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EDITORIAL

Welcome to the eighth issue of the New Zealand Medical Student Journal (NZMSJ). In addition to the usual high quality array of peer-reviewed student research and topical opinion pieces which the journal has a long established history of providing the medical student community, we are pleased to present the first ever issue of the journal containing a selection of articles centred around a theme, in this case, rural medicine in New Zealand.

Below are some thoughts on the importance of this issue from Dr Pat Farry, director of the University of Otago's Rural Medical Immersion Programme:

> *Overseas, it is well recognised that there is a world wide shortage of doctors, especially those working in smaller rural communities, which are particularly vulnerable because the loss of one doctor in a region can lead to a breakdown of services. This vulnerability does not only apply to rural primary care but also to rural secondary care services. Despite this, there have been until recently very few major workforce initiatives specifically targeted at addressing this issue, with medical officers working in rural hospitals having no specific vocational training or registration until as recently as earlier this year.*
>
> *Fortunately, there have now been some more significant developments to address the rural workforce problem. The Medical Council has recently formed a Branch Advisory Body for Rural Hospital Generalists. The Royal New Zealand College of General Practitioners have formed a Rural Faculty of College with a Division of Rural Hospital Medicine. These are very important developments for rural secondary care services and will hopefully result in improved retention and recruitment of rural hospital generalists.*
>
> *In addition, both the Auckland and Otago medical programmes now incorporate elective regional-rural immersion programmes into their curricula. The educational focus of these programmes differs from vertical silo learning in specialty topics seen in urban centres to parallel learning which may vary from topic to topic in the same day. A student may attend a patient with chest pain in the morning, a patient from a motor vehicle accident in the afternoon and attend a birth in the evening.*

Under Dr Farry's direction, Otago launched its rural immersion programme in 2007. Rachel Lynskey gives her reflections on her experiences as part of the initial cohort of students on page 12. Further to this, other novel opportunities for students to experience brief encounters with rural communities are also appearing. Michael Lee describes on page 16 how he and his research group travelled to the remote community of Kohukohu in the Hokianga region as part of a summer studentship in Auckland. He investigated the usefulness of natriuretic peptide biomarkers in detecting left ventricular hypertrophy in patients with type II diabetes. We offer special thanks to Associate Professor Warwick Bagg and Dr Farry for providing us with informative descriptions of the Otago and Auckland rural programmes respectively, which have been published accompanying Rachel and Michael's articles.

We extend our sincere thanks Dr John Adams, Dean of the Dunedin School of Medicine, for his generous sponsorship of this issue's Dean's Writing Prize. Aaron Ooi, a third year medical student at the Auckland School of Medicine was the worthy recipient of this prize for his piece on Alzheimers disease. Son T Pham received the runner-up prize for his work on signalling in rat cochlea. Congratulations are also due to Rachel Lynskey of the Christchurch School of Medicine who received our Features prize for this issue. We wish to thank our two academic advisors, Associate Professor David Perez and Dr John Alison as well as our expert reviewers from across New Zealand for their ongoing valued contribution.

We hope that you find the content of this edition of the journal to be an informative account of some of the key issues facing the future of medical practice in New Zealand and abroad.

The NZMSJ Executive

The NZMSJ editorial board maintains that the articles published under the heading "opinion" are the personal views of the author and the NZMSJ does not support or endorse these views in any way but respects the author's rights to voice his/her opinions.

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To the editors,

Re: Rural Medical Immersion Programme (RMIP)

Since 2001, the gradually-formed regional rural health clubs of New Zealand (Matagouri in Dunedin, Grassroots in Auckland, Country Scrubs in Christchurch and The Boot in Wellington) and the national body, Aotearoa Rural Health Apprentices (ARHA), have been working towards breaking down the endemic myths and negative attitudes towards training and working in rural New Zealand. In the most part devoid of financial support, these clubs have managed to enroot themselves, like the hardiest wild shrub, into the social and educational circles of their respective schools, and have bought their medical students such educational events as; Rural Health Week, suturing and plastering workshops (Get Plastered), Rural Careers Evenings, Rural Skills Weekend trips and emergency simulations; and social events including Town vs Country rugby league, Barn Dances, pub quizzes, barbeques and Rural Olympics, as well as establishing scholarships for rural training. But these efforts have been largely offset by the lack of any ongoing formal rural training schemes for those many interested students. Without co-ordination of undergraduate rural training and postgraduate rural career paths, the efforts of these motivated student groups threatened to amount to very little, as students moved on in their careers, and the positive associations made towards rural careers and training forgotten, as junior health professionals lived in large centres and continued to become more and more urbanised.

Across the ditch, since 1998 Australian medical students have been offered the opportunity to train and live in areas of rural Australia. This has been part of a wider government initiative aimed at encouraging members of their future health workforce towards careers in rural areas, and some twelve years on from its inception, the move is looking to have paid rich dividends. Research from Flinders University has shown that 85% of their Post-Grad Rural Curriculum (PRCC) graduates are now working towards a rural career. In other related benefits, the research has also proven that 86% of PRCC graduates stay in the state they were trained, are 20 times more likely to prefer a rural career than their peers in an urban area and are 5 times more likely to enter GP training (like New Zealand, an area of increasing workforce need). Sadly, in New Zealand, we had no equivalent.

But that was then, this is now!

ARHA are delighted that the NZ government and the Faculties of Auckland and Otago have this year implemented an equivalent Rural Medical Immersion Programme (RMIP) for the medical students of this country. For the first time, medical students will spend an entire year based in a number of New Zealand's more rural centres, learning the realities of practicing outside large base hospitals, and also experiencing all that these rural centres have to offer from a social perspective. ARHA strongly believes that these students will quickly dispel the myths surrounding a rural career, and hopes they will come back to their base centres and pass this message on. Already this year these RMIP students have been treated to scenic flights and fishing expeditions, have experienced emergency training, helicopter transfers and first-response to traffic accidents, heart attacks and more. There will be many more memorable experiences, learning and social, before they sit their final exams in November. ARHA are also confident that these students will fair equally as well as last years Otago 'pilot scheme' students, who all performed meritoriously in their exams and are proving to be excellent trainee interns this year.

In addition, ARHA hopes to be able to offer a further rural scheme to the medical students of New Zealand, potentially as soon as 2009. Pending funding form the government's Rural Innovation Fund, the 'ARHA Rural Scholarship Scheme' aims to allow 10 first year students the opportunity to experience that same rural lifestyle and training for two weeks a year, across their entire medical school training. The Scholarships will be won by second year medical students, and will involve flights, accommodation and expenses for them to spend two weeks of their holidays with the same practitioner in each year of their training. They will get to train clinically from their very first year, and will build up skills that help them in the future. They will also have the chance to experience the unique charms of some of New Zealand's most beautiful rural locations, and build relationships with the practitioners and districts that may last a lifetime.

ARHA wishes all this years RMIP students well in their studies, and hopes that they will provide the inspiration for future years of enthusiastic students to venture out beyond the big cities and base hospitals, and experience the health care model that supports those life-blood areas of our country. Whether you think a rural career is for you or not, you'll never know unless you take the chance of med-school lifetime, as these current students have done. And to all the staff from Otago and Auckland who have made this happen, and the regional coordinators and practitioners who we know will ensure the scheme is a roaring success, ARHA and the rural students of New Zealand offer you our deepest gratitude.

Keepin' it rural

Brad Stone

ARHA President 2008

NZMSJ ACADEMIC Writing Prize ISSUE 7 FIRST PLACE

Alzheimer's disease: Vaccination strategies using antibodies against ß-amyloid plaques: a cure?

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Aaron completed this review as part of a paper in the second semester in second year (2007). It has personal significance as he explains below.

"I have always been interested in the brain and how this one single organ ultimately makes us who we are, my fascination in Alzheimer's disease stems from ever since my grandma was diagnosed with it in 2001. Since then I have observed the progression of the disease on her, her long term memories have started to deteriorate recently as she is at the stage where she is unable to recognise people and thus my interest in the pathogenesis of the disease. As there is still no cure for AD, this is an area where I have always tried to keep up to date with, and this hence provided me with the starting point for my review."

Abstract

The utilisation of concepts of immunotherapy on ß-amyloid plaques involved in Alzheimer's disease has been a focus of major research over the recent years. Using original articles of studies conducted in this area, this paper will examine the feasibility and some of the key milestones that have been critical to this newly expanding area of research, in the bid to offer hope of finding a cure for some of the millions of Alzheimer sufferers worldwide.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder which presents with a progressive loss in cognitive function, impairments in memory and eventual loss of learned motor skills leading to death. Pathological hallmarks that are commonly seen in AD affected brains include loss of neurons, formation of ß-amyloid in neuritic plaques (containing abnormal insoluble aggregates of the ß-amyloid peptide) and neurofibrillary tangles[1]. These plaques are often found in large amounts in the association and limbic cortices, and are usually associated with activated microglia and astrocytes, adjacent to the core and surrounding the plaque respectively. In particular, the more hydrophobic species of ß-amyloid, ending at amino acid 42, $Aß_{42}$, predominates in these plaques, prompting current research to focus on this particular species[1].

As there is no cure for AD, the majority of treatment at the present time as part of the New Zealand guidelines focuses on cholinesterase inhibitors that aim at prolonging the action of Acetylcholine in the brain at the synapses. This thereby provides only temporary alleviation of symptoms, slowing the rate of decline; such treatments include Rivastigmine (Exelon) and Donepezil (Aricept)[2,3].

In New Zealand today, approximately 38,000 people are affected with dementia, and of that approximately 50-60% constitutes those affected by AD[4]. Although the cause of the disease is, at present, still unknown, a number of risk factors have been identified for this debilitating disease; gender, Apolipoprotein E genetic status, those suffering from Down syndrome and long term occupational exposure to solvents being a few, but the most crucial and notable being age[2]. It is a disease that predominantly affects those over the age of 65, with the risk of being diagnosed with dementia beginning at approximately 1% at the age of 60-64, rising 1-2% a year until it approaches approximately 30-50% by the age of 85. As the generation of post war baby boomers succeed the current elderly population, the proportion of those aged 65+ in New Zealand have been projected to increase to approximately 25% in 2050, almost double that of the current number[2,4]. It can hence be deduced that Alzheimer's disease will take on a significant burden with respects to New Zealand's health care system in the upcoming decades, calling forth the need for potential interventions to alleviate this impending burden.

The ß-amyloid hypothesis - the basis of current research

The ß-amyloid hypothesis establishes that the ß-amyloid protein (Aß) plays a causative role in AD, due to its neurotoxic properties ultimately causing neuronal degeneration. This is supported by the genotype-phenotype observation in the rare, autosomal dominant familial form of AD, in which mutations in the Amyloid Precursor Protein (APP), Presenilin 1 and Presenilin 2 (enzymes which are involved in the cleavage and processing of APP) lead to an increase in the production of the hydrophobic-42 amino acid form of Aß that predominate in plaques seen in the disease[1]. A study[5] conducted in 2005 also stands to support the claim of the significant role of Aß in AD by attempting to explain the mechanism by which ß-amyloid immunotherapy would be beneficial. Using transgenic mice models, it was observed that both passive and active immunisation resulted in the lowering of Aß levels, providing protection against the loss of synaptophysin (a presynatic vesicle protein found in the hippocampus and association cortices). This also prevented synaptic degeneration, a crucial process believed to be related to AD associated cognitive decline[5], evidence which consequently strengthens the ß-amyloid hypothesis.

Immunotherapy in transgenic mice models - the beginning of an era

Any assessment of immunotherapy in general necessitates the distinction between two crucial concepts; active and passive immunisation. The former involves immunisation with a specific antigen, in this case Aß peptide, which consequently results in an immune response, directed towards the antigen administered, from the host. This compares to the concept of passive immunisation whereby immune-mediated clearance of Aß is promoted

through the regular administration of anti-Aß antibodies.

The possibility of immunotherapy stemmed from the work conducted by Schenk et al. involving $Aß_{42}$ immunisation of both young and old PDAPP transgenic mice models. It was observed that mice which were immunised at the age of 6 weeks did not develop ß-amyloid plaque formation, astrogliosis or neuritic dystrophy[6], essentially preventing the development of the symptoms of Alzheimer's despite having a predisposition. It was also noted that treatment of the older mice (immunised at 11 months) had a lesser extent of the neuropathological hallmarks that accompanied AD. In addition, immunoglobulins (IgG) were also discovered around plaques following the use of immunohistochemistry[6], effectively sparking a new wave of interest as to the possibility of a cure of AD via this pathway.

Clinical trials of Aß immunisation

The success in stimulating the clearance of ß-amyloid plaques in these animal transgenic models, without any reported adverse effects, thus prompted the commencement of clinical trials using an aggregated $Aß_{1-42}$ peptide (AN-1792) combined with QS-21 as an adjuvant. After establishing the safety and tolerability of the vaccine with phase I trials without any significant problems, phase IIA for the same vaccine was launched involving 372 mild-to-moderate AD patients. This trial was also aimed to test the pilot efficacy in addition to the safety and tolerability of the vaccine, given at 0, 1, 3, 6, 9 and 10 months. This was however prematurely halted when 18 of the 298 participants who were given the intramuscular injection of AN1792 (6%) were diagnosed with aseptic meningoencephalitis (not observed in the 72 controls who received saline solution)[7]. Although it was eventually concluded that postvaccination meningoencephalitis occurred without any relation to the AN1792 vaccine itself and the presence of positive antibody titres, it was identified that microglial activation as well as a T cell mediated response could have been responsible[7,8], leading to a shift of focus towards the need to develop safer vaccines that avoided this pro-inflammatory response to evade such adverse associations in future clinical trials.

Another key study[9] was also conducted assessing the effect of antibodies in slowing the progression of AD. This involved a cohort of 28 patients from the original trial conducted by Orgozozo and colleagues, who, over a period of a year, received a prime and a booster immunisation of aggregated $Aß_{42}$. Results of the study showed that 20 of the patients who subsequently generated antibodies against Aß had a considerably slower rate of decline in cognitive function as assessed by a number of mental function tests, such as the Mini Mental State Examination (MMSE), when compared to patients in the placebo group. Although these results are promising, a number of limitations existed in this study. The sample size may not be large enough or representative if the data were to be extrapolated to the general population thereby requiring caution if this was to be done. Another concern raised was that the original trial also encountered early termination, after only 19.7% of participants in total had developed an antibody response, consequently calling for the need for future trials to be of a longer duration to in order to fully assess the efficacy of the vaccine.

The development and progress of a safer vaccine - Th1 vs. Th2 immune responses

The assumption of the involvement of T-cell mediated response via the Th1 pro-inflammatory pathway causing meningoencephalitis has also shifted the focus towards the creation of a safer vaccine ideally aimed at avoiding this pro inflammatory pathway and utilising a Th2 response involving antibody production. Supporting this statement were results from a crucial study conducted in 2003[8], examining the effects of neurotoxicity associated inflammation. These results found nitric oxide release, mediated by microglia (resident immune cells of the CNS), by Aß-reactive Th1 cells contributed to AD neurotoxicity, nonetheless this toxic effect was observed to be counterbalanced by activity of the Th2 cells[8]. This issue has been addressed in a number of studies, one of these being a key trial conducted employing the use of an adenovirus vector encoding 11 tandem repeats of $Aß_{1-6}$ (a more robust immunogen than $Aß_{1-42}$ vaccines)[10]. An immune response polarised towards an anti-inflammatory Th2 type response was able to be observed with immunoglobulin isotyping via this vaccine, with much higher titres being observed when co-administered with additional adenovirus vector encoding granulocyte-macrophage colony stimulating factor (GM-CSF) that served to increase its immunogenecity[10]. This has ultimately allowed for the option of a safer alternative to peptide-based vaccines but nonetheless, as with all other research conducted with animal models, caution is necessary before proceeding into clinical trials.

The development and progress of a safer vaccine - routes of administration and adjuvant toxicity

Apart from problems regarding Th1 immune responses, concerns have also been raised with regards to the toxicity of adjuvants prompting further exploration. In order to address both of these issues of adjuvant toxicity, a study was conducted by Asuni and colleagues using nonfibrillogenic, non-toxic Aß homologous peptides (K6Aß 1-30-NH2) and alum adjuvant (which had lowered toxicity) given by active immunisation. Results provided strong evidence promoting its use as a decrease in total ß-amyloid deposit burden was still seen in addition to the fact that neither alteration in vascular Aß nor increase in cerebral bleeding occurred[11]. Accordingly, this could possibly thus be another safer alternative when compared to the usual peptide-based vaccines.

Other concerns in relation to routes of administration being associated with microhaemorrhages observed in some studies utilising Aß immunotherapy have also been raised. It is important to note that in the majority of cases, Aß deposition not only occurs in the brain parenchyma, but also in the cerebral vasculature; known as cerebral amyloid angiopathy (CAA)[12]. In a study conducted by Ranke et. al., age dependant accumulation of Aß in isolated cerebral vessels have been shown to occur in PDAPP transgenic mice; it's composition being quite similar to that seen in sporadic AD in humans. The same study then examined administration of various types of monoclonal antibodies in the same models via passive immunisation, with results showing that N-terminal antibodies 3D6 and 10D5 were able to bind to their epitopes in the Aß peptide regardless of aggregational state; this was ultimately associated with increased microhaemorrhages and exarcebation of CAA already present[12].

Increased microhaemorrhages have also recently been shown to be associated with active immunisation by Wilcock and colleagues as part of a study investigating Aß vaccinations in comparison to non steroidal anti-inflammatory drug treatment and its effects on Aß deposition in the brain. In this case however, transgenic APP + PS1 mice were used and active immunisation performed using $Aß_{1-42}$. Although results showed a decrease in Aß depositon, increased levels of vascular amyloid and hence CAA as well as microhaemorrhages were also noted[13]. Both these studies consequently raises questions requiring the need for further experimentation with routes of administration of vaccines (both passive and active) in the attempts to avert such adverse effects; nonetheless, comparisons between both are difficult due to the different methodologies used. Moreover, it is also essential to remember that besides the varying routes of administration, combinations of adjuvants and the type of vaccine used would also ultimately play a role in the overall outcome and the interplay of negative side effects which are to be avoided, and as research continues to progress for a potential cure, all of these need to be taken into account.

Conclusion

With the world's continued aging population, the idea of using Aß immunotherapy in preventing the formation of plaques and also promoting the clearance of plaques from the brain is highly appealing, having the potential as a cure for this debilitating disease affecting many worldwide. Despite the fact that clinical trials have been halted and concerns raised, research in this area on transgenic animal models look promising with advances being made in reducing the AD related pathology of Aß plaques, as well as the creation of other safer alternatives besides the usual peptide

based vaccines. It is worth noting however, that current research relying on transgenic animal models may not be truly reflective of its efficacy in humans, as mouse Aß is only approximately 96% homologous to human Aß[14], thereby calling the need for the use and creation of better models whenever possible, which would undoubtedly aid clinical trials in the future. Further clinical trials should also proceed with caution as future directions in this area head towards the investigation of different routes of administration as well as experimentation with active and passive immunisation agents in the attempts to discover a safe vaccine for use in humans. Investigations to unravel the mystery of the mechanisms involved in the functioning of Aß immunotherapy may also be another area of development, in order to fully understand the pathways involved and to help minimise unwanted adverse effects such as inflammation and mircrohaemorrhages with use of such vaccines.

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How effective is the Human Papilloma Virus Vaccine?

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Anna is currently studying medicine at the University of Auckland and is interested in pursuing a career in women's health and would like to specialise in Obstetrics and Gynaecology. She also is involved in the Auckland University Medical Student Association (AUMSA) as one of the members on their executive.

Abstract

A review of several research papers that present findings from prominent clinical trials reveals that the current quadrivalent HPV6/11/16/18 vaccine demonstrates high efficacy against Human Papilloma Virus (HPV) related cervical cancer. This research supports the implementation of a HPV vaccination programme. With such a programme in place, the incidence of HPV16/18 related cervical cancer would be profoundly reduced.

Introduction

Cervical carcinoma is the largest cause of cancer death among women in developing countries and second among women internationally. It has been well documented that Human Papilloma Virus (HPV), enhances the risk of developing cervical cancer[1]. HPV is the most common sexually transmitted disease and contracting HPV can be greatly increased by exhibiting unsafe sexual behaviour[1]. Developing and distributing a vaccination against HPV provides an opportunity to considerably decrease the incidence of cervical cancer worldwide.

In New Zealand there is a sizeable public health need for an HPV vaccine and there are significant disparities between Maori and non-Maori concerning the rates of HPV and cervical cancer. Age standardised incidence of cervical cancer among Non- Maori New Zealand women was 8.2 per 100,000 in 1999[2]. The incidence of cervical cancer seen in Maori was approximately double these figures, 16.0 per 100,000[2]. Also Maori cervical cancer related mortality is four times that of Non-Maori[2]. In light of these disturbing figures the National Cervical Screening Programme (NCSP) encouraged women to have two smears, twelve months apart when they turn 20 years old, then a smear every three years until they reach 70, provided that the findings of their smears remain normal[2]. Due to the implementation of this initiative there has been a 22% reduction in the incidence of cervical cancer and cervical cancer related deaths in all New Zealand women, but there are still inequalities seen between the rates for Maori and non-Maori[2]. In conjunction with this already established screening programme, an HPV vaccine has the potential to considerably reduce the incidence of HPV related cervical cancer among New Zealand women.

There have been more than a hundred different HPV genotypes discovered and these can be classified into low or high-risk categories in terms of their carcinogenic ability. There are four main genotypes that are targeted by the quadrivalent vaccine HPV6/11/16/18. Two of the genotypes are low grade HPV6 and HPV11. These produce benign genital warts (condyloma accuminata). The others are high grade HPV genotypes, HPV16 and HPV18, which together account for 70% of the major pathological agents contributing to cervical cancer[3]. Developing and distributing a vaccine that incorporates these four main HPV genotypes will be a significant step towards reducing the incidence of HPV-related cervical cancer.

Vaccine efficacy

The efficacy of the HPV vaccine is best demonstrated by the meta-analysis undertaken and presented by Dr Kevin A. Ault[4]. This research combined the findings of four separate randomised control trials. These trials involved 20,583 women between the ages of 16 and 26. Participants were randomly divided into three groups. Two groups were treated with one of two vaccines, either the quadrivalent vaccine HPV6/11/16/18 "Gardasil" or the HPV16/18 vaccine "Cervarix". The third group received a placebo[4]. All participants underwent periodic Papanicolaou testing and when an abnormality was detected a colposcopy or biopsy was carried out[4]. The vaccine efficacy was determined by observing the incidence of HPV16/18 related cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ (AIS) and cervical cancer[4].

The data from the results of these trials was collected three years after the first dose of vaccine was administered. In women who were negative for HPV16 or HPV18 infection during the vaccination regimen, vaccine efficacy was determined to be 99%. It was also found that 85 women developed histologically confirmed HPV16/18-related CIN or AIS in the placebo group, in comparison only one case of HPV16-related CIN among the group who were allocated the HPV vaccine[4]. In an intention-to-treat analysis of all participants involved, including those who were naïve to HPV16/18 and those who were HPV16/18 infected, the vaccine efficiency was found to be 44%[4]. It has been determined as a consequence of these findings that the quadrivalent HPV vaccine is to be administered as a means of prophylactic treatment rather than providing a cure to those women already infected with the virus. This study provides strong evidence that the implementation of HPV vaccination in pre-adolescent girls and young adult women will profoundly reduce rates of cervical cancer worldwide.

Author & publication & year	Method	Study group and type	Findings
The Future II Study Group[5] New England Journal of Medicine 2007	Participates receive three doses of either HPV-6/11/16/18 vaccine or placebo, administered at day 1, month 2, and month 6.	Randomised, double blind trial. 12,167 women aged 15- 26 years assigned into vaccine group (6087) or placebo group (6080).	**Cases of HPV16/18 related CIN or AIS in restricted population:** 1 case in vaccine group, 42 cases in placebo group **Vaccine efficacy:** 98% **Cases of HPV16/18 related CIN or AIS in unrestricted population:** 3 cases in vaccine group, 62 cases placebo. **Vaccine efficacy:** 95% **Cases of HPV16/18 related CIN or AIS in modified ITT population:** 83 cases in vaccine group, 148 in placebo group. **Vaccine efficacy:** 44%
Villa LL et al.[7] Lancet Oncology 2005	Participates receive three doses of either HPV 6/11/16/18 vaccine or one of two placebo preparations, administered at day 1, month 2 and month 6.	Randomised, double-blind placebo-controlled phase II study. 1158 women aged 16-23 years, assigned into vaccine group (277) or one of two placebo groups (275).	**Efficacy of quadrivalent vaccine against persistent infection or disease associated with HPV 6, 11, 16, or 18:** 90% (95% CI 71–97, p<0·0001) **Efficacy of quadrivalent HPV vaccine against persistent infection or disease associated with HPV 6, 11, 16, or 18 in modified ITT analysis:** 89% (95% CI 73–96, p<0·0001)
Mao C et al.[8] Obstetrics & Gynocology 2006	Participates received three doses of either 40μg HPV16 L1 VLP vaccine or placebo, administered intramuscularly at day 1, month 2 and month 6.	Randomized, double-blind, placebo-controlled trial 2,391 women, aged 16-23 years, assigned into vaccine group (755) or placebo group (750).	**Cases of HPV16-related CIN:** 0 cases in vaccine group, 12 cases in placebo group. **Vaccine efficacy:** 100% (95% CI 65–100). **Cases of persistent HPV16 infection:** 7 cases in vaccine group, 111 cases in placebo group. **Vaccine efficacy:** 94% (95% CI 88–98).
Garland SM et al. [6] New England Journal of Medicine 2007	Participates received three doses of HPV6/11/16/18 or placebo administered at day 1, month 2 and month 6.	Randomised, double blinded, control trial. 5455 Women aged 16-24 years , assigned into vaccine group (2723) or placebo group (2732).	**Cases of HPV16/18 related CIS or AIS in per-protocol susceptible population:** 0 cases in vaccine group, 60 cases in the placebo group. **Vaccine efficacy:** 100% (95% CI, 88-100) **Cases of HPV16/18 related CIS or AIS in modified ITT analysis:** 104 cases in the vaccine group, 157 cases in the placebo group **Vaccine efficacy:** 34% (95% CI, 15-49)
Ault KA.[4] The Lancet 2007	Participates received three doses of either HPV6/11/16/18 vaccine, HPV16 vaccine or placebo, administered at day 1, month 2 and month 6.	Double-blind, placebo-controlled, randomised trials including a combined analysis of four randomised clinical trials. 20 583 women, aged 16-26 years were randomised to receive HPV6/11/16/18 vaccine (9087), its HPV16 vaccine component (1204), or placebo (10 292).	**Cases of HPV16/18-related CIN or AIS in pre-protocol susceptible population:** 1 case in vaccine group, 85 cases placebo group. **Vaccine efficacy:** 99% (95% CI 93-100). **Cases of HPV16/18-related CIN or AIS in unrestricted susceptible population:** 3 cases in vaccine group, 121 in placebo group. **Vaccine efficacy:** 98% (95% CI 93-100). **Cases of HPV16/18-related CIN or AIS in ITT population:** 142 cases in vaccine group, 255 in placebo group. **Vaccine efficacy:** 44% (95% CI 31-55)

Table 1. Displaying findings on HPV vaccine efficacy from five main clinical research trials: HPV-Human Papilloma Virus, CIN-Cervical intraepithelial neoplasia, AIS- adenocarcinoma in situ, ITT- intension-to-treat.

Limitations

While the results from the current HPV vaccine are encouraging, it is also important to recognize the limitations associated with the administration of the vaccine and the vaccine itself. The issues include the fact that even though the current HPV vaccine protects against two HPV genotypes which together account for 70% of all HPV related carcinogenic agents, it fails to include all aetiological determinants of cervical carcinoma[5]. Another limitation associated with the current HPV vaccine is that it does provide protection against HPV for naïve individuals but does not eradicate existing HPV infections[5]. Further concern surrounding this vaccine is that vaccinating against HPV is a recent development and the duration of protection of the vaccine and the required length of protection to prevent cervical cancer is information that is not yet available[5].

There are also practical limitations which include the cost and administration of the three dose regimen, and the possible need for an additional booster injection[5]. These practical concerns will most certainly limit the number of individuals receiving vaccinations, especially in countries where the rate of HPV is high, but follow up health care is inadequate and a vaccine is yet to be subsidised[5]. However the benefits of the HPV vaccine most certainly out weigh the limitations, but these factors need to be considered carefully because they directly influence the efficacy of the HPV vaccine.

Ethical issues

Although comprehensive vaccination provides the most effective means of reducing the incidence of cervical cancer, mandatory HPV vaccination raises several ethical and social issues of concern. HPV is a common sexually transmitted disease, so infection by the virus can be successfully prevented with abstinence and also by the use of condoms[6]. One of the most frequently discussed concerns is that vaccination against HPV may result in the promotion of reckless sexual behaviour and premature sexual activity among adolescents. There is not substantial evidence to support these assumptions however these concerns can be minimalised through appropriate education[6]. Education will ensure that the vaccination against HPV is perceived, by the health profession and the general public, as a prophylactic measure rather than something that would promote promiscuity[6].

Conclusion

Cervical carcinoma is the largest cause of cancer deaths among women in developing countries and second among women internationally. Extensive studies have demonstrated that developing and distributing the current prophylactic quadrivalent vaccine HPV6/11/16/18, has the potential to reduce the incidence of HPV related diseases among women worldwide and also here in New Zealand. The current HPV vaccination programme has some practical and ethical issues that need to be considered, as they have the potential to influence the efficacy of the vaccine. These issues are outweighed, however, by the benefits that this vaccine presents. Currently being researched is the link between HPV and other cancers such as rectal, penile, and oropharyngeal. This then raises the possibility of immunising males against HPV in the future. Implementing a vaccine that safeguards against cervical cancer provides the first step towards reducing the incidence of other HPV related diseases.

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Tracking Rhino and a cure for cancer

Alternative medicine:
Not so alternative

Kylie Keen
Fifth Year Medical Student
Wellington Medical School
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Kylie Keen is a fifth year medical student at the Wellington School of Medicine. She has a BSc (Hons) in chemistry and an interest in cancer research.

During my summer holiday at the end of my fourth year, as I was tracking the White Rhino in Zimbabwe and spotting exotic birdlife in the Amazon Rainforest of Peru, medicine was the furthest thing from my mind. That was until my guides began to tell me stories of plants and trees that had been used by their indigenous people and Shaman for centuries to treat ailments such as arthritis, impotence, anaemia and even cancer.

I heard accounts of villagers who had been cured of bowel cancer after drinking preparations of Uña de gato, and research teams who had patented components isolated from this plant. I decided to learn more about the scientific basis of the therapeutic effects of these medicinal plants.

Uña de gato

Uña de gato is the Spanish name in Peru for *Uncaria tomentosa*, also popularly known as 'Cat's Claw'. It is a woody vine found in the tropical jungles of South and Central America and derives its name from its claw-shaped thorns. Uña de gato is traditionally prepared by boiling 20g of root bark with 1L water for 45 minutes. The remaining liquid is then decanted and restored to 1L with additional water. The daily dose is 60ml. The Peruvian communities use its aqueous extract to treat cancer, arthritis, diabetes, and inflammation[1].

The compounds most prominent in *U. tomentosa* are alkaloids and these are responsible for the plants overall medical effects. The alkaloids are found in every part of *U. tomentosa* and stimulate the phagocytic activity of granulocytes and thus act as a stimulant for the immune system when the plant is ingested[1].

Commercially prepared products are available and vary from capsules of dried bark or root extract, to alcoholic tinctures and tea. Krallendorn® is the brand name of a standardised extract of the root of *U. tomentosa* manufactured by Immodal Pharmaka GmbH of Austria. This drug contains pentacyclic oxindole alkaloids that enhance phagocytosis and inhibit proliferation of highly active lymphocytes[2]. Krallendorn® is a prescription drug in Austria available for adjunctive therapy in the treatment of rheumatoid arthritis. A clinical trial of patients with rheumatoid arthritis using Krallendorn® showed that there was modest reduction in the number of patients with painful joints compared to placebo[2].

Krallendorn® has also been trialled on HIV positive patients[3]. Thirteen study participants took a daily extract of 20mg *U. tomentosa* root for 2.2 to 5.0 months. After this time the study observed the relative and absolute lymphocyte counts had increased in the participants, however there were no significant changes in the T4/T8 cell ratios. The effect seen has been attributed to the plants ability to induce human endothelial cells to release a lymphocyte-proliferation-regulating factor[3].

Tannins and various other phytochemicals have also been isolated from *U. tomentosa* and these have been shown to contribute to the antioxidant properties of the plant via hydroxyl radical scavenging activity[1].

Rooibos

In Zimbabwe I learned about the *Combretaceae* family of shrubs and trees. These plants are locally known by the name Rooibos. Members of this family are widely used in traditional medicines in Africa and Asia to treat disorders such as hepatitis and malaria, respiratory infections, dysentery and uterine cancer.

The most important chemical components isolated from the *Combretaceae* family are the combrestatins[4]. Combretastatin A4 (COA-4), an anti-vascular compound that acts as a tubulin binding protein, is the most active of these compounds. It inhibits tubulin polymerisation and thus prevents cells from producing microtubules[5]. Microtubules are essential to cytoskeleton production, cell movement, and formation of the mitotic spindle used in chromosome segregation and cellular division. COA-4 disrupts the cell's ability to successfully complete cell division and causes a change in shape in vasculature endothelial cells which results in necrosis.

COA-4 targets cells at the tumour 'core' rather than the tumour 'edge', therefore combination therapy with other drugs would be required to treat all parts of a tumour. The effectiveness of this approach has been shown in studies[6]. In July 2007 a Phase III clinical trial was initiated by the pharmaceutical company OXiGENE to evaluate the use of ZYBRESTAT™ which is a phosphorylated form of COA-4. This drug is being used in combination with carboplatin for the treatment of anaplastic thyroid cancer[7].

Cordoncillo

Cordoncillo is the local name in Peru for *Piper aduncum*. In other parts of South America it is known as 'Matico'. This plant is found in Asia, South America and tropical Latin America. The leaves of *P. aduncum* are traditionally prepared in infusions and decoctions[8]. The main ethnomedical uses of this plant are in treating digestive disorders, as an antiseptic wound healer, and as a haemostat for internal bleeding. Cytotoxic and antiviral activities have also been documented by research[9].

P. aduncum contains many active chemicals including flavonoids, sequiterpenes, monoterpenes, alkaloids, and benzenoids[11]. A group of chemicals called chromenes have been found in the leaves and essential oil of the plant. Chromenes have been found to have cytotoxic effects on cancer cells and bacteria[9]. Benzenoid chemicals found in the plant also demonstrate antibacterial and cytotoxic actions[10].

Despite its potential for medical use, *P. aduncum* is not without its risks. The plant contains small amounts of the chemical compound safrole. Once

widely used as a food additive in root beer, sassafras tea, and other common goods, safrole was barred from use by the Food and Drug Administration in 1964 after it was shown to be mildly carcinogenic[10]. Safrole is also a precursor in the production of MDMA (3,4-methylenedioxy-methylamphetamine) or ecstasy[11].

DISCUSSION

Alternative therapies and the use of herbs and plants for treating sickness is often poorly understood and regarded with much sceptism. Yet many plant therapies are based on sound scientific principles. Fundamentally plants contain chemical components that can either be isolated directly from the plant or synthetically manufactured in the laboratory. Their structure and the mechanism of their therapeutic effect can then be investigated. This acts as a foundation upon which further modifications to the structure and properties can be made with an aim of enhancing effectiveness and reducing side effects.

Conventional and alternative medicines are not necessarily separate streams of therapy. Many treatments and drugs used today have their basis in plant therapies that have been used for centuries by both traditional and non-conventional practitioners. Digoxin is one such example of a modern medicine derived from a plant that was initially used as a herbal remedy. These alternative therapies work because of the science that lies within.

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Shaman and Uña de gato

Map of therapeutic medicines garden in Peru

Tasting medicines in the Shaman laboratory

NZMSJ FEATURE **Writing Prize** ISSUE 7

A rural guinea pig

My perspective on the 2007 rural medical immersion programme

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Rachel plans to pursue a career in emergency medicine, eventually working in a rural area. She is about to leave for her elective period where she will be exploring these interests with six weeks of trauma in Cape Town and six weeks in rural South Africa. Her other interests (when she finds the time!) are in the outdoors, particularly whitewater kayaking and mountain biking.

Introduction

I spent six months of my 5th year in Greymouth, as a student of the pilot Rural Medical Immersion Programme. The programme was created with the objective of inspiring interest in rural medicine, hopefully leading to more doctors wanting to work in rural areas. It is already established in Australia, but had never been done before in New Zealand.

Dr Pat Farry (GP and RMIP Creator) sold the course to me on the first day of my fifth year. The thought of spending the year seeing patients instead of trying to stay awake in endless tutorials seemed too good an opportunity to turn down. Before I knew it this impulsive decision had sent me on the biggest challenge of my medical student years.

Preparing to be immersed

The programme began with five weeks of standard 5th year training in Christchurch to alleviate some of the concerns among consultants that we may not get any formal training in certain specialties, in particular psychiatry. As I was so late in signing up I was already assigned to obstetrics and gynaecology which is where I stayed. This gave me a taste of what 5th year would probably be like in Christchurch and allowed me to adjust to leaving. After five weeks of 8am starts for five hours of tutorials but no patients in sight, I wasn't regretting my decision.

RMIP Students and Grey Hospital Staff, from left to right, Michele Wilkie, Pat Farry, Anna Proverbs, Roger Mills, Vicky Carter, Rachel Lynskey, Naomi Crooks, Liz Dowd, Pradu Dayaram, Greville Wood, Malcolm Stuart, Lasantha Martinus, Tom Stevenson, Adele Pheasant

The first move came. We traveled down to Dunedin for three weeks of preparation and, of course, tutorials. There was some fun to be had however. This was mainly in the form of obvious personality clashes, as we tried to negotiate possible objectives and assessments for the year. These clashes were confirmed by Meyer's Briggs personality tests as we analyzed ourselves and each other. A simulated motor vehicle accident demonstrated we never know as much as we think and stressful situations can make even the calmest personality panic. We only lost one of the unfortunate 'victims!'

During the three weeks, each respective group visited their future rural centre for a day. Landing in Hokitika airport we had a picture perfect West Coast day. That is of course, radiant sunshine and clear blue skies as opposed to lashing rain and thunder. Definitely a day to make you feel like there is no need to be anywhere except the West Coast ever again. We were treated as celebrities as we were escorted around the hospital, and of course treated to one of the timeless 'Friday free lunches' after the Xray meeting. The Greymouth catering is not quite of the same caliber as Christchurch - a rural GP student from Dunedin assured us that the 'parcels of joy' were to die for but I never quite caught on to the craze over a deep fried bundle with unrecognizable filling. However, it was a good chance to meet the people who would become our future colleagues, friends and family.

The three weeks in Dunedin ended with a trip to the Rural GP Conference, held at Star City in Auckland, as rural as it gets! There was a huge amount of interest in us and the programme. Pat was even given a brief slot to introduce us, using what had become his favourite line "I knew the students who signed up for the rural programme would be adventurous, but I didn't realize they were going to be so smart!" The first time we heard this I think we felt like we were glowing with intelligence; by about the tenth time I think we were feeling a little cheesy.

After another week back in Christchurch for the school integrative week and a week holiday, we finally began in Greymouth. It was the 16th of April, close to one third of the way into 5th year and the year for me hadn't even really begun! This was a stressful thought for us when we knew final exams lay waiting for us in just a few months time.

Beginnings of rural life

The first week in Greymouth was an introductory week, to introduce us to the Coast and the 'Coaster's'. Greville Wood was our regional co-ordinator, and he made a point of us seeing as much of the coast as we could during the week.

Kayaking off Maruia Falls

A sunset on the drive down to Haast

The area from Karamea in the North, to Haast in the South is 509km in distance with 30,000 people living in the West Coast region. One of the beauties of the Coast is that it is so extensive and so sparsely populated. However, it is understandably a logistical nightmare to provide a reasonable health system with the funding available for this number of people. In South Westland for about 200km from HariHari to Haast, there is only one GP. Each small or tiny town has its own clinic which will be staffed by a highly trained and competent Rural Nurse. The GP will visit for a half day or full day once a week to provide anything that cannot be done by the rural nurse.

So basically, we were set loose to drive the coastal road stopping in at clinics as we traveled, as well as some touristy glacier stops. There is a certain appeal to this part of the country not just because of the breath taking beauty, but also it's relative inaccessibility. Although this is exciting for outdoor types like myself, it is not ideal for ambulance transport. If you can imagine having to drive an ambulance over 200km of winding narrow roads that is bad enough, but imagine being the unwell patient in the back. It is not surprising that the majority of patients who are transported become motion sick, end up vomiting and generally feel pretty grotty by the time they actually make it to hospital (whether they did when they left or not!). Helicopters are an obvious solution to this problem, but they cannot fly in all weather and the cost means they are generally reserved for emergency situations.

Having to drive these roads ourselves was a fantastic sightseeing opportunity, allowing us to experience the isolation, as well as the motion sickness!!

Other parts to the introductory week included stitching practice, mine shaft visits and of course another of the Friday free lunches.

The true West Coast experience

Finally we began what was the core of the rural immersion programme and started to have patient contact. While in Greymouth we did not do the five week 'runs' of various specialties. Each day would be something different. Our time would be divided between the emergency department, orthopaedic outpatients or surgery, psychiatry inpatients or outpatients, paediatric outpatient clinics and general practice. Then we would fit in the visiting consultants including ophthalmology outpatients and ENT outpatients. There was also the opportunity to follow a midwife and to spend time in gynaecology and obstetric clinics. In each of these areas we were able to see patients by ourselves, create management plans and then discuss these with the doctor or consultant we were with. Therefore, the majority of teaching was one on one and patient centered. For me this was ideal. I have spent a lot of time in tutorials and lectures day dreaming or sleeping and then having to spend my own time re learning this material. I found that it was much easier to retain information when I could relate it back to a patient. Everything became much more relevant and I was learning practical skills at the same time. My ability to communicate and relate to patients improved dramatically.

Another difference from 5th Year in Christchurch was I felt like one of the staff at Grey Base Hospital and was treated as such. There were only three of us and obviously less staff as it is a smaller hospital, so we all got to know each other and everyone knew us and greeted us by name.

Pradu Dayaram was the long standing orthopaedic surgeon at Grey Base Hospital. He was initially a cold, hard, scary teacher, similar to those stereotypes in the media who always pick on students, grilling them and then berating them when they don't know the answer. The nurses also found him difficult in surgery, pleasant one minute and then yelling about a mistake or the wrong equipment the next. However, I struggle to remember this scary side of Pradu that had me shaking in my boots for so long. Somehow the three of us managed to turn him into this lovely man who actually started to care and enjoy our company. He even softened in surgery, became fun and someone I would consider a friend. He began to let us perform knee arthroscopies on his theatre lists. However, Pradu is a perfectionist so it was never long before his patience ran out; he would become frustrated at our incompetence and have to take over.

Memorable Coast cases

The West Coast is known for it's eccentric characters. One patient in his late sixties was admitted for having a parsnip stuck in his rectum. How it got there is left to the imagination, perhaps he slipped while gardening naked, and the parsnip just happened to be growing the wrong way?! The surgeons had to cut it into bits in order to remove it. Unfortunately, they could not remove all of it the same way it went in and he ended up needing a laparotomy to ensure all bits were removed. If this wasn't embarrassing enough, his surgical incision then became infected and he had to return to ED in order to have it drained. He presented with his wife who oddly enough had been his support the whole time, and to add to his story he was now wearing a bright pink G-string! I saw him a few months later at a GP clinic, this time for an ingrown toe nail. I must admit I struggled to make eye contact.

As in all hospitals there were various traumatic injuries passing through the ED. The remains of a hand after it had passed through a circular saw and a man who fell 10 metres directly onto his head amongst the most dramatic. Patients also of interest on the Coast are those from Glorivale Christian Community. This is a closed, self sufficient community that began as the Cooperites in Canterbury a few years ago. One unfortunate young boy spent 15 days in the community with open compound fractures of two of his fingers. This was due to a misunderstanding between the rural nurse and a member of the community, so the fingers were never seen. The children are renowned for their very quiet well behaved manner, it's almost unnatural. However, I imagine it would have been quite a painful struggle for this particular boy.

RMIP students at the Rural GP Conference in Auckland, from left to right, Rachel Lynskey, Adele Pheasant, Tom Stevenson, Anna Proverbs, Liz Dowd, Naomi Crooks

South Westland characters

One of the highlights of the experience was two weeks based in South Westland with GP Martin London. He is one of the eccentric characters of the coast and also one of the most likeable. His home is in Whataroa with his wife Carol, his Kune Kune pigs, his 12 Belted Galloway cows and his 5 acres of hazelnut trees on 25 acres of land. He has clinics in Harihari, Whataroa, Franz Josef, Fox and every second week he spends a day in Haast. I was lucky to be there while Poppy (one of his kune kune pigs) had piglets and experienced the highs as he told all his patients he was a Grandad and the lows as one got lost in the night and died of exposure.

While down in South Westland I stayed on a farm with a host family. The farmer there was a classic coaster and within two hours of my arrival I had helped feed the calves, milk the cows and heard his whole life story (detail by detail).

The majority of people I saw as patients in South Westland were unlike any I have seen before. Some were very generous letting me remove moles and sebaceous cysts for the first time. I also attended some call outs with the rural nurse. One was to a young boy who had been riding on the front of a quad bike which his Mum was driving. He fell off forwards and was then run over by his mother. He was lucky to get away with just some bruises and grazes and his Mum was probably more distressed than he was. Shortly after this call, another call came over the radio about a car crash further south. By this time it was dark and pouring with torrential west coast rain. It seemed slightly surreal as we turned our siren and lights on and went screaming down the winding roads. My heart was racing as I thought back to the simulated MVA in Dunedin…'c9.It was unfortunately an anticlimax as another car arrived first to find an empty vehicle full of beer bottles and smelling of alcohol. It was presumed the victims had done a runner.

I was also lucky enough to get a free flight over Mount Cook while I was down in South Westland. This was on a stunning day and the view was unreal. The flight that I was lucky to get a seat on was going up for a couple as a 50th Wedding Anniversary gift.

Working in this isolated area meant a lot of driving every day. Initially there was an idea that we could have intelligent medical discussions to further my knowledge. However, these quickly turned into political and philosophical discussions about life. This was definitely one of the most educational times for me but perhaps, not in the medical sense as first intended.

Advantages of the rural experience

For me, the rural programme was not all about the patients and the medicine. I bought a whitewater kayak before I went to the coast, having done it a handful of times previously. I then managed to spend most weekends kayaking, despite it being Winter and freezing cold for most of the time I was on the coast. One weekend in Murchison comes to mind when we were driving to the river in a hoar frost at 11am. The fog still hadn't lifted and there was no sign of any sun. The previous day there had been icicles dangling from the trees into the eddies we were using. Another trip that stands out was on the Taipo River in torrential rain, hail, thunder and lightening! The weather and river were pretty exciting, but the bull guarding the bank of the river was probably the scariest part! I was also able to go for afternoon/evening trips on the local Arnold River which could never have happened in Christchurch. This was particularly easy to do when working with multisport and outdoor enthusiast Roger Mills in the ED. He thought that it was an integral part of my learning and was happy to let me leave anytime I wanted!

Of course there was also time for heli mountain biking, a trip up the Wanganui River to natural hot pools and general West Coast exploring. Plus there were the Greymouth salsa classes on a Friday night. These were slightly variable depending on which desperate middle aged men showed up, but they were always a good laugh.

Disadvantages of the rural experience

There were disadvantages to doing the rural programme as well. We were quite isolated from the rest of our peers, by distance and also by the fact that we were doing something completely different. This made returning for end of run osces and integrative weeks difficult. These trips back were usually quite stressful as we often felt we were missing out on things. However, I found when I returned back for good and to sit exams my class mates were very supportive and I was welcomed into study groups. The distance and the traveling also became tiring. Traveling back for exams meant we spent a lot of time sitting in the car which could have been used in more useful ways. We also faced a lot of negativity from consultants in Christchurch. This was mainly directed at Dr Pat Farry in regard to our teaching and what we might or might not be learning. Unfortunately it occasionally filtered through to us and there were a couple of confrontational moments for us that definitely didn't fill us with confidence about the upcoming exams.

Then there was trying to maintain a long distance relationship while doing the immersion programme and trying to study for final exams. Not surprisingly this deteriorated and by the time I returned to Christchurch and finished exams it was non existent.

Conclusion

Looking back from this year I have no doubt that I would make the same decision again. I learnt so much more about myself and other people than I believe I would if I had stayed in Christchurch. I have gained confidence with patients and myself, and developed a renewed interest in medicine. It is not always a busy, stressful and arrogant profession, in fact sometimes it can even be fun. Of course, it is easy in hindsight to look back because I have now passed the same finals as everyone else. I definitely spent a lot of energy worrying about whether I was learning enough or the same material as my peers.

This year, with the advantage of one year under their belts, the programme looks to be even better. There are twelve students in total, three in each of Dannevirke, Greymouth, Queenstown and Balclutha. The students were able to get straight into seeing patients from the start of the year so will have even more time to enjoy the fantastic experience. Each centre is now more organized and there is a better structure in place to cover all the material. Remembering of course, that it is mainly patient based learning and patient's don't walk through the door according to the fifth year objectives and curriculum.

The programme was designed to inspire interest in rural medicine, with the hope of more doctors wanting to work in rural areas. For me, it met that objective. I can definitely see myself working as a rural GP – but not until I'm ready to settle on 25 acres of hazelnut trees and cows (and maybe even Kune Kune pigs!). The course has sparked an interest and awareness in rural medicine that I didn't have before. Am very grateful for the opportunity that I had and look forward to hearing of similar experiences as the course expands.

Education and training for rural health

Dr Pat Farry
Director Rural Medical Immersion Program
Te Waipounamu Rural Health Unit
University of Otago

We invited Dr Pat Farry to comment on the Rural Medical Immersion Program at the University of Otago, providing his perspective on rural medical education as the driving force behind the establishment of this programme.

The rural medical immersion program

Following the success of the Dunedin School of Medicine's seven week Rural Rotational Program the Rural Medical Immersion Program (RMIP) commenced at Otago University in the 2007 academic year. The program involves fifth year medical students spending the academic year training with health care professionals in rural New Zealand. The pilot was enabled by sponsorship through the Minister of Health's discretionary budget in late December 2006.

The funding provision recognised the work force issues in the rural setting and also the current lack of provision in undergraduate medical training in New Zealand for rural medicine. The funding was provided to deliver a nationally innovative, patient centred, rural community based and educationally sound, full year rural medical curriculum based in rural Southland and the South Island West Coast.

The aims of the RMIP are:

1. To utilise real life experiential learning integrating primary, secondary and tertiary care.
2. To encourage interested students to pursue a career in rural medical practice
3. To enhance links between rural general practice, rural hospitals and urban tertiary teaching hospitals
4. To enhance the development of distance education technologies in undergraduate medical education
5. To provide rural academic career opportunities and hence encourage both recruitment and retention of rural doctors
6. To utilise the large range of rural community clinical learning experiences which are not available to students in tertiary teaching hospitals.

The group of six students in the 2007 pilot year was made up of three from the Dunedin School of Medicine (DSM) and three from the Christchurch School of Medicine (CSM). There were three students on the West Coast at Greymouth (two from CSM and one from DSM; all female) and three students at Queenstown (two from DSM and one from CSM).

The 2008 program is funded by the University of Otago and has an intake of twelve students, four from each of the DSM, CSM and Wellington School of Medicine (WSM). Two additional teaching centres have been established at Dannevirke and Balclutha for 2008 and two more centres are to be established for 2009 bringing the total number of RMIP students to twenty per year. Each teaching centre has a Regional Coordinator and teachers including GPs, rural hospital doctors, visiting specialists, nurses, midwives, physiotherapists and pharmacists.

The subjects learned are the same as the urban based curriculum but many patients seen serve as revision of fourth year subjects as well. Patients are seen in a large variety of situations and students are encouraged to follow their patients though their different treatments. Teaching takes place in GP clinics, rural or provincial hospitals, visiting specialist clinics, birthing units, physiotherapy clinics and ambulance.

The RMIP is based on real life experiential learning. The curriculum changes from vertical silo learning in specialty topics to parallel learning which may vary from topic to topic in the same day. A student may attend a patient with chest pain in the morning, a patient from a motor vehicle accident in the afternoon and attend a birth in the evening. Core case reports are recorded on a web based patient centred case reporter and this allows for marking at a distance by both a specialist in that topic and a rural GP academic from an independent medical school. There are audio and video conference tutorials and libraries of books and DVDs including recorded tutorials from the medical schools.

One week long residential workshops are held at each of the three medical schools during the year to fill some of the gaps in tertiary teaching particularly in bioethics, pharmacology, child development, Maori health, pathology and microbiology.

The students are provided with accommodation and travel costs, laptop computer with cellular wireless internet access to library and medical databases and their computers have an electronic logbook which records conditions seen and learned and skills performed.

All six students of the 2007 pilot passed their final fifth year examinations well and an external evaluation report by Prof Paul Worley and Dr Lucy Walters from Flinders University declared the programme "an outstanding success".

Now that we have a Faculty wide Rural Medical Immersion Program for Otago University and a seven week Rural Rotational Program at DSM it only remains to facilitate the development of further rotational programs for CSM and WSM so that all of our Otago medical students have sufficient exposure to rural medicine. After this is achieved we should be looking to interprofessional education and training.

Learning medicine at the bedside

Participation in clinical research in a rural community; reflections of medical students' learning experience

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INTRODUCTION

This paper explores the experiences of four medical students who as part of a summer studentship participated in a research visit at a rural location in New Zealand. This was a unique experience as the entire research laboratory was temporarily relocated from Auckland to the remote Hokianga community of Kohukohu. During this three day visit students were exposed to Maori culture as well as health and illness in a rural setting. There was an opportunity to interact with patients who do not usually interact with medical students and who participate in health-care in a way that is different from their city counterparts. Students had the opportunity to work closely with senior medical staff who were solely focussed on the site visit rather than being distracted by their many other responsibilities. Three students had just completed year 3 and one student had completed year 5 of the medical programme at the University of Auckland. This paper explores the social, medical, cultural and learning experiences during the research visit and contrasts them to the experiences gained while training in the city.

BACKGROUND

The research was investigating the hypothesis that natriuretic peptides are novel biomarkers are useful in detecting left ventricular hypertrophy in patients with type 2 diabetes. Patients with type 2 diabetes in the community were referred by their general practitioner for inclusion in the study. After a history and physical examination participants underwent echocardiography as the "gold standard" test for detecting LVH. Blood samples were taken for the measurement of various biomarkers; body composition assessed by bio-impedance analysis and an ECG was performed.

To ensure that the study (entitled 'Natriuretic Peptides in the Community II') results are applicable to a broad population of patients with diabetes in New Zealand it was decided to recruit patients from both a rural and urban community. The urban population was recruited from Auckland general practices. To recruit patients from a rural community links were established with the Hauora Hokianga Enterprise Trust. The Trust receives government funds so that it can provide "free" medical and disability services to about 6500 people in an isolated rural area of Northland.

Northland has one of the most deprived populations in the country. While 30% of NZ's population is in the lowest 3 deciles, the same measure for Northland is 49%. Deprivation is particularly high in the Hokianga region with 21% of the population unemployed compared to 7.5% for the rest of New Zealand. Maori, who make up 73.4% of the population in the Hokianga, have age-standardised mortality rates almost 2.5 times higher than non- Maori. Furthermore, the rates of both avoidable mortality and potentially preventable hospital admissions are higher for Maori than non-Maori .

The research team from the University of Auckland was made up of four doctors (two medical specialists, a GP research fellow, and a cardiology research fellow), a research nurse, a senior research fellow in cardiac ultrasound, two expert technologists (echocardiography and electrocardiography), and four medical students (three year 3, one year 5). As part of the planning an initial site visit was carried out some months before the research visit. During this visit some of the investigators met with a local GP and diabetes nurse educator, key members of the local health board and community leaders. Prior to the research visit the local health team screened their practice records for patients who met the inclusion criteria. Those who met the inclusion criteria were visited by the diabetes nurse educator and written consent to participate in the study was obtained. The study was approved by the local ethics committee.

Kohukohu clinic, one of nine clinics operated by the Hauora Hokianga Enterprise Trust, was selected as the site for the research visits. Kohukohu clinic is situated in the hillside settlement Kohukohu Township. The clinic serves the town of around 200 residents and also the surrounding area, to make a total practice population of approximately 450 people. The township is situated on the Hokianga harbour, about 3 hours drive north-west of Auckland. There was little traffic and plenty of parking set aside for participants. On each of three days, 16 patients from Kohukohu and other Hokianga settlements were scheduled for a two-hour visit, which included a rotation through four rooms where different study related procedures were undertaken. Forty of these patients attended the appointment, 91% of the attendees were Maori. Five patients were excluded from the study because they did not meet the inclusion criteria.

After appropriate training, year 3 medical students performed electrocardiograms (ECGs), reviewed patient records, conducted bioimpedance body composition measurements, blood pressure measurements, and the initial processing of blood samples. One student was a trained phlebotomist and assisted with blood letting. The year 5

medical student performed a focused history and examination on all patients, under the supervision of one of the medical specialists.

Reflections of Medical students

Perceptions about Hokianga life were gained from discussions with the study participants and other local people. This was not formal research but casual observations, which mainly occurred as patients completed the four stations that made up the research appointment.

The Culture

The local Kohukohu community was very welcoming of the research team. A powhiri welcomed the research team to the community. A lavish meal was prepared for the team, and we felt very privileged and humbled by the lengths to which the community went to make us feel welcome. Such an experience in a community is all but impossible to obtain in a city setting, highlighting the value of this trip to pre-clinical medical students. Previous cultural experiences had been limited, and were largely confined to theoretical discussions in lecture theatres. This visit provided a 'hands-on' learning experience and truly emphasised the importance of cultural competence. At the conclusion of the visit, a poroporoake was held to farewell the team – a further tangible demonstration of the community's appreciation.

The cultural experience was hampered by the fact that most of the research group were not able to speak Maori. However, the year 5 student was able to speak Maori and with respectful shyness, she attempted to Korero, using a language she had learned for the previous 15 years. She described the experience as "the best environment for its use that I could possibly imagine". As cultural experience may be enhanced by understanding of, and perhaps learning to speak another language, offering a Maori language option during medical training may be helpful. This is especially so for those students who may be interested in practicing in rural communities, where significant proportions of the population are Maori.

The Community

Some participants had returned to the rural environment to get away from the "rat race" of city life and enjoyed the peace and quiet and slower pace of life in the Hokianga region. It was also an opportunity to return to their roots. City life now seemed foreign to them; although many had spent the majority of their working lives in the city. Some participants reported having less financial resources than their city counterparts or when they had lived in the city. This did not seem to matter much to them. Some older participants described a "worn out" feeling and felt they were now "useless", yet, they are often looking after children and grandchildren. This perception was less true for the younger people living there. Participants enjoyed the close knit community but a few also commented on how it was difficult to maintain privacy.

The participants all seemed willing to include new-comers, such as ourselves, into their lives. The research team felt very welcome and privileged in this environment and felt it would be a useful for other medical students to experience the closeness of the Hokianga rural community.

Four patients that were scheduled for the research visit did not attend. The common factor was that the diabetes nurse specialist had not personally visited them about the study but had simply sent them written information. This seemed to demonstrate the key role of the close relationship between healthcare workers and the community who greatly valued personal contact and invitation. The closeness and friendliness amongst health professionals, support staff and patients was very appealing.

The Medical Practice

The Hauora Hokianga Enterprise Trust rural doctors work in a community team relying on the Community Health Nurses, Kai manaki tangata (community support people), clerical assistants and the Diabetes Nurse Educator to share community knowledge to enhance practice. The whole team is involved in providing "health care" in its broadest sense. It is often the trust placed in team members, who mostly live in the area, that gets the patient to the doctor and ensures recommend treatments are followed. Each member of the team is valued - it is an integrated service. We noted that some of the population make use of traditional Maori remedies. However, there did not appear to be much resistance to conventional medicine in the group of patients we interacted with.

The most noticeable difference between rural and city medical practice was the apparently closer relationship between the patient and the doctor. The doctor takes on the role of "carer of the community" and is well respected and loved by the community. Patients seemed to trust the doctor and willingly follow medical recommendations or interventions. Overall it appeared to the students that general practice was very "patient friendly" in Kohukohu.

It seemed that GPs working in these circumstances may have a much better idea of the impact of patients' lives in a broader social context on the management of chronic illness. In the city some patients visit accident and emergency facilities and appear not to have regular follow-up with the same doctor. Similarly, medical students do not always have the opportunity to follow-up patients. Being involved in a community provides an excellent opportunity to see and understand both the impact of an illness on a patient's life and the consequences of medical interventions, be they for good or for harm. Such an experience would complement the health psychology lectures which discuss the impact of illness on people from a theoretical perspective.

Some patients encountered in the Hokianga seemed to view significant chronic illness from a less debilitating perspective than their city counterparts. One lady that was excluded from the research cohort casually remarked that she had had five heart attacks as if this was of little consequence. She went on to say "When you don't look after your body like I did when I was going through a rough time, you get heart attacks and that's just what happens." She did not seem troubled by the implications of having had heart attacks in the past and merely put it down to a consequence of her action and accepted the consequences. There was an overarching feeling of perseverance, of "getting on with things", of "making the most of what you have".

The Clinical Learning

To the best of our knowledge, this study, which mobilised the Cardiovascular Research Unit to a rural area, is a novel experience in New Zealand. The fact that there were few major hiccups and the high productivity during our relatively short stay, are important points in themselves. People in rural communities, because of their isolation, may have limited access to secondary and tertiary healthcare facilities in addition to other barriers to care. As such, these patients may be at increased risk of disease and complications. We saw tangible evidence of this as some of previously undiagnosed cardiac/medical conditions were detected and referral made to appropriate services.

The medical students reviewed all patient files to confirm histories or to identify other pertinent points. Through this process, students realised the importance of detailed patient summaries, especially those which recorded what investigations and procedures had been undertaken in secondary care facilities. This highlighted the need for an integrated record system between primary and secondary care providers. The need for clear, detailed notes became apparent through this process, and will certainly influence the students note taking in future. The register of retinal screening and the electronic clinical and laboratory diabetes database was particularly useful in identifying the history of a patient's diabetes and possible diabetic complications.

The year 3 medical students enjoyed the opportunity to work closely with senior clinicians. The fact that clinicians were solely focused on the

research effort meant that a very close interaction could occur between students and clinicians that would be unlikely to occur in the city. In addition patients seemed very willing to allow students to participate in their care. These two factors combined so that students enjoyed an excellent learning experience. This clinical experience boosted confidence and provided an early opportunity to practice clinical examination skills and professionalism. Involvement in clinical research has stimulated the students' interest in pursing research during their career.

Although the year 5 student had just completed her year end medical and surgical short-case examination, she was responsible for taking the history and examination of all patients, under supervision, and found the experience enormously rewarding. Having both her history taking and examination skills directly observed while clerking 40 consecutive patients proved to be an excellent experience, which greatly boosted her confidence, prior to her starting as a Trainee Intern. She commented "I found myself shoulder deep in pathology, although mainly benign, the kind that twenty medical students would hover over in the city." Students noted that the participants seemed genuinely glad to see them there, unlike when they had been involved in patient care in the city.

The research visit also offered insights into the importance of team work – the students were part of a highly skilled, multi-disciplinary team. The importance of clear communication, respect for each person's role, and the ability to compromise were clearly demonstrated as the team worked to together to ensure a smooth research visit. The ability to make things happen and resolve challenges that arose were clearly evident.

CONCLUSION

The research objectives of collecting data which is representative of the broader community were clearly met by this experience and in time will provide some interesting clinical results. In addition, working in a multi-disciplinary research group, in a rural community, with predominantly Maori people was an excellent early learning experience. The hands-on nature of the visit seemed more valuable than working on a theoretical project.

How much is gained from such an experience is very much a matter of how much effort is put in. While the community were extremely welcoming and more than willing to assist with medical education, it is ultimately the student that must engage with patients, learn about their culture and discover how best to interact competently with those from a different ethnic group. This is a crucial part of providing excellent medical care, making practical experiences such as this rural research visit all the more valuable.

ACKNOWLEDGMENTS

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The Pukawakawa story

Auckland School of Medicines Northland Regional - Rural Medical Programme

Associate Professor Warwick Bagg
Endocrinologist, Department of Medicine
Faculty of Medical and Health Sciences
University of Auckland

Associate Professor Warwick Bagg is the coordinator of the Pukawakawa programme, the University of Aucklands Northland Regional - Rural Medical Programme. We invited him to share some background on the course and the significance of its name.

From 11 February 2008, a group of 20 year 5 medical students from the University of Auckland will be living and learning in the Northland region. This is a new initiative for the Medical School made possible by additional MBChB funding received in 2006 and close collaboration with the Northland District Health Board. It is anticipated that the programme will assist with long-term medical staffing in Northland, especially in the peripheral areas of the district, by allowing students to develop their own links with these areas and experiencing the type of work they would carry out in those settings. The programme will also strengthen the links between NDHB and The University of Auckland.

The model for learning is based on the current undergraduate medical programme, with modifications to the design and delivery to take account of the unique nature of healthcare provision and population needs in the various Northland settings. Learning will occur in both regional and rural settings. Each student will spend about 18 weeks in Whangarei Hospital and 7 weeks in Kaitaia, Dargaville or Rawene. In the rural areas students will experience working with GPs in outpatient settings and GP led hospitals, as well as a range of community health expert practitioners. They key focus in these settings is to understand the range of skills needed for rural medicine and to identify when limitations require interaction with more specialist regional or urban facilities. Students will see many patients in the diagnosis phase of medical practice, and will have the opportunity to examine the continuity of care models and the importance of community agencies in the role of chronic care. The specific nature of this programme draws on research elsewhere, particularly in North America and Australia, on what makes for successful rural medical education. Importantly, it provides an environment in which students will become more familiar with Maori health from a number of dimensions. This initiative is a true partnership with the Northland DHB and all Northland PHOs, including the independent Hauora Hokianga Integrated PHO. The Northland DHB has refurbished the previous student nurse accommodation to meet the living needs of the medical students, and has provided space for teaching and learning environments within its precincts. Over 40 students applied for the 20 places available, indicating a strong demand to study in such regional-rural environments.

The name of the programme is Pukawakawa. Outlined below are the reasons why the programme was named Pukawakawa.

The Pukawakawa Story

The Northland District Health Board Kaunihera Kaumatua (Council of Elders) has provided the name Pukawakawa for the Northland Regional-Rural medical programme.

There are many korero from different points in time and perspectives concerning the name Pukawakawa. Most importantly, the site where the Whangarei hospital is located was a Te Parawhau pa (the local hapu). That pa is still known as Pukawakawa. On the ridge and cliff face above the hospital running towards Maunu were large unusual reefs of rocks, some are still visible today amongst the houses. To Te Parawhau, they were steeped in cultural significance and secrecy.

Pukawakawa also refers to:

- the pa was shaped in a manner like two arms 'to embrace, or defend the people;
- Pukawakawa was also the name of a traditional Whare Wananga (place of learning)
- Pukawakawa also makes reference to the Kawakawa, a plant used as a rongoa (medicine) by Maori. This plant is still commonly found in Te Tai Tokerau and is abundantly found on the grounds of the hospital.

While the name Pukawakawa is perhaps most deeply connected to the Whangarei locality, the Kaunihera noted the references to the Kawakawa plant as a rongoa and a traditional Whare Wananga and in their view, this makes Pukawakawa an apt name for all sites in the programme.

The University of Auckland and the Faculty of Medical and Health Sciences is honoured to accept this name for the Northland Regional-Rural programme.

He honore nui tenei, mauri ora ki a tatou katoa!

The Pukawakawa programme is an expansion of the University of Auckland's presence in Northland. The Faculty of Medical and Health Sciences runs a postgraduate nursing programme for Northland-based nurses. The University's Business School has a satellite campus in Kawakawa for Northland students taking the Graduate Programme in Business (Maori Development), and the Faculty of Education runs the Te Tai Tokerau Education Campus in Alexander Street, Whangarei.

Rural in the south - a student perspective

Philip Daniel
Fifth Year Medical Student
RMIP Greymouth
University of Otago

Philip Daniel is a 5th year medical student from the Otago University, Christchurch School of Medicine, on the Rural Medical Immersion Programme in Greymouth.

While on the obstetric ward of Grey Base Hospital on the West Coast of the South Island, a midwife asked me, 'When were you born?' We wandered down the hall to a small room stacked with clean flannels, boxes of lactation cups, and piles of records. There in the birthing record from 1981 was my name, and there beside it was hers - this was the woman who had delivered me. 'I thought your face was familiar,' she said.

I am very pleased to be spending this, my fifth year of medical training, on the Otago University Rural Medical Immersion Programme (RMIP) in Greymouth. The West Coast is home for me and it is great to have the opportunity to do academic study over here. Even without this added bonus I was very keen to apply for this programme and all my experiences of the first 4 months have been positive. What follows are a series of thoughts and anecdotes that I hope will be of interest to all, but which are especially aimed at Otago University fourth year students, who I encourage to consider the RMIP for next year.

Clinical Opportunities

Grey Base Hospital serves a population of around 30,000 people. It offers a range of secondary services including obstetrics and gynaecology, orthopaedics, general surgery, and general medicine. Visiting specialists run clinics in otolaryngology, paediatrics, rheumatology, ophthalmology, plastic surgery and dermatology. The three RMIP students here in Greymouth have almost unlimited access to these services, and to the patients attending them. There are very few registrars at the hospital so that in most cases we sit in with the consultant, or even better, see patients on our own before presenting to the consultant. Either way, we receive much one on one time with experts.

On the other hand specialists are not the only ones who are special and general practitioners are not just GPs - as one GP I met put it "they should really call specialists 'particularists'." The programme here involves 8 weeks with Martin London, travelling GP serving 300kms of South Westland from Hari Hari to Haast. This gives an amazing taste of remote medicine as well as hours of informal teaching whilst driving the most beautiful roads in the world.

And the patients? Do I see the range of patients and do all the interesting cases get transferred to Christchurch? Remember that common conditions are common - we are tripping over Osteoarthritis, Ischaemic Heart Disease, and Type Two Diabetes. Rare conditions are rare, and no matter where you are you will see some rare conditions and not see many, many others. My first two case reports this year covered a patient with a cerebellar arteriovenous malformation, and a neonate with persistent pulmonary hypertension of the newborn. When I flew to Christchurch with the neonatal retrieval team I met up with friend who exclaimed, "Neonates! I've got a test on them this afternoon but I've never seen one."

Formal Teaching

One of my greatest concerns about the RMIP was missing out on formal teaching. Fifth year in Christchurch is recognised as a year packed with tutorials and sparse on patient contact. Here on the West Coast our only limitation on patient contact is our own time whereas formal teaching is limited. We do receive quality tutorials from local clinicians who bring their own experience and have access to the teaching notes from our home schools. However these are fewer in number and often have a different focus to the tutorials on offer in the major centres. Some topics are at risk of being insufficiently covered - for example pathology. Most resources are available to us on paper, on the web or on DVD, but we have to be more active in our self-directed learning and proactive in questioning our clinicians - there is plenty to eat but you have to hold your own spoon.

Also, the style of formal teaching is different from the city schools. Our small group tutorials involve 2 or 3 students and sometimes as many tutors. We also have fortnightly teleconferences in groups of 6. If your preferred learning style is voyeuristic - sitting back without adding to the group, then the intensity of these sessions might put you off. On the other hand, those who enjoy getting involved, having your questions answered, and having your knowledge probed would be well suited.

Support

I have found the level of financial, academic and welfare support to be generous. We have our accommodation paid for on the West Coast, plus our travel to, from and around the Coast is reimbursed. This has been a great help, and I am very grateful. I have heard the argument made that city students do not have their accommodation paid for so we should not either. Firstly, I would say that that the extra support is appropriate given that it is difficult to arrange rental properties in many small towns, and given that the added disruption of moving town, finding a place, and leaving it 8 months later would otherwise be a considerable disincentive. Secondly, this scheme was specifically funded by the government to support and encourage rural medicine - rural practice is incentivised, so now is rural study.

Pat Farry and Mich Wilkie in Dunedin and Greville Wood here in Greymouth provide great support in administration and for academic problems. They also offer a point of call for welfare problems if they should arise.

Lifestyle

It's fifth year! Is not the biggest lifestyle question which biscuits to bring to study group?! Seriously though, despite being a busy year we have made time to explore some of the gorgeous hills and mountains of the coast. There is plenty of mountain biking and kayaking and most nights we walk or run on the beach watching the setting sun turn Mount Cook red 150km down the coast. We have been back to Christchurch to visit friends, and

many have promised to come and visit us. Junior doctors and other young locals have been very welcoming. There is a range of clubs, pubs, and night classes so there is no risk of not filling your time. You do not have the constant contact and support of a large group of friends but you also avoid the increasing collective stress of approaching exams. The occasions you do catch up with friends are great fun.

Overall

I would recommend that all Otago University fourth year students consider the RMIP. To everyone else I hope you enjoyed reading more about the programme. I do not think the programme is suited to everyone. If you love sitting back and watching, and if taking responsibility for you own learning sounds as bad as chewing off your arm then stay in the city. But, if getting involved, learning from patients, feeling like a member of the care team, and getting a feel for rural health sounds like you then go for it. I am loving my time on the West Coast and I am sure that it will help me to be a better doctor. I also reckon learning to be a better doctor is the most rewarding and perhaps the best way get through those pesky exams.

Rural in the north - a student perspective

Hannah Giles
Fifth Year Medical Student
Northland Regional - Rural Medical Programme
University of Auckland

Hannah Giles is a 5th year medical student from the University of Auckland School of Medicine, on the Northland Regional - Rural Medical Programme. She is also the Grassroots Northland Clinical Representative and ARHA Northern Co-President

Pukawakawa is the Northland Regional - Rural Medical Programme, designed by the University of Auckland, in which 20 5th year students spend their entire year based in the Northland region. Being in the first group of students to undertake this programme we were in a unique situation as we couldn't always get definitive answers to some important questions; it was therefore a leap of faith based on a lot of assumptions and expectations on what we believed this programme would deliver. Six months into the year I can confidently say that, amazingly, Pukawakawa has managed to exceed my expectations.

For most students there are a few key areas which are really important and are the kind of questions which can only really be answered through experience. I hope that by sharing some of our experiences thus far, it will help to answer some of your questions.

These are the main areas that I feel influenced me to undertake this programme and I think are key for anyone considering undertaking this programme:

1. Teachers & teaching
2. Clinical exposure & opportunities
3. Accommodation & Travel
4. Social & sporting

Teachers & Teaching

There are lots of factors which make a good clinical teacher, and lets be honest really good teachers are hard to find and this was something I was most anxious about. I have heard some really amazing feedback from the other Pukawakawa students who are doing various medical and surgical placements in Whangarei. The main thing being that people want to teach us, they know we are coming, they make room and time for us and it is their intention to teach us because they recognize that the effort they put into us is an investment in the future of their health workforce. Everywhere we go we are welcomed by the staff and patients as an asset to the hospital and community rather than a burden, which is often how I've felt on previous runs. I have been so impressed not only with how nice, enthusiastic and welcoming but also with the wealth of knowledge and skills amongst the clinicians in Whangarei.

Personally, in the short time I have been in Whangarei I have come across not just the good but also the inspiring. In O&G the top dog is a very tough Pommie chap called Ian Page, who integrates high standards and a barrage of questions with some amazing teaching every morning, and thus ensures absolutely NO snoozing during handover.

Everyone I have come across in Paeds is lovely, the two stand outs are the chap they call the Baby whisperer, an amazing African doctor whose velvet voice lulls any screaming baby to sleep. And the master of 'Sarcastic Paediatrics', Dr Chris Williams, the most humble and humorous doctor I've ever met and just so understated, considering his knowledge and experience. You may have heard the story on the news of a young girl of about 7 years old who was shot in the chest with a slug gun up in Whangarei. That was Chris' patient. They knew she had a bullet in her somewhere, but she was stable so they prepared her for transfer by helicopter to Auckland. Just as they were about to put her into the helicopter, she crashed and her BP dropped like a stone. Realising she was in cardiac tamponade, one of the physicians said he had an adult percardiocentesis kit. Chris said "Great, go for it" and he replied "No way I'm not touching a kid!" Chris then stuck in the needle while on the helipad; aspirated some blood and the BP bounced back - Halleluiah. The bullet was later found lodged in the posterior heart wall.

Clinical Exposure & Opportunities

A common concern among students is "Doesn't all the complex stuff go to Auckland? So won't I be missing out.?" The reality is that it's pretty unlikely we will get to scrub in on anything that's going down to Auckland by chopper anyway. The whole idea of this programme is that you will get more clinical exposure and opportunities and learn to work more independently to develop your clinical skills and judgment, which will

hopefully be later put to good use in the regional-rural workforce.

Some of the key benefits are:

- 90% of the time you are working directly with consultants and the ratio is normally 1:1
- You are encouraged and expected to be working independently, you are seeing and assessing patients and reporting directly to your consultant with your findings, impression and management plan etc.
- Increased patient contact as there are less students
- More opportunities to do procedural skills

A good example is that of a young Maori boy who was sent to hospital by his GP. I was called at 10pm when he arrived in ED to come and take a history and do the examination, review his test results and present to the consultant. He had sinus tachycardia, a grade 3 systolic murmur and looked very unwell, we decided to observe him over night and booked an echo for the morning. I took him down for the echo the next morning, which showed a significant pericardial effusion and sever MR amongst other things. We then spoke to the cardiologist in Auckland, arranged an ambulance transfer, I wrote the transfer letter and accompanied him to Auckland doing manual obs on the way down after the battery on the obs machine ran out. I then handed him over to the on call Paediatrics Registrar in Auckland. Our diagnosis of acute Rheumatic Fever was later confirmed by the team at Starship.

This was probably one of the most amazing experiences I've had, being on the front line and able to think a situation through and do it all myself, with expert supervision and guidance. That experience really encapsulates this programme, because it's all there for the taking and there are more opportunities than we have time to take up.

Accommodation & Travel

Due to the significance of this programme it was really important that the best possible people were selected for the 20 available spaces. With this in mind the principle of cost neutrality was agreed upon; this means there were to be no financial barriers that may prevent students from taking part in this programme.

Thus accommodation in Northland is provided free of cost, based at Whangarei where we each have a room for the entire year, and we are also provided with a room in Kaitaia, Dargaville or Rawene for the 7 weeks of our integrated attachment. The rooms are fully furnished double rooms with broadband internet. The kitchen, lounge and bathroom are extremely well equipped, including multiple ovens etc, cooking equipment and a TV/DVD player. Plus there is ample basement storage for surf boards, bikes, kayaks etc.

In keeping with the principal of cost neutrality, petrol vouchers are provided for all mandatory journeys.

Social & Sporting

There's no doubt that lifestyle is a significant factor in anyone's decision to undertake this programme. There are so many resources at our fingertips and we have all been making the most of them. We have had a weekend away in Patau with the legendary Peter Ogle who took us fishing, diving, kayaking and walking around this picturesque spot. We have found plentiful spots for free diving and the trusty Mike Macloed never fails to produce a cray-fish for our table.

The surf is always up on one of the beaches, two of our boys have joined Hora Hora rugby club and I have made some fantastic contacts in the horse world. Unfortunately the student sports team has yet to make a significant impression in the hospital sports league, but this is something that next years crew can improve on. We have access to the hospital gym and swimming pool, as well as the social club which is a fantastic place to get to know people from all over the hospital over a $2.50 glass of wine or handle.

In summary Pukawakawa is an amazing and unique opportunity for any medical student, enabling us to live the lifestyles we want to live whilst having a first class medical education. Exposure to facets of medicine and culture unique to these regional-rural communities is providing us with a much deeper insight into healthcare in a wider sense, equipping and inspiring the next generation of rural doctors. Pukawakawa will, no doubt, change the fortunes of the regional-rural workforce by showcasing the diverse and challenging lifestyle and career opportunities that it presents, ensuring rural health is a viable and sought after career for young graduates.

RURAL**FEATURE** : CONFERENCE REPORT

New Zealand rural general practice network conference 2008: "Working Together, Doing It Better"

Emily Rainsford
Second Year Medical Student
Auckland School of Medicine
University of Auckland

Emily grew up in Opotiki and Kawerau in the sunny Bay of Plenty and indulged her love of language with a BA at Victoria University of Wellington before finally embarking on medical school at Auckland University, where she is now enthusiastically relishing the challenge of second year.

The New Zealand Rural General Practice Network (RGPN) is a not-for-profit, membership-based organisation focused on representing rural general practice and rural health workforce issues in New Zealand on a national scale. From 28 to 30 March 2008, the RGPN held its Annual Conference in the Garden City of Christchurch with the theme 'Working together, doing it better'. The conference was eagerly attended by over 250 health professionals already working in and dedicated to rural health. An eager contingent of medical students were also present, including a 12-strong gaggle of rural-minded Auckland University medical and nursing students, proudly attending under the auspices of Grassroots, Auckland University's student rural health club.

In the spirit of 'working together' and learning from each other, the conference was opened, after a rousing powhiri, with an address from the International Keynote Speaker, Dr. James Rourke, from the Memorial

Damien O'Connor - Associate Minister of Health; Hannah Giles - ex Grassroots President & current Grassroots Northland Clinical Rep; Matt Rowe - Grassroots President; Philip Daniel - Country Scrubs President; Brad Stone - ARHA President.

Laura Keyte, Auckland 3rd year; Pamm Wilson, conference organiser; and Lada Kordich, also Auckland 3rd year.

University of Newfoundland, Canada. Dr. Rourke highlighted the similarities between the New Zealand and Canadian rural health situations and the problems we face in workforce recruitment and retention, before sharing some models experiencing success in rural Canada today. These were largely based around the concept of moving towards more integrated health centres in rural areas, as opposed to the traditional sole-owner-operated GP model. He also demonstrated how teleconferencing can be used to ensure high quality patient care in remote areas, another excellent example of how it really can be 'done better' by 'working together'.

This was followed by two days of streamed sessions on a wide variety of topics, ranging from chest pain to acupuncture, head trauma to Maori health. A highlight from the first day was a presentation by Gaynor Fiske on the success emerging from the Northland PHO "Mental Health Service in Primary Care" Pilot Project being run in Kaikohe. This initiative is focussed on the de-stigmatisation and treatment of mental health issues within a primary care setting, and has experienced heartening results.

One of the best sessions of the weekend was an overview of the latest research in areas of Women's Health and Endocrinology by Dr Anna Fenton, a gynaecological endocrinologist active in both practice and research. She presented compelling evidence to effectively debunk many media-propagated myths in areas such as Hormone Replacement Therapy and Polycystic Ovary Syndrome.

Another well-received session was a presentation of up-to-the-minute research by Mr Richard Stubbs, a hepatobiliary and upper GI tract surgeon at Wakefield Hospital in Wellington, and Director of the Wakefield Gastroenterology Research Institute. Some of his latest research suggests that, contrary to popular belief, diabetes and hypertension are not in fact caused by obesity, but rather all three issues share the same causal link to insulin resistance. He presented good evidence for his hypothesis that the answer lies in a hormone 'Factor X' secreted in the duodenum. He posited that it is the bypassing of this factor which leads to the rapid and long-lasting success of the 'Fobi pouch' method of gastric bypass surgery he performs. His passionate presentation left the delegates lucky enough to attend his stream looking eagerly towards the future of this exciting and relevant area of research.

The second morning of the conference saw three important events take place. First was the session entitled "New Zealand's Rural Health Clubs: Who are we and why should you care?" by fellow medical students from both Auckland and Otago. Brad Stone and Philip Daniel from Otago University gave an introduction to the efforts of the Aotearoa Rural Health Apprentices network in raising student interest in rural health. They then handed over to Hannah Giles and Matt Rowe, the previous and current presidents respectively of Grassroots, Auckland University's rural health club. They gave an inspirational presentation of the huge successes achieved by the club in raising awareness and interest in rural health among Auckland health students. The amazing Pukawakawa rural fifth year immersion initiative was also presented. Their success serves as a model to inspire rural health clubs throughout the country.

Secondly, was the honouring of the much-revered Dr Tim Molloy, who is stepping down from his position as Chair of the RGPN Executive Committee. He was recognised with speeches and gifts for his huge and selfless contribution to the organisation and to rural NZ health issues in general, especially in the political arena.

Thirdly, Associate Minister of Health Damien O'Connor addressed the delegation to declare the Government's commitment to the rural health of NZ communities. He outlined some of the assistance and initiatives that have already been introduced in various areas, as well espousing a desire to maintain and continue rural health's position of high priority in the healthcare agenda.

The RGPN conference was an educational and inspiring experience. It looked at the great progress being made in the rural health issues facing our country today, while still recognising the vast improvement that still needs to be seen. We were all reminded that it is through collaboration, passion and integration that we will truly see the rural communities at the core of our New Zealand society being fully serviced and cared for by medical professionals. In this way, we can all move towards the possibility of a healthy, happy nation, free of discrimination on any basis and providing equality for all.

Attending this conference gave us much more than just an increased awareness of the issues facing rural health in New Zealand today. We also found it valuable and exciting to hear about some of the research emerging in different areas of medicine, and some of the initiatives experiencing success around the country. The students in their clinical years gained valuable clinical information in the knowledge-focussed sessions, while the pre-clinical students were infused with enthusiasm for their chosen profession. We all came away inspired, with increased knowledge and heightened awareness of the issues pertinent to medicine in New Zealand today.

The author would like to give special thanks to Grassroots, Auckland University and the RGPN itself, for their support of the future of healthcare in New Zealand through enabling and subsidising the attendance of the Auckland University medical and nursing students at this event.

For more information log on to: **www.rgpn.org.nz www.grassroots.org.nz**

The Rhodes Scholarship:
One junior doctor's journey

Sophie Parker
Third Year Medical Student
Dunedin School of Medicine
University of Otago

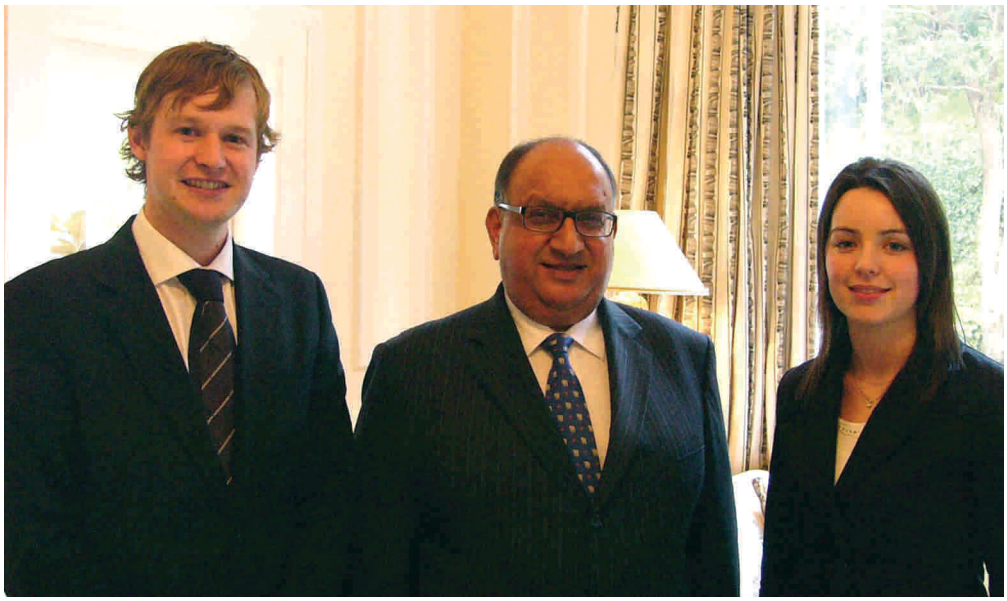
Sophie Parker is a 3rd year medical student in Dunedin. She has previously completed a BSc in biochemistry and has an interest in neuroscience research.

Rhodes Scholarships are awarded annually to three of New Zealand's highest achieving students. This year, the New Zealand Rhodes Scholarships were awarded to Jesse Wall, Amanda Gilbertson and Julia Matheson. Mr Wall, from Palmerston North, is completing an LLB from Otago University while Ms Gilbertson, from Hamilton, is currently completing an MA in Anthropology from Victoria University of Wellington. Dr Julia Matheson, from Dunedin, has completed an MBChB with Distinction from Otago University and will commence her postgraduate study in Oxford in September this year. I had the priviledge of talking to her about the Rhodes Scholarship, her achievements so far and her future plans.

History of the Rhodes Scholarship

For over a century, Rhodes Scholarships have supported thousands of exceptional students from many countries in their ambition to study at the University of Oxford. Oxford is the oldest university in the English-speaking world, and has an outstanding reputation of academic excellence. The Scholarships are funded by the Rhodes Trust, which was set up by the Will of Cecil John Rhodes in 1902. Cecil Rhodes, a British philanthropist, spent much of his life expanding British imperialist interests in Southern Africa. He was Prime Minister of the Cape of Good Hope from 1890-96 and made his fortune in diamond mining in South Africa. A student of Oxford himself, he envisioned that the Rhodes Trust would help educate future world leaders, because it was his view that the unique environment at Oxford encouraged "broad views and personal development". He specified in his Will that the Scholarships were for countries in the British Empire, as well as the USA and Germany, because he saw these countries as advanced nations capable of bringing "peace, progress and prosperity" to the world. Times have changed, and the Scholarships have expanded: Rhodes Scholars are now selected from Australia, Bermuda, Canada, Commonwealth Caribbean, Germany, Hong Kong, India, Jamaica, Kenya, New Zealand, Pakistan, South Africa and neighbours (Botswana, Lesotho, Malawi, Namibia, Swaziland), USA, Zambia and Zimbabwe. The Scholarship was only made available to women in 1977, and since then has been awarded to over 500 women. Currently, there are approximately 90 Scholars selected worldwide each year.

The Rhodes Scholarship is an award for two years postgraduate study, but can be held for only one year, or extended to three years in the case of study towards a doctoral degree. As well as University and College fees being paid by the Trust, Scholars receive a monthly stipend to cover living expenses. They are also welcome at Rhodes House, a beautiful mansion built in 1928 as a memorial to Cecil Rhodes. The House contains a dining hall, gardens, a library, study areas and many other rooms – all available to Rhodes Scholars.



(from left) Jesse Wall, another Rhodes Scholar, the Honourable Anand Satyanand, Governor-General, and Julia Matheson [photo courtesy of Otago University]

Rhodes Scholar profile: Dr Julia Matheson

Julia attended high school at Columba College in Dunedin. In her final year, she was both Head Prefect and Dux, and attained an A Bursary with 6 scholarships. She is a talented musician and enjoys playing piano and cello. Julia graduated from Otago Medical School at the end of 2006, and was awarded the Emily Hancock Siedeberg Memorial Prize for the female student with the highest overall performance in all years of the course.

In her elective at the end of her trainee intern year, Julia was one of 50 students successful in securing a 6 week placement at the Radcliffe Infirmary at Oxford. Surgery is a particular interest of Julia's, and her project at Oxford allowed her to develop her skills with work in plastic and reconstructive surgery. She also built up knowledge in this area, spending time in theatre and clinics, as well as meeting numerous consultants. During this time, Julia stayed in Balliol College at Oxford. This college is made up of a mix of residents studying various different subjects, many of whom were international postgraduate students. As well as being a nice change from always being around medical students, Julia found that she was exposed to different ways of thinking, and described how this allowed learning to continue outside the classroom. Her time at Oxford made her see that it was a "unique, special place" and that she would enjoy pursuing further study there.

Commonly, a student wishing to study at Oxford will approach a potential research supervisor via email or through contacts in New Zealand. Medical research at Oxford has a wide scope, encompassing themes such as cancer, cardiovascular science, infection and immunity and neuroscience. Julia will be working in the areas of clinical oncology and colorectal surgery. Her research will focus on the genetic aspects of colorectal cancer, rates of which are particularly high in New Zealand. This research is expected to take three years and will enable her to complete a doctoral degree, known as a DPhil. Julia will start at Oxford in September this year, and is currently working at Dunedin Public Hospital as a House Surgeon. Although Julia likes to travel, she always enjoys coming back home. Her long term plan is to have a career in surgery in New Zealand.

Information for aspiring Rhodes Scholars: The application process

There are several conditions of eligibility to consider when applying, and these are outlined on the New Zealand Vice-Chancellor's Committee (NZVCC) website. An important one for medical students to keep in mind is that applicants must not have passed their 26th birthday by the 1st of October in the year for which they are elected. Candidates must also be New Zealand citizens or British subjects.

In his Will, Cecil Rhodes outlines four standards by which to judge candidates. These are:

1. literary and scholastic attainments;
2. energy to use one's talents to the full, as exemplified by fondness for and success in sports;
3. truth, courage, devotion to duty, sympathy for and protection of the weak, kindliness, unselfishness and fellowship;
4. moral force of character and instincts to lead, and to take an interest in one's fellow beings.

The New Zealand guidelines to application state that "proven intellectual and academic ability of the highest standard" is the first quality required of applicants. They also point out that "Sporting prowess … is not essential if applicants demonstrate in other ways the physical vigour which will enable a Rhodes Scholar to make the effective contribution to the world around him or her which Mr Rhodes clearly expected in expressing the hopes that a Rhodes Scholar would come to 'esteem the performance of public duties as his (her) highest aim.'" The Will also clearly states that selection of Scholars will in no way be influenced by race or religious opinion.

Applications for the Rhodes Scholarship are due on the 1st August. Among the required documents applicants are asked to submit, particular importance is placed on the personal statement. This statement outlines a candidate's general interests and activities, the proposed course of study and future work intentions, as well as stating why the candidate wishes to study at the University of Oxford. Another key component of the application is six letters of reference, of which at least three will be written by people under which the applicant has studied. Other referees may outline a candidate's sporting or cultural acheivements.

In New Zealand, The Scholarship is administered by the Vice-Chancellor's Committee. This committee decides which candidates are selected for local interviews. Last year, 57 applicants were selected locally. After local selections have taken place, national ranking occurs and a handful of candidates are selected for interviews in Wellington.

Although the application process can seem daunting, Julia advice is to not let this intimidate you. For her, assembling her application material then going through the interview process was a "huge learning curve" and very beneficial. Her opinion is that even if you are not successful in your application, simply the experience will be valuable, as you are gaining skills that can be used in your future career, especially in areas such as job interviews. Her advice to prospective applicants is to get onto the application as early as possible because it can take a considerable amount of time. Julia also points out that there are many scholarships out there. For example, another scholarship similar to the Rhodes is the Woolf-Fisher, a New Zealand based scholarship, which allows successful applicants to study at the University of Oxford or the University of Cambridge.

The inspirational Oxford campus

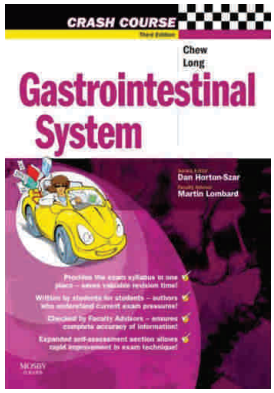
These titles are available from Elsevier Australia (www.elsevier.com.au) or your favourite university or medical bookshop

Kirollos Kamel
Third Year Medical Student
School of Medicine
University of Otago

Kirollos Kamel is a third year student in Dunedin and is our book reviews editor, he has reviewed both books for us this issue. He has special interest in neurology and general internal medicine.

Gastrointestinal System: Crash Course. Third edition

Chew and Long. Publisher: Elsevier RRP: $71.00



Medical students tend to forget very quickly, perhaps because of the large amount of new information they constantly have to take on board. Whether you are revising for an exam or just want to refresh your memory, "Gastrointestinal System Crash Course" will come to your aid! This member of the famous Crash Course series combines the core medical sciences of the gastrointestinal (GI) system, the main disorders affecting each organ, and common presentations of GI disease and how to approach them; all in to one convenient reference, saving you the trouble of searching through dozens of lectures and hefty textbooks to get the information you want.

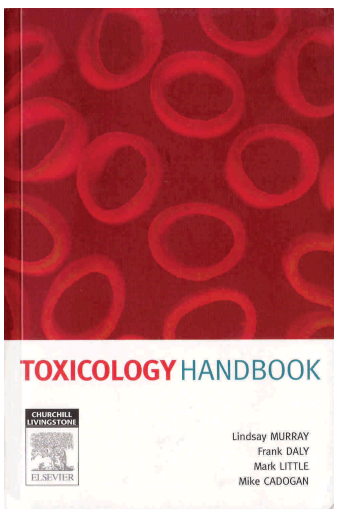
The book is divided into two sections: the "core sciences" section and the "clinical assessment" section. The first section is divided into seven chapters, the first being a general overview, while each chapter after that covers a specific component of the GI system, from mouth to anus. For each organ, the chapter covers anatomy, embryology, histology, and physiology in moderate detail – just enough so you can keep it all in your head! The chapter then describes a number of common disorders of the specific organ, with a focus of the pathogenesis and, where relevant, pathology. Intestinal microflora are superficially covered in the chapters on small and large intestine, perhaps in less detail than you'd like even for a concise crash course. Pharmacology is generally spread out, with the exception of motility drugs being lumped together in the chapter concerning the large intestine.

The second section is much more clinical, taking the common presentations of the GI disease & dissecting each of them in terms of what it means, subtypes (where relevant e.g. in the case of jaundice) and how to investigate the presentation. Two features make this section highly attractive: the first is the tables comprising differential diagnoses for the commonest presentations including indigestion, nausea & vomiting, diarrhoea and abdominal pain. Where the differential is limited, it is included in the text. The second feature is the use of flow charts to advise on how to handle each of these common presentations, including what to ask, what to do and how to treat. These flow charts provide a methodical and hence time saving approach, which allows for early diagnosis and intervention. The rest of this section covers history, examination, investigations and imaging of the GI tract. The coverage of GI imaging is relatively deficient; and endoscopy gets less attention that it should.

Like all members of the Crash Course series, the book ends in a self-assessment section, which allows you to test what you've learnt and consolidates your knowledge. The questions are in a number of different formats, and answers are included and adequately explained.

All in all, the book is a good way to refresh your memory on the GI system. Having said that, if you are approaching the book from a surgical or an anatomical perspective then you might be disappointed, because the book's coverage of anatomy is not extensive and the diagrams are generally oversimplified, especially with regards to the vascular and neural networks supplying the various organs. I would recommend that you use an anatomy atlas along with the book for more realistic representations and maximal benefit.

In conclusion, I recommend this book to medical students in general, as well as House Surgeons and General Practitioners. Remember though – it is NOT intended as a textbook on the Gastrointestinal system, but as a source of revision for someone with little time.



Toxicology Handbook

Lindsay Murray, Frank Daly, Mark Little and Mike Cadogan
Publisher: Elsevier RRP: $82.00

When you watch 'House, M.D' – do you ever notice how often they consider drugs and say to yourself, 'I wish I knew the side effects of all of these'? If your answer is yes, this book is the one for you. Written by experts in Clinical Toxicology, this text is as concise as it gets. It contains summaries about the most common drugs and toxins you will see in the ED. Presentation, diagnosis, management – this book has it all …and more!

'Toxicology Handbook' is written in a style that befits a handbook! The first chapter covers general aspects such as how to assess a patient, resuscitation and what investigations you should order based on the authors' experience (they suggest, for example, an ECG and a serum paracetemol level for every patient). It also provides general guidelines on gastrointestinal decontamination and enhancing the urinary excretion of toxins. One thing it does not cover is how to elicit the history for each case. The authors assume that in the majority of cases the substance of abuse is found by the Paramedics at the site.

The second chapter introduces specific signs and constellations of signs and symptoms and focuses mainly on their management; rather than establishing a diagnosis, which makes sense considering these situations are emergencies. It also addresses patients with special circumstances such as pregnant women, children and the elderly. It suggests how the presentation differs in these groups and how the management may be made more suitable to improve the outcome.

The third chapter addresses an impressive list of toxins – ranging from common substances of abuse, such as alcohol and opioids, street drugs, and heavy metals to prescription medicines. Each substance is covered in terms of risk assessment, signs and symptoms of use/overdose, investigations, management and follow up. The organisation and level of detail is extensive (to say the least) and time-saving for the clinician who would like to look things up in case of an emergency.

The fourth chapter focuses on antidotes and is very MIMS-like in appearance with the advantageous addition of key points regarding the pharmacodynamics and pharmacokinetics of each agent.

The final two chapters focus on envenoming by snakes, fish and insects, with particular focus on species that are endemic to New Zealand, Australia and the South Pacific. An example would be the Australian Inland Taipan Snake, whose bite contains enough venom to kill 150 human adults! The book deals with identification of the suspect animal from the appearance of the wound site, to management on site and at the hospital and antivenoms, making it valuable as an all round source.

Overall the book is excellent. It is packed with "Handy Tips" and "Pitfalls" reflecting the authors' vast experience in the field. The book is also very detailed when it comes to dosage calculations. Much of the information is provided in useful table form which is convenient. Unfortunately, the book does not deal with history taking or possible drug interactions very much, both of which can influence the patient's presentation. Finally, the references listed at the end of each subdivision of a chapter tend to annoy you after a while; perhaps the authors could have listed them at the end of each chapter.

In conclusion, I recommend the book to anyone who practises in an Emergency department, be it a House Surgeon, Emergency Physician or Nurse. Paramedics and Pharmacists would also benefit from reading it. The book is not suitable for pre-clinical medical students, who at this level need more theory and less technical detail. It also cannot be used to learn the mechanism of toxicity behind the various substances because this is not covered in sufficient detail.

AMSA - Asian Medical Student's Association

The inaugural exposition celebrating student research

Annie Jo
Fourth Year Medical Student
Christchurch School of Medicine
University of Otago

Simon Fu
Fifth Year Medical Student
Christchurch School of Medicine
University of Otago

Annie got involved with AMSA International last year while teaching English in Korea. She will be attending her third AMSA conference in July and wants to share the opportunities that AMSA offers. Simon had a great time at EAMSC and would like to share the conference experience with other medical students.

Introduction

The New Zealand Medical Students' Association has now reached out to the medical students of the Asia-Pacific region by being in the process of becoming a full member of the Asian Medical Student's Association (AMSA). This is a great opportunity to network with future colleagues who are neighbours to New Zealand. Perhaps it is pertinent to say we can network with students of New Zealand too - as this may be the case when you are overseas and need to represent Aotearoa. Although the name AMSA suggests it is just for Asian students, as I originally did, this is definitely not the case. AMSA aims to be a representative body of medical students in the Asia-Pacific region. At the conferences there have even been delegates from Austria and Mexico. The benefits to be gained from a conference based organisation are huge as AMSA's three philosophies: knowledge, action and friendship encompass everything of value to its members.

History of AMSA

AMSA was established in 1979 after Thai medical students invited students from surrounding countries to discuss the issue of refugees at the Thai-Cambodian border from a medical perspective. From these roots of unity and co-operation, the association formally founded themselves in 1985 at the 6th conference in the Philippines. There were nine founding members of which included Australia and Indonesia. From these beginnings- AMSA now holds 2 conferences a year. These are called the Asian Medical Student's Conference (AMSC) and East Asian Medical Student's Conference (EAMSC). Currently twenty eight AMSCs and twenty one EAMSCs have taken place where every conference has a key health topic. These are usually chosen from a humanitarian or public/ global health issue. Some of the latest topics have included: Cancer in Asia, Technology in Medicine and Traditional medicine.

AMSA today

AMSA is run by an International Executive Committee (EC) and Regional Coordinators (RC). The RC is the chairperson of their country's AMSA branch. Currently there are over ten full member AMSA branches and two associate members, who are countries that have AMSA, outside of the Asia Pacific region such as the United Kingdom.

AMSA may seem similar to IFMSA in the way that it is a non-political and non-profit medical student organisation. However both parties have acknowledged differences in the characteristics and focus of their organisations and have signed a Memorandum of Understanding to co-operate with each other. This is important with the similar interests of AMSA's conferences and the Asia Pacific Regional Meeting (APRM) that IFMSA runs. A joint conference between IFMSA's APRM and AMSA's EAMSC is under planning stages for 2010.

All AMSA branches work with the three philosophies. 'Knowledge' means that exchanging medical information is essential in any conference. Thus lectures and paper/ poster presentations always feature in these conferences. It is a great experience for students to be involved with presentations in an international conference setting. Furthermore the Secretary of Academics of the EC is in charge of an International Research Project (IRT). The IRT usually researches the health topic of the AMSC that year where each AMSA branch helps out by collecting information from their region for the Secretary of Academics to collate, analyse, and complete. 'Action' promotes the idea that medical students can achieve change through initiatives like community work. For instance, in 2005, AMSA ran International relief projects for the Tsunami victims and the Pakistani earthquake victims. Finally 'friendship' means the chance to form networks all around the Asia-Pacific region as well as making use of the opportunities for student exchange. Currently Asian Medical students' Exchange Programme (AMSEP) is aimed at short term visits between AMSA member countries.

AMSC is the main conference and is held around August each year whereas EAMSC is the shorter conference held around January each year. Before and after each conference, AMSA branches are encouraged to organise a pre and post- conference project back in their country. These usually vary from national meetings, public health projects, community activities and public lectures. An academic benefit for the students, especially in the pre-clinical stage, is the chance to get more exposure to evidence based medicine. This is usually gained from collating information for the

projects or listening on the paper and poster presentations done by their peers. Some may partake in AMSA's annual IRT for further research experience.

AMSC 2007

This was hosted by Korea, one of the founding member countries, during July 22nd-29th in the capital city of Seoul. The health topic was 'Cancer in Asia- Incidence, Suffering and Prevention' with more than 400 students attending. This was also the first AMSA conference to have a New Zealand delegate attend so I was lucky to be invited to the executive committee meetings.

One characteristic of AMSA conferences is to be placed in a designated group that you tend to experience the conference with. It is a great chance to really get to know a few delegates from each country as the groups are well balanced and have local students to oversee the group. These local students are called Group moderators and are great in taking the group out on sight-seeing trips!

The paper presentation and poster presentation competitions allow each country a chance to enter a team with an overview on information and data relevant to the health topic, in this case it was cancer, in the delegate's country. This is special as it is a case of students who teach other students the information they have prepared prior to the conference. It was amazing to see the top cancers that each country has, the patterns in Korea are different to western countries such as Australia or our own. Also I felt privileged to be given the chance to have lectures from some leading lecturers in Korea as well the chance to visit many major hospitals.

The community service time was great as we handed out brochures on "10 steps for cancer prevention" at an urban hub and answered any questions the public had for us. However the cultural activities were the highlight for me. It is fulfilling to know that you are learning about the culture of the country you are visiting. The afternoon of Korean cultural activities was a busy one with the amount of activities that were offered. Even with my Korean heritage, I found it informing and entertaining.

Another must have at the AMSC is the cultural show. This is held at the end of the conference and each country fervently practices their cultural piece well into the night during the conference! It is all worthwhile as the final night bursts into a vibrant and colorful show celebrating cultural diversity.

EAMSC 2008

The 21st EAMSC was held in Bangkok-Pattaya, Thailand, between 9 -13 January. It was an amazing experience meeting over 200 medical students from 12 different countries. It was good to have Simon come along to this conference to boost the Kiwi delegation! By the end of the conference we got to know many delegates. It was interesting to learn what medical education was like overseas. For example, Hong Kong students in clinical years have virtually no holiday, university students in Thailand have to wear uniform, and learning frog anatomy is part of the medical curriculum in Taiwan.

The theme for EAMSC was 'Alcohol: medical and social aspects'. We had many key note lectures and hospital visits, and we particularly enjoyed the student oral and poster presentations. It was a unique opportunity to find out how alcoholism affected various parts of Asia, and the strategies developed by different governments to combat alcohol-related problems. For example, in Thailand where Buddhism is the national religion, Buddhist ideology was used as a motivation to reduce alcohol consumption. Alcohol abstinence was promoted during the Buddhist Lent Period in the 'Stop drinking at Lent Period' campaign. In this period, Buddhists reinvigorate their spirits by practising asceticism, which includes giving up alcohol.

Although the conference itinerary was packed, we still had time for sightseeing. We visited the magnificent temple Wat Phra Kaew, bought our souvenirs at Siam Paragon (a huge shopping mall complex) and a Night Bazaar, and the dinner cruise along the river running through Bangkok was simply beautiful. The cultural night at the end of the conference was a showcase for medical students to stage their talents, which ranged from traditional singing to modern hip hop break dancing unique to each country.

We thoroughly enjoyed the time at the EAMSC. It was a wonderful experience with precious memories and long lasting friendships.

How New Zealand can be more involved

With a wider awareness in the medical student community - we can get more involved by forming a core AMSA New Zealand committee and recruiting more student members. This means that a larger number of students can attend and experience the conferences leading to better involvement in the paper and poster presentations on a health aspect from New Zealand. With the framework to make pre and post conference projects a reality means that the students back home who could not attend the conferences can also benefit by being able to learn about those health issues. It is great to get a broader overview of the medical issues in the Asia Pacific region as this will mean that as physicians, we can be more understanding of a diverse range of patients.

Unlike IFMSA who charges an annual membership fee, it is free for countries to join AMSA, so there are no real monetary barriers to having an AMSA New Zealand as an international organisation for medical students here. Looking at our neighbour Australia, who have maintained their membership to AMSA successfully, it is reasonable to think that New Zealand medical students can have long term ties to the students of the Asia-Pacific. All that the Kiwi students have to have are an interest in the health issues in the Asia-Pacific region and the desire to make changes for our community, particularly in public health promotions. In the future it would be a great honour to host a conference right here in New Zealand!

Future conferences

We need a big Kiwi delegation. A booming Haka at the cultural show will really make our presence known! The AMSC 2009 is to be held in Tokyo, Japan. The health issue is non-communicable diseases. The EAMSC 2009 is to be held in Malaysia. The AMSC 2010 is to be held in Indonesia.

For more information on AMSA: Please contact Annie Jo, Regional Chairperson of New Zealand. **joha6699@student.otago.ac.nz** Check out the AMSA Website **www.amsainternational.org**

Choreoathetosis in a patient with diabetes mellitus

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Having completed a medical degree at Auckland University in 2007, Bodhi is presently a house surgeon at North Shore Hospital and is particularly interested in General Medicine and Endocrinology.

A 73-year-old Fijian Indian man presented to the Auckland Hospital Emergency Department (ED) with a two-day history of uncontrollable writhing and jerking movements of his right limbs, severe paroxysmal cramping pain in his right arm and an unsteady gait. He reported no other symptoms including headache, limb weakness or fever. He had had a recent flare of gout in his right wrist and had been commenced on prednisone and colchicine by his general practitioner two days ago.

This patient had multiple co-morbidities, including poorly-controlled type 2 diabetes mellitus (DM), hypertension, gout and chronic renal failure. His chronic renal impairment was related to a background of having one remaining kidney after a live kidney donation in 1984. In 2006 he had been diagnosed with gastric adenocarcinoma and was due for surgical treatment. He had no history of cerebrovascular disease, ischaemic heart disease or peripheral vascular disease. He was an ex-smoker with a 50 pack-year history and did not consume any alcohol. His regular medications were cilazapril 5mg once daily and glipizide 5mg twice daily; however he reported that he "only takes one tablet a day". He had no known drug allergies. Family history was unremarkable.

The patient had been diagnosed with diabetes in 1992. He had a history of poor compliance with his medications and diabetic clinic attendance. At the most recent clinic in 2002 he had been found to have peripheral neuropathy, mild retinopathy and moderate nephropathy at the time. His HbA1c was 9.0%.

On examination the patient appeared to be distressed by his symptoms but fully alert, conscious and oriented. His vital signs were stable including a blood pressure of 140/78mmHg. The most prominent finding was a choreoathetoid movement of both the upper and lower right extremities. His gait was mildly impaired with a tendency to sway to the right. Finger-nose-finger testing was normal. Power and tone were normal in all his limbs. His reflexes were symmetrical with absent ankle reflexes bilaterally. There was a loss of vibratory sensation in his feet. Cranial nerve examination was normal. There was no evidence of inflammation of any joints including his right wrist.

Laboratory studies revealed that complete blood count and electrolytes were normal. His creatinine level was 272umol/L. His random blood glucose level was markedly elevated at 30.7mmol/L as was his HbA1c at 14.0%. The initial impression was that he might have suffered a cerebrovascular accident affecting the basal ganglia. A head computed tomography (CT) scan did not reveal acute haemorrhage or ischaemia, but showed old mild to moderate small vessel ischaemic change in the white matter, predominantly in both frontal lobes. A neurologist suggested that the patient had suffered a probable ischaemic stroke in the deep left white matter.

Prednisone and colchicine were stopped and he was administered eight units of actrapid insulin in the ED. By the second day of admission, his blood glucose level had been reduced to 16mmol/L. He was transferred to the ward and continued on subcutaneous insulin therapy for another day, then restarted on glipizide. Glipizide was increased to 5mg mane and 10mg nocte due to suboptimal control. It was felt that given his history of poor compliance it would be impractical to commence treatment with subcutaneous insulin injections. He was assessed by the physiotherapists regarding his poor balance and discharged home. On discharge, he still had right-sided choreoathetosis but at a slightly reduced level. Aspirin and simvastatin were added as secondary prevention measures for possible ischaemic stroke. The patient and his family were educated about the importance of reducing his cardiovascular risk.

Discussion

The case illustrated posed several diagnostic challenges. Firstly, it was recognised that the patient's main presenting symptom was a unilateral dyskinesia. The movements of his right limbs could best be described as choreoathetosis. The pathophysiological basis of movement disorders such as Huntington's disease (a hyperkinetic disorder) and Parkinson's disease (a hypokinetic disorder) is dysfunction of the extrapyramidal system or basal ganglia. This complex system comprises the caudate striatum, subthalamic nucleus, substantia nigra and parts of the thalamus. The most common cause of unilateral dyskinesia is a focal vascular lesion in the contralateral basal ganglia[2]. In this case, the patient had several major risk factors for cerebrovascular disease, including hypertension and poorly-controlled diabetes mellitus. A CT scan done at more than 48 hours after the onset of symptoms failed to reveal any ischaemic or haemorrhagic changes consistent with a cerebrovascular accident, although there was evidence of old infarcts.

The patient had a significant background of poorly-controlled diabetes and the administration of prednisone is likely to have precipitated the acute hyperglycaemic episode on admission. An interesting question that arises is whether the temporal relationship between the commencement of prednisone and onset of dyskinesia is of significance. A survey of the literature revealed that chorea or ballism is a rare but recognised complication of hyperglycaemia without ketosis. According to a meta-analysis, in the period 1985 to 2001 only fifty-three cases of this condition had been reported[3]. The patients described with chorea or ballism with associated hyperglycaemia were mostly elderly with diabetes, with an average age of 71[3]. The average age of patients with dyskinesia secondary to a focal vascular lesion was generally lower, around 66[3]. Interestingly, most of the reported cases thus far were of Asian origin[2-4]. The chorea/ballism has been unilateral in most cases, although generalised chorea has also been reported.

More recent reports of patients with unilateral symptoms have documented characteristic brain imaging findings within the corresponding contralateral striatum. These include high density changes without mass effect on CT. However, there have been several cases with no CT changes, as in the case illustrated[5]. High signal intensity on T1-weighted magnetic resonance imaging (MRI) scans have almost consistently been found in cases when an MRI was performed at presentation. In most cases, the imaging features had completely reversed on follow-up scans and correlated well with clinical improvement[2]. Positron emission tomography (PET) scans in patients with hemichorea/ballism secondary to hyperglycaemia have shown reduced cerebral glucose metabolism[4] and concomitant hypoperfusion in the contralateral basal ganglia seen on single photon emission computed tomography (SPECT)[2-6].

Previous studies have shown that chorea associated with hyperglycaemia may resolve with the correction of blood glucose level[2]; or may be slow, taking months to resolve[6]; or may be persistent[5]. However in the majority of cases the prognosis of hemichorea/ballism secondary to non-ketotic hyperglycaemia has been favourable. A meta-analysis found that the abnormal movements had resolved in 97% of patients within 6 months[3].

Researchers have endeavoured to provide an explanation for the association between hyperglycaemia and chorea/ballism. An early hypothesis was that in hyperglycaemia, cerebral metabolism shifts to the anaerobic pathway with inhibition of the Krebs cycle. Gamma-aminobutyric acid (GABA) may then be utilised as an alternative energy source leading to a reduction of GABA in the basal ganglia and subsequent chorea[3]. However the phenomenon of delayed recovery despite normalisation of blood glucose has led some researchers to question this hypothesis. Some entertain the possibility that delayed improvement may simply be part of the natural history of diabetic chorea[6].

With the consistent finding of hyperintensity on T1-weighted MRI of patients with chorea/ballism associated with hyperglycaemia, researchers are recognizing this as a unique clinicoradiological syndrome[3]. Unilateral findings on MRI also argue against a solely metabolic mechanism of disease.

The current consensus appears to be that of a multifactorial aetiology where both vascular and metabolic factors play a role. Pre-existing microangiopathic disease and damage such as lacunar infarction leading to local failure in vascular autoregulation during an episode of hyperglycaemia is one possibility[1,4]. Another explanation is that transient focal cerebral ischaemia during a period of hyperglycaemia may lead to partial striatal damage, as opposed to complete infarction. This may then cause transient regional metabolic failure[4].

The unique clinicoradiological syndrome of chorea, non-ketotic hyperglycaemia and high signal intensity on T1-weighted brain MRI may have significant implications in the case illustrated. Several important questions arise. Would an MRI brain study have been a useful investigation in this case? Would diagnosis of this particular syndrome affect management? As described earlier, the detection and correction of hyperglycaemia could potentially lead to full recovery in some patients diagnosed with this syndrome. Thus, the clinical prognosis of this syndrome would be more favourable than if the patient had sustained a cerebral infarct. However, given his background of poor compliance with medications, long-term prognosis may be poor. In this case, it seems that achieving good glycaemic control would be an important part of management, regardless of the aetiology of the dyskinesia. Educating the patient and his family about the importance of reducing other cardiovascular disease risk factors would be essential.

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NZMSJ ACADEMIC Writing Prize ISSUE 7 RUNNER UP

Characterisation of ecto-5'-Nucleotidase (CD73) and nucleoside triphosphate diphosphohydrolase-8 (NTPDase8) expression in rat cochlea

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Son is a Vietnamese citizen who came to New Zealand as an international student in 2002. He graduated from the University of Auckland in 2007 with a Bachelor of Technology in Biology with First Class Honours, and was awarded a three-year PhD scholarship at the end of 2007 to study the nature of Hepatitis C Virus at the University of New South Wales, Australia. After completion of his PhD study, he wishes to pursue a science career in infectious diseases, possibly becoming a virologist.

Research Project Summary

The purinergic signalling pathway provides an important homeostatic regulation of sound transduction and neurotransmission in the cochlea[4]. This pathway involves extracellular nucleotides as signalling molecules acting on P2 receptors (use adenosine 5'-triphosphate (ATP) as the ligand) and nucleosides acting on P1 receptors (use adenosine as the ligand), and the enzymes collectively known as ectonucleotidases. Many pathophysiological and therapeutic potential issues regarding the cochlea are directly linked with this signalling pathway[2]. ATP and adenosine are extracellular signalling messengers that can modulate a number of physiological processes in the cochlea (auditory neurotransmission, electrochemical homeostasis, signal transduction) and also protect the cochlea from oxidative stresses (noise, ototoxicity)[2,8,11]. However, there is still insufficient understanding of the involved mechanisms, especially of the ectonucleotidase enzymes involved in regulating this extracellular ATP to adenosine in the cochlea.

There is strong evidence from previous studies[8-11] for the expression of certain members of these ectonucleotidases, the ecto-nucleoside triphosphate diphosphohydrolase family (NTPDase1, 2, 3) in the cochlea. Before these projects were conducted, however, there had never been any evidence for NTPDase8 expression. In addition, although the evidence for ecto-5'-nucleotidase (CD73) activity has been provided in studies showing the hydrolysis of AMP to adenosine following its perfusion through the cochlear fluid compartments, there had been no confirmation on the expression of this enzyme in the cochlea. Due to these reasons, the Deafness Research Foundation funded this project to characterise both NTPDase8 and CD73, in terms of their mRNA expression and distribution in the cochlea. An advanced imaging technique - confocal immunofluorescence microscopy - was used to investigate the localisation of these enzymes in rat cochlea.

The project was performed in the Auditory Neurobiology Laboratory, in ten weeks from November 2006 to February 2007, under the supervision of Dr. Srdjan Vlajkovic, an expert in purinergic signalling. The study represents the first attempt to investigate the expression and distribution of these two key enzymes' likely involvement in regulating ATP signalling in the cochlea. These findings, along with previous reports, provided good evidence for the enzyme cascade involved in the hydrolysis of ATP to adenosine. At the health significance end of this project, the confirmed findings highlighted novel molecular mechanisms involved in regulation of hearing. Furthermore, the results from this project provide deeper insight into the purinergic control of sound transduction and neurotransmission in the cochlea, and serve as an important reference point for future gene therapy and other hearing-loss treatments.

ABSTRACT

In the cochlea, ectonucleotidases regulate the signalling levels of extracellular nucleotides by hydrolysing adenosine 5'-triphosphate (ATP) and the related purine nucleotides. The surface-located enzymes include members of the E-NTDase family (CD39/NTPDase 1, 2, 3 and 8) and the ecto-5'nucleotidase (CD73). In previous studies, three members of the E-NTPDase (NTPDase-1, -2 and -3) were localised. Activity of CD73 in the cochlea was also reported. The present study focuses on the mRNA expression of CD73 and NTPDase8. Western blotting confirmed the expression of these enzymes in the cochlea. Confocal immunofluorescence localised CD73 to the basal and intermediate cells of the stria vascularis, capillaries and small blood vessels throughout the cochlear compartments. NTPDase8 was immunolocalised to the interdental cells of the spiral limbus, to Claudius cells and to the root region of spiral ligament. In the past, NTPDase8 was reported to have a higher affinity for ATP than for ADP[1], while CD73 was known to break down AMP to adenosine. These differential expressions, functions and localisation of NTPDase8 and CD73 along with previously reported NTDase-1, -2, -3 together suggest a possible interaction cascade between these enzymes and the spatial, as well as temporal, regulation of P2 receptor signalling in the cochlea.

INTRODUCTION

ATP is well-known for its role as a cellular energy-driving molecule. In the nervous system, particularly in the cochlea, there is strong evidence that extracellular ATP and its corresponding nucleoside, adenosine, have multiple physiological and pathophysiological roles in purinergic signaling, acting via P2 receptors (ATP as ligand) and P1 receptors (adenosine as ligand)[2]. Ectonucleotidases are important in regulating the effects of P2 receptors by hydrolyzing extracellular nucleotides[7]. The expression and distribution, as well as their roles in hydrolyzing cochlear ATP and ADP, of the three cell surface-located members of the ecto-nucleoside triphosphate diphosphohydrolase family (NTPDase1, 2, 3) have been previously reported [8-11]. There is also evidence for ecto-5'-nucleotidase (CD73) activity involved in the hydrolysis of AMP to adenosine following perfusion through the cochlear fluid compartments[12]. The present project aimed to address the mRNA expression and provides the immunocytochemical localisation of the membrane-bound E-NTPDase enzymes NTPDase8 and CD73 in the cochlea, and to extend the characterisation of tissue-specific P2 receptor signalling.

MATERIAL AND METHODS

Animal and cochleae preparation

The experiments were carried out on adult male Wistar rats weighing around 250 g. All procedures were approved by the University of Auckland Animal Ethics Committee. The animals were deeply anesthetized and then perfused with 0.9% NaCl and 4% paraformaldehyde (PFA) in 0.1M phosphate buffer (PB: Na_2HPO_4 77.5 mM, NaH_2PO_4 22.5 mM, pH 7.4). The cochleae were isolated and trimmed under a dissecting microscope. They were then used directly for mRNA extraction or post-fixed overnight in 4% PFA at 4°C.

Cloning and sequencing

NTPDase8 and CD73 cDNA were amplified from rat cochleae. Primer pairs, specific for each cDNA, were designed based on the reported sequence of NTPDase8 (GeneBank® accession # NM_001033565) and CD73 (GeneBank® accession # NM_021576). Primer sequences are shown: (NTPDase8F: GCCTTTGGTTGGATCACTGT / NTPDase8R: CAATCCTCTTGGCCC TTACA) and (CD73F: GACCAGCAACTCAATGAGGCA / CD73R: CATTGGCAGGAAGAC AGGAG). Rat cochleae were removed and mRNA extracted using the Dynabeads mRNA DIRECT Kit® (Dynal Biotech Ltd, Oslo, Norway). The mRNA extract was reversely transcribed to cDNA (5µ L mRNA, 1µ L depc water, 1µ L random hexamers, 10µ L 2X 1st strand reaction mix, 2µ L Superscript III / RNAse OUT enzyme mix, Invitrogen) using standard reverse transcription protocols. The first cDNA strand was then used for PCR amplification.

PCR was performed using standard procedures. Platinum® DNA polymerase High Fidelity was purchased from Invitrogen with 3'-5' proofreading property to minimize the chance of getting errors. The PCR was run at 40 cycles. The PCR product was then purified using the Roche High Pure® PCR Product Purification Kit with supplied protocol.

The purified PCR product was cloned to pCR®2.1 plasmid using Invitrogen TA® cloning kits with TA overhangs for improved cloning efficiency. Clones were screened and selected based on white/blue selection on XGal and Ampicilin-treated agar plates. Plasmids DNA from positive clones were purified using the Qiagen Plasmid Midiprep Kit®. The plasmids were subjected to restriction analysis with EcoRI to confirm the size and orientation of the insert. Purified DNA plasmids were sent to the sequencing facility at the School of Biological Science, the University of Auckland, to confirm the identity of the insert.

Western blotting

Cochlear and liver proteins were dissolved in both non-reducing Laemmli's sample buffer (1% SDS, 20% glycerol, 0.1% bromophenol blue, 125mM Tris at pH 6.8) and reducing buffer (45µ L 0.1M DTT, 7.5µ L mecaptoethanol in 97.5µ L non-reducing buffer). The treated protein mixtures were then separated by SDS-polyacrylamide gel electrophoresis and electrophoretically transferred to a polyvinylidene fluoride (PVDF) membrane (Roche Diagnostics, Auckland, New Zealand). Blocking (5% skim milk, 2% normal goat serum in TBS-T - 20mM Tris-base, 137mM NaCl, 0.1% Tween20) was followed by probing using the primary antibodies (with concentration of 1:500 titre for polyclonal guinea pig anti-rat NTPDase8 antibodies and pre-immune serum control; 5µ L/g for monoclonal mouse anti-rat CD73 antibodies and mouseIgG control). The NTPDase8-blotted and CD73-blotted membranes were incubated for one hour with rabbit-peroxidase anti-guinea pig IgG (1:2000 dilutions) and goat-peroxidase anti-mouse IgG (1:3000 dilution), respectively, before the bandings were visualised by chemiluminescence (ECL Western Blotting Analysis System, Amersham Bioscience).

Confocal Immunofluorescence

Polyclonal NTPDase8 and monoclonal CD73 (0.5mg/mL, BD Pharmingen) primary antibodies were raised in guinea pigs and mice respectively. Pre-immune serum controls (for NTPDase8) and Mouse IgG controls (for CD73) were used to test the specificity of these antibodies. Specificity was re-confirmed using Western blotting against proteins extracted from liver tissue, where the expression of NTPDase8 and CD73 had been confirmed previously.

The rat cochleae fixed in 4% PFA were decalcified in 5% EDTA / PB solution (pH 7.4) for seven days then cryoprotected in 30% sucrose / PB solution overnight at 4°C. They were then rinsed in 0.1 M PBS and snap-frozen in ice-cold N-Pentane. Sectioning was carried out at 30µ m in a cryostat and the sections were placed in a 24-well plate. Antibody concentrations were: NTPDase-8 (1:500 and 1:1000) and CD73 (1µ g/mL and 5µ g/mL). Each well was then rinsed with 0.5 mL sterile PBS 0.1 M (Na_2HPO_4 77.5 mM, NaH_2PO_4 22.5mM, NaCl 154mM, pH 7.4), and permeabilised with 1% Triton-X for one hour. Non-specific binding sites were blocked using 1.5% normal goat serum (NGS). Primary antibodies were incubated overnight at 4°C.

Secondary antibodies for NTPDase-8 (Alexa 594 goat anti-guinea pig IgG conjugate) and CD73 (Alexa 488 goat anti-mouse IgG conjugate) were applied for two hours in the dark at room temperature. The tissues were then rinsed and mounted on microscope slides using anti-fading reagent (CITIFLUOR). They were screened for NTPDase-8- and CD73-specific immunofluorescence using a confocal microscope (Leica Leisertechnik, Heidelberg, Germany)

RESULTS

Expression of NTPDase8 and CD73 in the cochleae

The agarose gel electrophoresis of PCR products (figure 2A, 2B) revealed the expression of both CD73 and NTPDase8 enzymes in the cochleae. Cloning and sequencing of the purified plasmids was carried out in the Sequencing Facility (School of Biological Sciences, University of Auckland), using the AB Applied Biosystem 96 sequencing machine. Sequence analysis confirmed the exact identities of the submitted DNA sequences. In western blotting, NTPDase-8 antibodies bound to the 70-75 kDa protein (figure 2D) in both rat cochlear and rat liver tissues, under both reducing (R) and non-reducing (NR) conditions, suggests that NTPDase-8 exists in monomer form. The size is consistent with the predicted size[3]. On the other hand, although CD73 western blot result showed weak bands in rat cochlear extracted protein lanes (figure 2C) - possibly due to tissue size, expression and protein degradation - CD73 antibodies did bind to 60-65 kDa bands in the liver lanes and in both reducing and non-reducing conditions. This is consistent with the predicted size[14,15]. The observed smearing bands in figure 2C are explained by protein fragmentation due to the freeze-thaw treatment of proteins prior to western blotting. No negative controls (pre-immune serum control and mouseIgG control) showed banding, which indicates no unspecific binding of primary antibodies. Also, recall that rat liver expresses both NTPDase-8 and CD73[3,15]; binding of primary antibodies to the expected cochlear and liver proteins confirmed the specificity of these primary antibodies for NTPDase-8 and CD73.

NTPDase8 Immunolocalisation

The cochlear spiral ligament, the interdental cells of the spiral limbus and the Claudius cells exhibited prominent NTPDase8 immunofluorescence (figure 3E-F) consistently in all three cochlear turns - basal, middle and apical (data not shown). The strong NTPDase8-specific immunofluorescence in the spiral ligament showed branching, characteristic of cells in the root region (figure 3E). No immunofluorescence was observed in the organ of Corti, spiral ganglion or blood vessels (figure 3F).

CD73 Immunolocalisation

CD73-specific immunofluorescence was prominent in the basal and intermediate cell layer of the stria vascularis (figure 3H). CD73 was also localised in capillaries of the stria vascularis, spiral ligaments, spiral limbus and spiral ganglion (figure 3G). Immunofluorescence was consistent in all

Figure 1

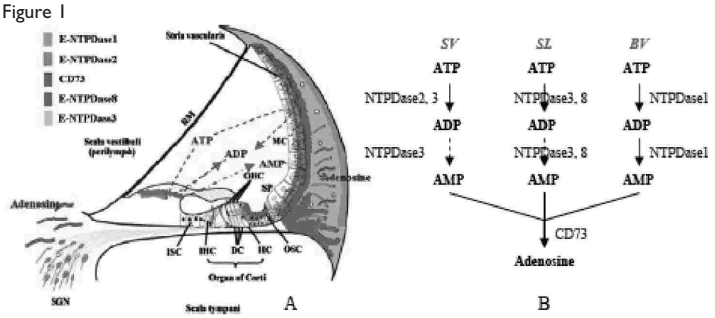

Figure 2

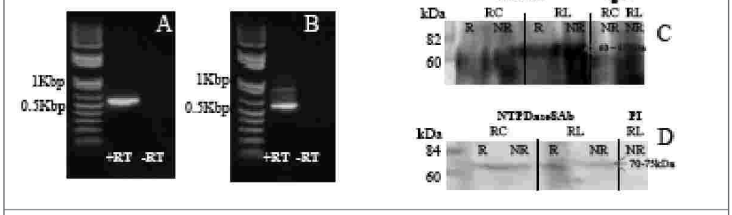

Figure 3

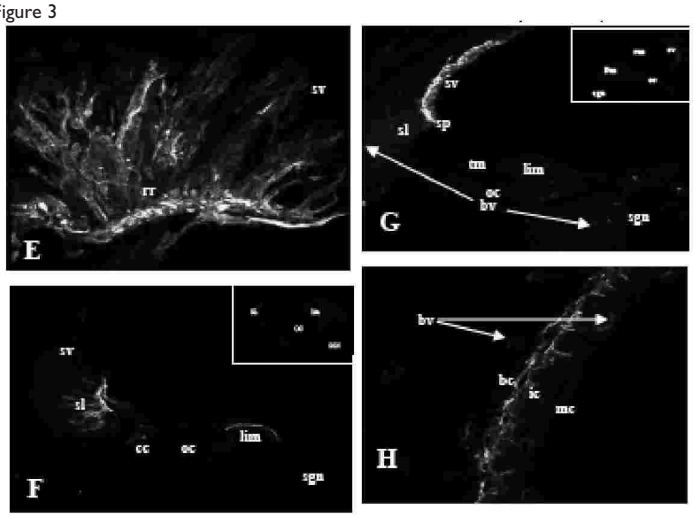

Figure 1: (A) Summary of the differential distribution of E-NTPDase8 and CD73 in conjunction with the previously reported E-NTPDase1 and -2 and -3 in the rat cochleae. NTPDase8 and CD73 show distinct tissue-specific localisation in the cochleae. Only spiral ligament localisation of NTPDase3 is shown in this figure. NTPDase2, -3 and CD73 show partly overlapping localisation in the stria vascularis (expression of NTPDase3 in this region is not shown in this figure), while NTPDase1 and CD73 overlap only in the vasculature. NTPDase3, -8 shows overlapping localisation in the root region of the spiral ligament. However, NTPDase8 does not express elsewhere in the spiral ligament. A possible pathway for ATP regulation is also depicted. Modified with permission from Vlajkovic SM (2002)[8]. **(B)** The three hypothetical ATP hydrolysis cascades in the spiral ligament (SL), blood vessels (BV) and the stria vascularis (SV): solid arrows.

Figure 2: Expression of NTPDase8 and CD73 in rat cochlear tissues.
RT-PCR: CD73 **(A)** and NTPDase8 **(B)** cDNAs generated by RT-PCR from rat cochlear mRNA (in SYBR safe agarose gel). The molecular size of CD73 PCR products were 539bp and of NTPDase8 PCR products were 522bp. Western blot characterisation of anti-peptide antisera used for immunohistochemistry for CD73 **(C)** and NTPDase8 **(D)** proteins. See results section for further explanation.

Abbreviations: RC: rat cochleae; RL: rat liver; R: reducing condition; NR: non-reducing condition; PI: pre-immune serum; IgG: MouseIgG control

Figure 3: Confocal Immunofluorescence: (E-F) NTPDase8; **(G-H)** CD73. Insets F and G show no primary antibody control with the same confocal microscope setting. Good signal-background differences indicate specific binding of antibodies both primary and secondary. **(E)** 100X magnification of the fluorescent signal in the root of the spiral ligament shows branching, characteristic of the root cells. **(F)** 1:500 titer of anti-NTPDase8 primary antibodies: strong signal in the root region of spiral ligament, Claudisu cells and the spiral limbus was observed. **(G)** 5μ g/mL of anti-CD73 primary antibodies; **(H)** 100X magnification on stria vascularis shows the fluorescent signal in the basal and intermediate layer of this region.

three turns (data not shown). CD73-specific immunofluorescence was not observed in the organ of Corti, the spiral limbus or the spiral ligament (figure 3G).

DISCUSSION

In the central and peripheral nervous system ATP acts as a neurotransmitter and as a neuromodulator[1]. It has been reported to be released during cochlear injury such as noise trauma[2], when it acts on P2 receptors, particularly the ATP-gated ion channels which may trigger cytotoxic cascades[4]. Inactivation of ATP in the cochleae involves a variety of enzymes that dephosphorylate ATP to adenosine and the subsequent reuptake of adenosine. These are important steps in the regulation of ATP signalling. The hydrolysis of ATP to adenosine also serves to salvage purines within the cochlear compartments[12]. Our study addresses the distribution, expression and possible functions of the two ectonucleotidases that may be involved in regulation of cochlear sensitivity by hydrolysing extracellular ATP and its metabolic products.

NTPDase8 expression in the scala media: putative role in electrochemical homeostasis

NTPDase8 shows specific expression in the tissues bordering the scala media: strongly in the root cells of spiral ligament, in Claudius cells and in the interdental cells of the spiral limbus (figure 3F). These regions are involved in K^+ cycling and may have a role in pathophysiology of noise-induced hearing loss[6]. This role is accomplished by regulating the activation of several P2X and P2Y receptor subunits expressed in these regions. As NTPDase8 hydrolyses ATP and ADP, with a stoichiometry of (ATP:ADP) of 3:1[1], this region-specific localisation of NTPDase8 suggests roles for NTPDase8 in both the spatial and temporal regulation of ATP and ADP levels, and in the differential P2 receptor activation in these compartments. Another suggested role for NTPDase8 is actually in common with NTPDase3 which hydrolyses ATP to AMP in the stria vascularis and spiral ligament. The expressions and co-localisation of NTPDase8 and NTPDase3 in the spiral ligament of rat cochleae[11] suggest that tight regulation of $P2X^2$ subunit activation is likely to be involved in K^+ cycling. Each of these enzymes has different nucleotide-hydrolysis profiles. This again indicates complex regulation of the endocochlear potential which is the driving force for sensory transduction. Especially the sole expression of NTPDase8 in the root cells of the spiral ligament may imply an important, but yet fully-understood, role in this region (figure 3E).

CD73 expression in cochlear blood vessels and stria vascularis: putative role in adenosine production, cochlear blood flow, haemostasis and thrombogenesis

In contrast with the function of NTPDases, the ecto-5'nucleotidase (CD73) is evidenced to be involved in the final step of the inactivation and catabolism of ATP and the formation of adenosine by hydrolysing AMP to adenosine[12]. The expression of CD73 in the capillaries in various compartments (stria vascularis, spiral ligament, spiral limbus and spiral ganglion) suggests spatial regulation of adenosine production in cochlear tissues (figure 3G). Along with the presence of NTPDase1 which hydrolyses both ATP and ADP equally in blood vessels[1], vascular CD73 would complete the ATP-adenosine hydrolysis cascade in the cochlear vasculature (figure 1B). Moreover ATP can also modulate blood flow in the cochlea via G-protein-coupled P2Y receptors. Extracellularly released ATP and ADP

during inner ear injury modulates thrombogenesis at the site of vascular injury via G-protein-coupled $P2Y^{1}$ and $P2Y^{12}$ receptors on platelets[5,10]. This possible cascade for ATP hydrolysis via CD73 and NTPDase1 in the blood stream may be crucial for maintaining purine-regulated cochlear blood flow, vascular haemostasis and thrombogenesis. This additionally implicates vascular CD73 as another possible target for the therapy of various blood-flow related disorders in the inner ear such as sudden deafness and Meniére's disease. On the other hand, because extracellularly formed adenosine may also modulate neurotransmission by inhibiting the release of other neurotransmitters such as glutamate[12], vascular CD73 may also involve indirect adenosine-mediated regulation of sensory transduction and serve to salvage purines. Finally, recall that NTPDase2 hydrolyses ATP 30-fold preferentially with respect to ADP, and NTPDase3 hydrolyses ATP two-fold more rapidly than ADP[1]. The co-localisation of these enzymes[8,11] in the basal and intermediate cells of the stria vascularis, which is important in providing the cochlear potential, would imply another cascade for ATP hydrolysis via NTPDase2, NTPDase3 and CD73 in this compartment (figure 1B). This also reveals the role of CD73 in cochlear electrochemical homeostasis. Nevertheless, due to limitations of this study further investigation is needed as discussed below.

Possible ATP-regulation pathways

This study revealed two possible ATP-hydrolysis cascades: via NTPDase1 and CD73 in the blood stream, and via NTPDase2,-3 and CD73 in the stria vascularis (figure 1B). On the larger scale, assuming that ATP is not completely region-specific, inactivation of ATP would start with NTPDase2, -3 and 8 in the tissues bordering the scala media, when the ATP level is high. While ATP is a limiting factor for NTPDase2[1], transiently accumulated ADP would then be hydrolysed by NTPDase3 and NTPDase8. The transient accumulation of ADP delays the formation of adenosine by inhibiting CD73[1]. This would help complete the hydrolysis of ATP all the way down the cascade to AMP before AMP is hydrolysed by CD73. This is consistent with previous publications showing that rapid hydrolysis of ATP to ADP is followed by slow AMP accumulation due to feed-forward inhibition of CD73[1,13]. However, the rate of ADP hydrolysis is also facilitated solely by the presence of NTPDase1 in the blood vessels, suggesting that ADP hydrolysis is tightly regulated in this cellular compartment. In general, the difference in expression and hydrolysis profiles of all of these enzymes suggests spatial, and importantly, temporal regulation of the rate of ATP hydrolysis: rapid hydrolysis of ATP to ADP by NTPDase2, accumulation of ADP then followed by rapid ADP hydrolysis by NTPDase1, -3, and -8, and production of adenosine by CD73 (ecto-5'-nucleotidase). The overall hypothetical pathway is fully illustrated in figure 1A and B.

LIMITATIONS AND FUTURE STUDIES

This study did not employ any quantitative methods to explore the capacity for gene expression. The study also did not involve any in-vivo analysis to study the temporal activity of such enzymes. Immunohistochemical data have not been collected due to time constraints and may need to be in any future studies to re-confirm the confocal immunofluorescent data. Within the allowed timeframe, findings from this study can still serve as a reference point for future studies and perhaps as important implications for inner ear therapy. In order to provide more information on the temporal effects of these enzymes as well as their other possible roles, future studies would need to involve further quantitative investigation such as real-time PCR or noise-induced experiments and in vivo controlled ATP concentration experiments.

CONCLUSION

In conclusion, this study demonstrated the expressions and distributions of NTPDase8 and CD73 in rat cochlea, and implicated roles for NTPDase8 and CD73 in purinergic regulation of cochlear electrochemical homeostasis, sensory transduction, blood flow, vascular haemostasis and thrombogenesis. This study also implies the spatial and temporal organisation of extracellular ATP hydrolysis, which directly influences cochlear electrochemical homeostasis.

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Abbreviations used in the article

oc: Organ of Corti; sv: Stria vascularis; sgn: Spiral Ganglion; sl: Spiral ligament; lim: Spiral Limbus; cc: Claudius cells; rr: root region; bv: Blood vessel; mc: marginal cells; ic: intermediate cells; bc: basal cells; tm: tectorial membrane; rm: Reissner membrane; is: inner sulcus; isc: inner sulcus cells; os: outer sulcus; osc: outer sulcus cells; sp: spiral prominence; osl: osseous spiral lamina; ihc: inner hair cells; hc: Hensen's cells; dc: Deiter's cells; ohc: outer hair cells;

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