sports grounds, beaches and particular streets.[1] Private places like marae, homes and cars have largely been exempted—except where that place is also a workplace, such as a residential care facility or a prison.

Recently there has been a call to ban smoking in cars when children are present with strong public support claimed for such a move.[2] This would help to reduce infant and child exposure to secondhand smoke (SHS), moves to denormalise smoking [3] and potentially could reduce the risk of children taking up smoking.[4] However, little is known about the prevalence of smoking in cars when children are passengers.

Some studies found that over 25% of adolescent students self-reported having been exposed to smoking within cars.[5, 6] A recent roadside study (n=149,886 vehicles) within New Zealand reported that 3.2% of vehicles observed had smokers and of these 4.1% had children present.[7] That is, just 0.13% had smoking in cars while children were present, a far cry from the 25%+ prevalence quoted in the self-reported studies.

An earlier New Zealand study (n=16,055 vehicles) found the smoking prevalence in cars was 4.1% and of these 23.7% had other occupants (not just children) exposed to SHS.[8] This works out to be approximately 1% of occupants being exposed to SHS within a car. Thus, the prevalence of smoking in cars with children inside was at most 1.0% in 2005 and drifted downwards to 0.13% in 2012.

In the current study (2012) some student nurses set out to determine the frequency of adults smoking in cars with children present in Auckland.

Methods—The Auckland suburbs of Newmarket, Mangere and Manurewa were chosen to provide a comparison between areas of high versus low deprivation. Newmarket was considered a low deprivation area whereas Mangere and Manurewa were considered to be medium to high deprivation areas.

Observation times were randomly generated (between 9am and 5pm) and on two random days in a week. Randomisation was carried out via computer to minimise bias. Observations were concurrently carried out over two one-hour periods during one week of the 2012 Easter School Holidays (5th April to 10th April).

Cars were categorised as follows:

- Cars with adult(s) not smoking;
- Cars with adult(s) smoking;
- Cars with adult(s) not smoking and with child(ren); and
- Cars with adult(s) smoking and with child(ren).

Trucks were included as private cars as truck drivers are permitted to smoke (subject to their company policy). Cars with tinted windows were excluded as it was too difficult to ascertain whether smoking was actually taking place. Buses, taxis, public shuttles were excluded as passengers in such services would not be permitted to smoke. Motorcycles and scooters were excluded.

A child was defined as anyone who looked under 14, including babies. Ethnicity was inferred as either Māori, Pacific, European, Indian, Asian or Other based on the observer's judgement. The weather, day, time and location were noted. The prevalence(s) were not adjusted for any covariates (e.g. number of people in the car, type of vehicle, ethnicity or socioeconomic status [SES]) or any type of weighting for cluster effects.

Results—Of the 2857 eligible vehicles observed (combining the three suburbs) only 63 (2%) carried adults smoking while children were present (Table 1). Of these the ethnic breakdown was: Māori 57%, Pacific 27%, European 11%, and Indian 5%.

Over the three suburbs, the prevalence of cars with adults smoking while children were present ranged from zero in Newmarket and Mangere to 7% for Manurewa. There was a definite SES gradient with more adults smoking in cars while children were present in the highest deprivation area.

Table 1. Categories of cars and smokers by suburb

Auckland suburb	Cars with adult(s) non-smoking Count (row %)	Car with adult(s) smoking Count (row %)	Car with adult(s) not smoking & with children Count (row %)	Car with adult(s) smoking & with children Count (row %)	Total Count (row %)*
Manurewa	516 (57%)	118 (13%)	211 (23%)	58 (6%)	903 (99%)
Mangere	794 (75%)	27 (3%)	228 (22%)	5 (0%)	1054 (100%)
Newmarket	755 (84%)	18 (2%)	127 (14%)	0 (0%)	900 (100%)
Total	**2065 (72%)**	**163 (6%)**	**566 (20%)**	**63 (2%)**	**2857 (100%)**

* Percentages may not add up to 100% due to rounding

Discussion—The 2% prevalence of children in cars with adults smoking was relatively higher than the study prevalence inferred by Patel, Thompson & Wilson[7] which was 0.13%. Two-thirds of our sample, however came from low SES suburbs, where there are more smokers with children. We can, though, use the 2% prevalence as an upper limit.

Latest national population statistics suggested that there were 892,900 persons under 15 years at 31 March 2012.[9] Taking the 2% prevalence of adults car smoking with children inside, this equates to 17,858 children affected nationally. Using Patel, Thompson and Wilson's[7] estimate of 0.13%, equates to 1161 children affected by smoking in cars. Thus, somewhere between 1161 and 17,858 children are exposed to smoke while passengers in vehicles at any point in time.

This was a small observational study with several limitations: Firstly, ethnicity was inferred. We had no way of confirming the demographics of the population observed. Secondly, observations occurred in one week only. There could be something peculiar about the Easter period that limits the generalisability of the study. Other limitations include: not being able to observe a cars whole trip. Adult passengers may have smoked sometime on their journey but not when observed. We did not record the number of children per vehicle. Thus, we conclude that our counts and prevalence(s) are underestimates of the reality.

Whilst legalised bans can modify public behaviour, the policy and parliamentary process of lobbying for successful passage of a law change has considerable opportunity cost (in time spent and financial expenditure) attached to it. If the law changes, a public education campaign would need to preface its introduction much like that required to inform the public of the recent Land Transport (Road User) Amendment Rule 2011[10] driving rule change. The Government would also need to commit ongoing resources to law enforcement, debt collection for unpaid fines and prosecution.

Whereas now many vehicle passengers who smoke, do so with a window down[8] the proposed ban would encourage smokers in cars with children present to contain their smoking within the vehicle perhaps by closing windows, using tinted windows or holding their cigarette below the window line of the car—as cell phone users do with their mobile to avoid detection by police or traffic officers.

Whilst it could be inferred that smoking in vehicles with children present is more likely to occur in populations and areas with higher smoking prevalence, our study supports that this is so. If legislation was introduced to ban smoking in cars when children are present, Māori and Pacific people would disproportionately be affected by this. That is, Māori and Pacific people would disproportionately find themselves in breach of such a law. It has been inferred that if implemented in New Zealand, breaches of the law would incur a fine.[11] In Australia fines range from $A75–$A200. Māori and Pacific people already face significant inequities (in employment, health care, education and justice).[12,13]

Is a law change to ban smoking in cars when children are present warranted given the proportionately small number of children actually affected by exposure to smoke in vehicles and the possible negative social and economic consequences for Māori and Pacific people. Could an equivalent amount of effort and funding not be directed towards assisting low SES Māori and Pacific smokers to quit?

Rather than a punitive approach that would contribute to significant ethnic social and economic disparities, at-risk children's families could be supplied with tobacco-

smoke alarms for their vehicles. Each Plunket or for-hire infant or child car seat could be fitted with one.

As Māori Party co-leader Tariana Turua has rightly pointed out, 'offenders' are not hard to spot, [14] so interventions could be directed at those observed. They could be offered smokefree car kits including for example: a smokefree car sticker, an activity book for children, a sample pack of nicotine replacement for use when driving, a CD-based programme to assist with not smoking while driving and information on where to get further cessation assistance.

Conclusion—Our study confirms that some adults who smoke still do so in the relatively small and enclosed confines of a vehicle when children are present. There is no doubt that this is harmful to the children and contributes to their higher morbidity from smoking related illness than children of non-smoking parents. That this is more likely to occur in areas of high deprivation is consistent with previous studies[7, 8] and with higher smoking prevalence in populations in these areas.[15,16]

But we argue that the time for a ban on smoking in cars when children are present has passed. The practice is already declining and is largely confined to more deprived groups who have not benefited from the same level of public health education campaigns that has driven the behaviour down.

The risk of alienating Māori and Pacific with such a policy change is high. A more helpful approach directed at the small population still smoking in cars should suffice to snuff out children's exposure to smoke in cars for good.

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PHARMAC's updated guidelines for cost-utility analyses, with new QALYs per $1M metric

PHARMAC has recently updated the Prescription for Pharmacoeconomic Analysis (PFPA)—the document that outlines the methods PHARMAC uses when conducting cost-utility analysis (CUA). The updated document is available at http://www.pharmac.govt.nz/2012/06/26/PFPAFinal.pdf[1]

The PFPA has high importance to PHARMAC as it describes the approach we take when doing CUA. PHARMAC uses CUA to compare the cost-effectiveness of a pharmaceutical with other pharmaceuticals that could be funded instead. CUA is a form of cost-effectiveness analysis that considers the impact of treatment on patients' quality of life as well as length of life. In addition, PHARMAC CUAs also include effects elsewhere on the New Zealand health sector, such as potential savings from reduced hospitalisations that may occur as a result of funding a pharmaceutical.[2] This type of analysis is imperative, as cost-effectiveness is one of nine decision criteria that PHARMAC uses to make funding decisions.[3]

The first version of the PFPA was drafted in 1999, and a revised second version was published in 2007 (PFPA Version 2.0).[4] Subsequently a number of its recommendations have been reviewed, and several minor changes have been made to the second version. These changes are documented in Appendix 1 of the updated PFPA.[1]

The key amendment to the PFPA is that results of CUAs are to be reported using incremental utility cost ratios (IUCRs),[5] i.e. the incremental quality-adjusted life year (QALY) gains per unit net cost.[6] These reflect the opportunity cost of investment decisions when operating within a fixed budget,[7,8] and are expressed as QALYs per $1 million of the total budget invested (see Footnote *).

In addition to this amendment, version 2.1 of the PFPA provides further information on factors to consider when critically appraising clinical trials and the transformation of clinical evidence in economic modelling.

PHARMAC will continue to review and update its methodology for undertaking cost-utility analysis. We welcome any further feedback.

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Footnote:

* The traditional measure used to calculate and present the results of CUAs has been ICURs (incremental cost-utility ratios, being the incremental cost per QALY). This long-established metric was reported by PHARMAC in the past and is still typically reported for most CUAs internationally. However, PHARMAC considers that IUCRs are more consistent with PHARMAC's funding setting as they better emphasise health gain, by presenting the result as maximising health gains as opposed to minimising cost. In addition, this approach better illustrates the trade-offs between treatment due to the non-linear relationship between QALYs per million and cost per QALY.[9]

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The operative treatment of goitre

Excerpt of an article written by Dr AA Martin (Palmerston North) and published in NZMJ 1912 May;11(42):111–117.

THE OPERATIVE TREATMENT OF GOITRE.

By Dr. A. A. Martin, Palmerston North.

Thyroidectomy has in the past been an operation associated with a high mortality. It is still an operation of magnitude and of hazard to the patient. Modern methods have increased the safety of the operation enormously, but still the beginner in surgery would be wise if he avoided this operation altogether at first and waited till years of experience had ripened his judgment and completed his manipulative skill. In this paper my only concern is the technique of the operation and the after treatment, and the remarks apply more particularly to Exophthalmic Goitre. In Exophthalmic Goitre the patient should be operated upon before myocardial degeneration occurs. When the stage of cardiac degeneration has been reached surgery is quite out of the question, and the patient will die of the disease.

The five great dangers to be avoided in removing a Goitre are: (1) Removing (accidentally) the Parathyroid glands; (2) Haemorrhage; (3) Insufficient or Inefficient drainage; (4) Injury to the Recurrent Laryngeal nerves; (5) Crushing and bruising and squeezing of the gland.

Preparation of the patient: All these patients are highly excitable and mentally unstable, and hence are very liable to shock. They are anaemic and easily fatigued. They are very prone to dyspepsia—a dyspepsia produced by the malady itself and very often by the indiscriminate use of drugs such as belladona, arsenic, digitalis, and various animal preparations.

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Antipsychotic drugs versus placebo for relapse prevention in schizophrenia

Schizophrenia is a debilitating, often lifelong disease and studies have shown that about 80% of patients relapse within 5 years. On the other hand, antipsychotic medication is expensive and these drugs have a substantial adverse effect profile. This systematic review and meta-analysis addresses these issues. The researchers identified 116 suitable reports from 65 trials, with data for 6493 patients. Antipsychotic drugs significantly reduced relapse rates at 1 year (drugs 27% vs placebo 64%; risk ratio [RR] 0.40.). Fewer of the patients on antipsychotics required hospital readmission. Weight gain, movement disorders and sedation were moderately increased in those on antipsychotics compared to the placebo cohort. Depot preparations reduced relapse rate more than oral medication (0.31 vs 0.46 relapse rates). The researchers concluded that maintenance treatment with antipsychotic drugs benefits patients with schizophrenia. The advantages of these drugs must be weighed against their side-effects.

Lancet 2012;379:2063–71.

Proton pump inhibitors and *Clostridium difficile* (*C. difficile*) infection

Established risk factors for *C. difficile* infection include antibiotic exposure, immunosuppressive treatment and prolonged hospital stay. More recently the association between proton-pump inhibitors (PPI) and *C. difficile* infection has received much attention. This report concerns a case-control study to examine the relationship between PPI and polymerase chain reaction (PCR)-proven *C. difficile* infection in 137 hospitalised patients in a tertiary hospital in Western Australia. Exposure to antibiotics in the three months prior to *C. difficile* infection was shown to be statistically significant. However, long-term PPI usage and intensity of PPI exposure prior to onset of diarrhoea were not significantly associated with *C. difficile* infection.

Int Med J 2012;42:591–4.

Antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis

This report concerns the issue of whether the safety and efficacy of antibiotic treatment for uncomplicated acute appendicitis are comparable to those of appendicectomy. Four randomised controlled trials with a total of 900 patients (470 antibiotic treatment; 430 appendicectomy) met the inclusion criteria. Antibiotic treatment was associated with a 63% (277/438) success rate at 1 year.

Meta-analysis of complications showed a relative risk reduction of 31% for antibiotic treatment compared with appendicectomy (risk ratio 0.69, p=0.004). They conclude that antibiotic treatment is both effective and safe as a primary treatment for patients with uncomplicated acute appendicitis and merits consideration as a primary treatment option for early uncomplicated appendicitis.

BMJ 2012;344:e2156.

Drug-resistant tuberculosis in China

Drug-resistant tuberculosis, especially multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis, is a major threat to the control of tuberculosis worldwide. China is one of the countries with the highest burden of tuberculosis with 1 million incident cases annually. This report from the Chinese Centre for Disease Control and Prevention defines the problem of drug-resistant tuberculosis by reviewing its incidence in new cases. In this group 34.2% had some form of drug resistance, 5.7% had MDR and 0.5% had XDR tuberculosis.

Overall 1 in 10 patients with tuberculosis in China has MDR tuberculosis and 1 in 120 has XDR tuberculosis. Obviously, a major health problem for China and possibly the rest of the world.

N Engl J Med 2012;366:2161–70.

Delamanid for multidrug-resistant pulmonary tuberculosis

Drug-resistant tuberculosis has been a problem for decades but it is burgeoning worldwide, particularly in China (see above). So the emergence of another effective treatment is welcome. Delamanid is a new anti-tuberculosis medication that inhibits mycolic and acid synthesis and has shown potent in vitro and in vivo activity against drug-resistant strains of *Mycobacterium tuberculosis.*

In this trial 481 patients with multidrug-resistant tuberculosis were randomised to receive delamanid or placebo in combination with a background drug regimen. Those receiving delamanid had a significantly increased sputum culture conversion rate at 2 months compared with the placebo group. Adverse effects were evenly distributed across the groups. Prolongation of the QT interval in the electrocardiograms of the delamanid group were seen more frequently, but there were no cardiac clinical events noted.

N Engl J Med 2012;366:2151–60.

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Rex Livingstone Sinclair

1 July 1923 – 26 January 2012

Rex completed 60 full years of general practice in Takapuna and Taihape before finally hanging up his stethoscope in 2010.

Rex was the first-born son of David Sinclair, a country GP from Taihape, and his wife, Edith. Rex started boarding at Nelson College at the tender age of 8 years old, accompanied by his 5-year-old brother, Ian.

Due to his mother's early death from cancer, Rex was brought up by his aunt and uncle David and Emily Gudex with his cousins Jack and Bob Gudex. He maintained his close ties with them during his medical school years with Bob as a class mate and Jack a few years ahead. This bond between the Gudex and Sinclair families has continues down the generations, with numerous members of the families passing through Auckland and Otago medical schools and Universities.

Rex began Otago Medical School in 1941, accompanied by his cousins Jack and Bob Gudex. While in Dunedin, Rex excelled in his sporting interests playing rugby for Otago, boxing or University and also winning alpine skiing events at Ruapehu.

In 1950, Rex joined the exodus of NZ graduates to UK to further his medical career. He undertook GP locums in England, Italy and Germany and worked in hospitals in London including 18 months as the resident surgical officer at Barnett Hospital. He was able to further his interest in general and plastic surgery, gaining skills which would equip him well as a rural GP in isolated Taihape. While in London Rex met and married Lorraine Leicester—a Wellington-born teacher and family therapist.

In 1954, Rex and Lorraine, accompanied by their first born Mick, returned to Taihape to take up a general practice. Rex's return was a welcome relief helping to share the load of 24/7 GP cover as well as managing a hospital with his father and one other GP. Taihape's catchment area very large and was predominantly mountainous terrain with very poor roads.

With many roads impassable in winter and significant trauma common, Rex and the others two GPs needed to be self-sufficient—dealing with surgery, anaesthetics and X-rays. Rex's practice included the obstetric cover for the Waiouru Military Base performing emergency Caesareans with no blood transfusion cover.

With huge support from Lorraine, Rex completed 9 years of General Practice in Taihape. Rex and Lorraine moved to Auckland accompanied by their four children: Mick, Gilli and twins Pippa and Josie. Rex joined Drs Faris, Finlayson and McCann at the Hauraki Corner Medical practice in Takapuna. With his experience as an independent rural GP, and his surgical training in the UK, Rex enjoyed a full urban GP career interspersing medicine with a significant amount of minor surgery.

Rex's wealth of medical knowledge and his interest in computers and business helped him develop his practice. He took these skills to Byron Chambers when he joined Drs Bryant, Eason, Emmanuel and room in 2000 shortly after the early death of Lorraine.

Rex's sense of humour and fun was widely regarded. Rex had a unique ability to entertain his paediatric patients- many of them refusing to be treated by anyone else. Rex was a compassionate man with strong loyalties to friends, family and his beloved animals. He actively participated in organisation of his medical class reunions which are still continuing.

Rex was an innovator—creating and developing many quirky inventions around the house. He was an accomplished businessman involved in car dealerships, importing medical and sporting goods and deer farming. He raced rally cars and yachts in his spare time. Rex lived his life to the full but always had plenty of time for his family. His beloved wife Lorraine passed away in 1992.

Rex was a man before his time—he strongly supported equal opportunities encouraging people to follow their dreams. Rex is survived by his grandchildren and his four children: Mick, an entertainment lawyer; Gilli, project director; Pippa, a district court judge; and Josie, an orthopaedic surgeon.

Rex's children (Mick, Gilli, Josie and Pippa) wrote this obituary.

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Patrick William Cotter

Pat[rick] Cotter died on 26 June 2012 after suffering a massive stroke the night before. He was 3 weeks short of his 93rd birthday and had led an active and productive life up until that time.

Pat was born in Runanga in 1919, the son of William Makuri and Sophie Cotter. At this time his father was the GP and he knew well many of the eventual leaders of the Labour Party who 15 years later became Cabinet Ministers in the first Labour Government. A year or two later his parents took Pat and his younger sister to the UK where Bill undertook surgical training. After a short time Pat was brought back by an aunt to live with his Aunt Con and his grandmother on a farm in Pahiatua until his parents returned in 1926 when Pat was 7; he barely knew them.

Pat was educated briefly at St Mary's Convent and then at Fendalton School, entering Christ's College in 1933 and leaving in 1937 in which year he was a House Prefect, Captain of Swimming and in the Athletics team and 2nd Rowing Four. He took Medical Intermediate at Canterbury University College and entered the Otago Medical School in 1939 together with no less than 17 boys from the same 6th Form year at Christ's College.

At Otago he rowed in the University VIII and he joined the Otago University Medical Company and went to numerous camps in his holidays. He was commissioned 2nd Lieutenant in 1942, his 5th year of the medical course. After graduating MB ChB at the end of 1943 he spent a year as House Surgeon in Christchurch and in 1945 he was posted in the NZMC to Fiji with the rank of Captain. He returned to New Zealand in 1946 leaving the Army and in January 1947 married Prudence (Prue) Mary Pottinger from Wellington and went to London by ship in March; Prue following 2 months later.

He studied for the Primary Examination and passed it and then attended courses and lectures at Guy's, St Thomas' and the Royal College of Surgeons and Clinics with Stanford Cade, Norman Tanner and others and did locum jobs at St Peter's and Great Ormond Street and a Registrar job at St Giles, Denmark Hill, before passing the Final FRCS in 1949.

They now had two children and returned to Christchurch to be Senior Surgical Registrar in 1950–51. He then moved into private practice in rooms with his father and did private surgery, brief GP locums and Insurance work.

He became FRACS in 1955 and was appointed to Burwood Hospital on a small number of sessions the following year. Upon the opening of The Princess Margaret Hospital in 1960 Pat was appointed to a General Surgical position there.

In 1963 he moved to Christchurch Hospital where he formed a surgical“team”with Rob Davidson until his retirement in 1985.

Pat Cotter’s contributions to medicine in general and surgery in particular were immense.

He was on the Canterbury Divisional Committee of the NZMA for 10 years, was Delegate to Council and was on the Central Specialists’ Committee and was Treasurer for the Biennial Meeting of NZMA in 1979. He spent 6 years on the Editorial Committee of the *New Zealand Medical Journal*. He was Publicity Officer for the 1982 General Scientific Meeting in Christchurch.

He was too busy to publish much but a most important piece of work was the publication, with Derek Hart and Bill Macbeth, of the results of a study of the levels of blood alcohol in patients involved in motor vehicle accidents. He took his findings to present to a Select Committee of the House and legislation followed in due course. The genesis of this study lay in one of his many visits to “Bill” Hughes (later Sir Edward and President of the College) in Melbourne. They became firm friends.

The Royal Australasian College of Surgeons was an abiding interest. He was a member of the NZ Committee for 10 years, on the Court of Examiners for 8 years, Joint Secretary of the Annual Scientific Meeting in Christchurch in 1966 and organised a successful ASM in Fiji in 1970.

He had a special regard for Fiji and its people from his time there at the end of the War, and returned to help with teaching and operating on a number of occasions over the years.

Pat developed a very busy Private Surgical Practice based on great service especially to the country GPs and their patients. His greatest service to private surgery itself was the founding (in 1960) of the Surgeons’ and Anaesthetists’ Instrument Pool which eliminated the chaotic system of each surgeon turning up to operate at a private hospital with a bag of instruments which then required sterilisation.

So on a given weekend every surgeon brought his instruments on which his initials were engraved (lest he should want them back) and these were sorted into sets and kept sterilised and ready for use for a small fee. Furthermore operations were arranged in lists at given times and days and the system was rationalised. Pat and Keith Drayton ran the Pool until they retired.

Pat was one of the “dissident coterie” of members of the Medical Assurance Society who realised that all was far from well and, against strenuous opposition from the then Directors, changed the entire culture and direction of the struggling Society into a sound business for which many, especially in Christchurch, are presently extremely grateful. He continued as a Director from 1972 to 1980.

Pat developed an early interest in Medical Education through the Branch Faculty which eventually became the Christchurch Clinical School of Medicine and finally the Christchurch School of Medicine of the University of Otago. He served on the Joint Relationships Committee of Branch Faculty and Hospital Board and was the one of the so-called "Gang of Four" with Don Beaven, Fred Shannon and George Rolleston in the Chair who met with increasing frequency from 1967 to 1972 to plan the teaching facility.

It was a remarkable achievement to have the School up and running for student entry in 1973. His outstanding contribution was to the Canterbury Medical Library which he served for 30 years, latterly as Chairman, and eventually handed it over to the University as a flourishing concern firmly embedded in the heart of the School.

Amongst his medical activities, Pat had several other interests which he pursued with equal vigour. His father introduced him to a real-estate friend who guided him in the purchase of commercial property and he bought, built and owned many properties in association with his son Paddy, including farm developments on Banks Peninsula. He was the Chairman of a number of companies. He developed an enthusiasm for and great knowledge of silviculture and particularly Farm Forestry.

In 1960 Pat and Prue bought a bare section at Charteris Bay in the Lyttelton Harbour and built a holiday cottage and developed the steep hillside with paths, steps, dry rock walls and much planting of all sorts of trees and shrubs. If he ever went down to the foreshore it was usually armed with a crowbar, to rearrange the rocks into bathing pools and generally tidy up!

Then he leased a peninsula opposite and planted it entirely in a stand of *Pinus radiata* trees which is now mature and has been sold.

Finally in 1980 they bought land at Pigeon Bay where Pat could give full rein to the ideas he had been developing in association with other keen and knowledgeable tree men and planted a great variety of trees both in close forestry and more spread out in Farm Forestry fashion and employing a farm manager to take care of the stock.

They built a beautiful cottage to replace the old wooden house with a view down the Bay to the sea and surrounded it with rhododendrons, fruit trees, flowers of all descriptions and lots of tree lucerne to encourage the wood pidgeons. In the midst of all this splendour Pat and Prue celebrated their 60th wedding anniversary in January 2007.

In the early 1980s Dr Ross Fairgray asked Pat, who was a well-known hoarder, to form a Committee to collect " Items of Historic Interest" of a medical nature, fearing that the new management engendered by the Health Reforms might be inclined to dispose of our medical history.

The collection grew apace and a means of looking after it long-term was needed so Pat and Prue settled the Cotter Medical History Trust, to "collect, preserve and display" items of an historic medical nature. Many permanent displays have been placed; an outstanding collection of old microscopes has been purchased; many books have been catalogued and photographs and plans identified and filed, by a loyal and enthusiastic band of volunteers inspired by Pat.

He has also documented the lives of many doctors mostly but not exclusively in Canterbury and there are now about 1000, many of which have been archived nationally.

Pat was never a man for the limelight but he received two Awards late in life which pleased him. The first was the Christchurch Civic Award which was given in 2005 for his work with the Medical History Trust. The other was his appointment as Officer of the New Zealand Order of Merit in 2009 (see photograph).

Pat Cotter was a splendid colleague. Everything that he did was thoroughly researched, properly executed and carried through to a satisfactory conclusion. As his son Christopher said at his funeral " Pat was a complex individual. He was opinionated and outspoken…He was fiercely focussed…and to an extent obsessive. At the same time he could be remarkably generous and extraordinarily parsimonious".

Prue has been a tower of strength especially in these last years when one eye had been removed and the other failing. His balance was bad but his brain was still remarkably agile.

Our sympathy is extended to her and to his children, Christopher, Kate, Paddy and Jane, his 14 grandchildren and one great grandchild.

Mr Rob Davidson, a colleague and friend of Mr Pat Cotter, wrote this obituary.