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EDITORIAL

Welcome to the seventh issue of the New Zealand Medical Student Journal (NZMSJ). The NZMSJ was founded in the summer of 2002/2003 by a small group of students who had completed research towards summer studentships and BMedSci degrees at the University of Otago. It has since grown into a nationwide initiative and we are proud that the journal is a member of a small collection of student-based medical journals throughout the world. The early pioneers in this field include the McGill Journal of Medicine, a biannual newsletter started in 1994 by students of McGill University in Montreal, Canada and perhaps the best known student medical journal, the Student BMJ which was established in 1995. Since then a number of other student journals have started up in various formats and we are pleased to observe the recent establishment of a student version of the leading UK medical journal, the Lancet albeit as a solely online publication.

The above history illustrates that, over time, the importance of student research has become increasingly recognised amongst the medical community. This shift parallels many changes in attitude towards medical education, another being the increased focus on the biopsychosocial model of medicine which focuses on a more holistic approach to the treatment of illness. This combines the medical model with other social factors which influence ill-health. Medical students should take this model into account throughout their medical education and throughout their vocational lives when considering patient management. Becoming a doctor is not simply about cramming in knowledge on anatomy, physiology and pathology; it is also about critically challenge existing knowledge, investigate those questions with colleagues and learn how to make improvements through public health and political change.

The NZMSJ aims to help the medical students of New Zealand develop and celebrate this holism by publishing examples of students creating change (see page 18 for Jash Agraval's thought-provoking piece on the global small arms trade), questioning aspects of current medical practice (as seen in Anna Choi's article on depression and Sarah Peter's look into the role of public health in clinical medicine) and questioning what imparts us with that knowledge (exemplified by our increasing number of book reviews). We encourage all medical students to continue to embrace the goal of becoming a holistic doctor and take up every opportunity achieve this. For those of you who have an issue you feel passionate about, we also welcome letters to the editor for publication

We extend our sincere thanks Professor Iain Martin, Dean of the University of Auckland Faculty of Medical and Health Sciences, for his generous sponsorship of this issue's Dean's Writing Prize. Greg Tarr, who is currently a BmedSci (Hons) student at the Dunedin School of Medicine was the worthy recipient of this prize for his research piece on stent thrombosis. Kate Rapson received the runner-up prize for her work on the efficacy of Trastuzumab. Congratulations are also due to Sarah Peters of Auckland School of Medicine who received our Features prize for this issue – a copy of the recently revised Dorland's Illustrated Medical Dictionary. We wish to thank our two academic advisors, Associate Professors David Perez (University of Otago) and Cristin Print (University of Auckland) and our expert reviewers from across New Zealand for their valued contribution which allows us to continue to develop our flagship peer review process. Finally, we congratulate all our contributors on their initiative and efforts and hope you feel deservedly proud on seeing your work in print. We look forward to receiving future quality submissions from our readers both in New Zealand and abroad.

The NZMSJ Executive

Credits

Stent thrombosis

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INTRODUCTION

Cardiovascular disease is the major source of mortality in the Western world, killing around one-third of all individuals.[1,2] Coronary artery disease is the source of half of cardiovascular deaths, and kills 3.8 million men and 3.4 million women every year worldwide.[1]

Percutaneous coronary intervention (PCI) and coronary stenting is the most common intervention in the treatment of coronary artery disease, but has the two major drawbacks of restenosis and stent thrombosis. In late 2006, drug-eluting stents, hailed as a breakthrough for the treatment of restenosis, were reported to have increased rates of stent thrombosis.[3]

This review will investigate the controversy surrounding drug-eluting stent thrombosis.

BACKGROUND

Percutaneous coronary intervention was developed in the late 70's.[4] It was thought to be an interesting but esoteric intervention, suitable for maybe 5% of those who would have otherwise had coronary artery bypass grafting. However, it's use expanded beyond the simplest lesions and in ten years, the volume of procedures matched that of CABG, around 250,000 in the USA.[5] The success of plain balloon angioplasty was limited by two main factors, acute thrombosis from arterial injury, and restenosis, the re-closure of treated lesions by elastic recoil and negative remodelling,[6] requiring revascularization in up to 50% of those treated.[7]

These limitations were addressed with the development of the coronary stent, introduced in 1987.[8] Coronary stents are metal cages which prop treated arteries open, practically eliminating the elastic recoil and negative remodelling which dogged balloon angioplasty.[6]

Coronary stenting had it's drawbacks as well, with rates of thrombosis of up to 24%,[9] and clinical restenosis rates of around 20%, although by a different mechanism.[6] These problems were attacked and with improved anti-platelet therapy, thrombosis rates dropped to about 1.2%.[9] Restenosis was resistant to treatment and rates remained similar. With the addition of a permanent foreign body to arterial injury, inflammation was increased, probably due to fibrin deposition on the stent surface and the mismatch between the compliance of the artery and the rigid stent. With increased inflammation, increased arterial repair was noted.[10] This is manifest by the migration of vascular smooth muscle cells to the intima, the inner layer of the artery, and their proliferation once there. They then differentiate into a synthetic phenotype, producing a collagenous "scar", neo-intimal hyperplasia, approximately a 50:50 fibrocellular lesion.[11,12] This lesion grew in between the stent struts re-narrowing the arterial lumen.

Despite this, during the nineties and early this decade stenting became increasingly popular, with close to one million stents being placed worldwide annually.[5]

DRUG-ELUTING STENTS

Fast forwarding to 2003, the first drug-eluting stent (DES), Cordis' Cypher (J&J), was approved by the US FDA[13] on the basis of the SIRIUS trial, a multi-centre, prospective, randomized, double-blind trial of 533 participants with Cypher and 525 with bare metal stents (BMS). The outcome of reduction of the composite endpoint, target lesion revascularisation, MI and cardiac death, at 9 months was achieved. Target lesion failure was significantly reduced from 20.0% in the BMS group to 4.9% in the DES group,[14] however the only significant individual outcome was target lesion revascularisation, there was no significant difference in MI or cardiac death. Multiple studies agreed with the SIRIUS trial - Cypher was efficacious at reducing intimal hyperplasia. One year later, Boston Scientific's Taxus DES was also approved, although there were no significant differences between the two with respect to clinical outcome.[15] Both stents release cytostatic drugs, previously approved in cancer therapies, which broadly inhibit cell function.[16] Preclinical studies showed delayed endothelization with paclitaxel eluting stenting, with an increase of inflammation, postulated to be from a reaction to the polymer.[17] Early after FDA approval of Cypher, a number of cases of both stent thrombosis and hypersensitivity reactions were reported. The FDA responded by requesting that Cordis perform a 2000 participant post approval study,[18] and based on this they concluded that there was no significant difference in stent thrombosis or hypersensitivity compared to bare metal stenting.[19]

With fears allayed, drug-eluting stenting became increasingly popular, growing to around 90% of the stenting market in the US,[20] and around 80% in Europe, with around one and a half million stents placed annually worldwide.

There were a few sceptics - one group of pathologists in Washington published extensively on the pathology of DES. They described delayed endothelialization,[17,21] persistent incomplete endothelialization[22] and a lack of neo-intimal coverage of stent struts,[23] as well as reporting on hypersensitivity reactions[24] and stent thrombosis;[25] mostly poor healing

and the consequences. However, no significant increase of adverse events was noticed in clinical trials, and the suspicion did not influence clinical practice much.

The ability of drug eluting stenting to reduce intimal hyperplasia and therefore restenosis led to use in a broader range of patients than BMS were generally used for.[26] While BMS had similar outcomes to CABG for simple lesions, DES were used in far more complex lesions without any rigorous evaluation. However, from clinical anecdotes this appeared to be successful. Studies that looked at known risk factors, such as left main disease and diabetes were hopeful.[27]

Cost effectiveness has been a weak point. Drug eluting stents appear to be less cost effective than CABG in unselected patients.[28] In the US, use is unselected but in New Zealand, the use is restricted to around 20% of those eligible for stenting.(Chu, JSW. Personal communication)

It was in the long-term follow-up for one of the cost effectiveness studies that a difference in stent thrombosis was first seen. Presented at the 2006 American College of Cardiology Scientific Sessions in Atlanta, the BASKET LATE study,[29] investigators saw a statistically significant rise in cardiac death/non-fatal MI in the DES group, with 1.3% of the BMS group suffering cardiac deaths and non-fatal MIs, and 4.9 % in the DES group, excluding results outside of the months 7 - 18.[28] The results of this analysis galvanised the interventional cardiology community into action.

The first step was to perform a meta-analysis of all trials currently available. This was performed and presented in September that year, at the European Society of Cardiology Annual Meeting/World Congress of Cardiology Meeting.[29] The results were that at 12 months onward, there was a significant rise in thrombotic events in both Cypher and Taxus groups compared with BMS.[3]

So how did the stent thrombosis phenomenon escape detection before?

The most important answer is the statistical power (the probability of a sample actually showing a significant difference when one is present) of all of the trials. The primary outcome the trials were designed to test was a reduction of target lesion revascularisation. With the 20% of BMS recipients and 5% of DES recipients suffering restenosis, only a sample size of 120 for a power of 80% (the recommended level), whereas to see a rate of stent thrombosis which is 1% for BMS and 1.5% for DES, upwards of ten thousand participants would be needed for the same power.[30] Even with meta-analyses of all trials, the power levels sit somewhere around 30%, with less than 50 events experienced by trial participants and a difference is probably only seen because of the different time frames of the thrombotic events, which is the second answer. It may be that the group of Washington pathologists were vindicated after all. They noted that there was persistent incomplete re-endothelialization with DES, which is a plausible pathological mechanism for thrombosis.[22] The time frame of BMS thrombosis was up to thirty days, as the lesion was re-endothelialized,[31,32] and consequently anti-platelet therapy was maintained over that period. Anti-platelet therapy was extended to 3 to 6 months in DES, as it was known that poor endothelialization, which could lead to thrombosis, was an issue. DES thrombosis seems to appear after 12 months, and many of the approval trials were for only one year, thus excluding them from being able to detect stent thrombosis.

However, it was noted that the definition of stent thrombosis was variable between trials. A group of medical and stent industry experts proposed a comprehensive definition of stent thrombosis. They included definite thrombosis, with angiographic or autopsy evidence; probable thrombosis, an unexplained event which is likely to be stent thrombosis; and possible thrombosis, an unexplained event which is consistent with stent thrombosis. They then reworked the original data from the original approval trials. With these more robust definitions, the difference between groups disappeared.[33]

To sort out what was actually happening, the FDA organised a conference of many of the world experts to meet on the 7th and 8th of December 2006 to discuss the issue of stent thrombosis. They reviewed existing evidence as well as new data, with the most significant findings published in a special edition of the New England Journal of Medicine.

Firstly, re-workings of the original randomised clinical trials with thorough definitions of stent thrombosis showed no difference of stent thrombosis rates with Cypher versus bare metal stenting,[34] no difference in stent thrombosis between DES and BMS[35] and no difference in mortality between DES and BMS.[33,36]

In addition to this, data from a large registry from Sweden was published. Nearly all patients receiving a stent from the beginning of 2003 until the end of 2004 were recruited, 19,771 patients. Recipients of BMS (n=13,738) were significantly different in many areas from those who received DES (n=6,033) with DES recipients having more stents, more triple vessel disease, longer lesions, indication and geographic location. A propensity score, analysing the likelihood that a particular variable was associated with treatment was used to reduce bias from non-randomization. The mortality outcomes for the BMS and DES groups were similar at 6 months but diverged after that, favouring the BMS group. Having a DES was associated with a relative risk for mortality of 1.32 (95% CI, 1.11 - 1.57).[37] While this result does not necessarily suggest that rates of stent thrombosis or even mortality are higher with drug eluting stenting, as the treatment groups still are not comparable, it is compelling to see real world data with long term follow up and large numbers. The result does bring up the need for trials of DES in patients with more severe disease. The trials designed to show the efficacy of DES, and approve them for use excluded patients with all but very simple disease. It is these patients who DES are FDA approved for, but it is estimated that 60% of use is in patients with more severe disease. This registry data suggests that outcomes for DES are significantly worse than BMS in "real world" usage.[38]

In addition to the papers published by the New England Journal of Medicine, the Lancet, another of the high impact medical journals published an article of a smaller registry, n=8,146. Angiographically documented stent thrombosis was noted at a steady rate, around 0.6% a year, with no evidence of dropping off. This is consistent with the biology of incomplete healing. This is an observational trial with no BMS group, so it is more difficult to draw definite conclusions, but the result adds to evidence demanding larger trials.[39]

Low powered studies and short-term follow up prevented the early detection, despite some suspicion. It seems likely that the BASKET LATE trial saw a real result by chance, and the re-working of the trials saw no effect because either in that patient population, those with simple lesions, there is no difference, or merely because of low power.

The registry data are compelling, because the studies are powered to see differences in the region of the magnitude stent thrombosis and differences in mortality are likely to appear in, <1%. In addition, they speak of the real world usage, which the approval trials do not. One plausible explanation is that the differences noted are related to discontinuation of anti-platelet therapy, a large known risk factor of stent thrombosis.[40,41] One group looked at mortality with respect to stent type as well as use of the universally used anti-platelet agent, clopidogrel. Their results suggest that perhaps the differences seen in the clinical trials and the registries could be due to medication with clopidogrel - the group with the highest mortality, 5.8%, are those who received DES but were not on clopidogrel at 6 months. However, the group with the lowest mortality, 1.6%, are those who received DES and were on clopidogrel at 6 months. Mortality for BMS was not significantly different with respect to clopidogrel at 6 months, at 3.9% with and 4.5% without clopidogrel. Again, this is an observational study and does not compare identical groups, but it does reflect what is happening in actual clinical practice.[42]

The FDA concluded that drug-eluting stents are associated with a "clinically important excess" of stent thromboses later than one year after stent placement, although the magnitude was unknown. Based on data from the approval trials, there appeared to be no increase in MI or cardiac death, although that may be because of small sample size or due to restenosis related death in BMS recipients. The panel agreed that there was insufficient evidence to certainly say whether one stent was superior

but safety concerns appeared to be justified equally in both. It was agreed that there was no increase in all cause mortality, and that when used according to the FDA approved guidelines[13,15] the benefits outweigh the risks. The recommendation for clopidogrel was increased to 12 months, while acknowledging that the optimal length of treatment was not known.

It was recognised that follow up was too short, and treatment groups too small, with the panel calling for bigger, longer trials for both approval and safety studies, taking care to look at compliance with treatment.[3]

Lastly, the panel agreed that off-label use should be limited.[3]

A recent Nature Clinical Practice article by top cardiology experts reflected on the controversy.[43] Farkouh et al. admit that the widespread adoption of DES was not based on the same rigorous analysis that other cardiovascular technologies were received. While most commonly used cardiovascular therapies were first evaluated in high risk groups, then evaluated in low risk groups, DES were tested in low risk individuals and use then broadened into high risk patients, for whom no data existed. Current views on DES range from disregarding stent thrombosis as an important outcome and promotion of unrestricted use to a panic reaction and widespread restriction of use.

However, individualized therapy could minimize restenosis while minimizing stent thrombosis, by weighing up risks and benefits. In addition, it is noted that widespread adoption is not as cost-effective as use in selected populations.

Key variables that should be taken into account include the cumulative risk of stent thrombosis, the risk of bleeding associated with long-term clopidogrel and the risk of in-stent restenosis.[43]

CONCLUSION

Stent thrombosis occurs at a very low, but clinically significant increased rate with drug-eluting stents compared with bare metal stents. Optimal use of drug eluting stents will be based on the risks and benefits to individual patients, and cost effectiveness will be increased.

Use of drug-eluting stents in high-risk patients should be limited until prospective, randomized trials give data on their efficacy in such situations.

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Efficacy of Trastuzumab as a single agent and combined with Paclitaxel or Docetaxel as treatment for HER2-positive breast cancer

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ABSTRACT

Breast cancer is a significant health condition in New Zealand; it is the most frequent cancer registration for females and contributes the largest proportion of female cancer deaths. Trastuzumab (Herceptin) has been proven to be an effective single agent against HER2-positive breast cancer showing a 26% response rate. More recently it has been shown that combining trastuzumab with chemotherapeutic agents such as docetaxel or paclitaxel (both taxane drugs) has an even greater effect with response rates of 61% and 36% respectively at one-year follow-up. Although trastuzumab does not usually show the adverse effects associated with chemotherapy it can cause cardiotoxicity although this can usually be reversed with careful management while continuing trastuzumab treatment. For New Zealand's HER2-posistive breast cancer patients Pharmac has decided to fund nine weeks of trastuzumab treatment combined with docetaxel.

INTRODUCTION

Breast cancer is the most common cancer for females comprising approximately a third of the total cancer registrations in New Zealand, second only to prostate cancer[1]. In 2003, 2325 women were diagnosed with breast cancer, accounting for 27% of female cancer registrations, and 647 women died[1]. The 2003 age-standardised registration rate for breast cancer was 81.5 per 100,000 female population, and this was 5.3% greater than the 1995 rate, but 8.4% less than the peak that occurred in 2000. The 2003 age-standardised mortality rate (20.7 per 100,000 female population) was 16.7% lower than in 1995[1].

Human epidermal growth factor receptor 2, known as cErbB2 or HER2, is one of four transmembrane tyrosine kinase receptors that mediate growth, survival and differentiation of cells[2]. The HER2 gene is amplified or the receptor over-expressed in approximately 15-25% of breast cancers[3], which is associated with aggressive tumour growth and a poor clinical outcome: shorter survival and decreased time to relapse[2,4]. This is because the over-expression of HER2 is an early pathogenic event in breast cancer and can lead to malignant transformation[5].

Trastuzumab is a recombinant monoclonal antibody that was developed from a murine antibody. The antibody is now 95% humanized to avoid patients developing neutralising antibodies against a murine protein. Trastuzumab has been developed to bind to the extracellular domain of HER2 expressed on cells. This causes a down-regulation of the p185ErbB2 protein and subsequent inhibition of downstream signalling, eventually leading to inhibition of ErbB2 cleavage and consequently decreased growth effects[6]. Thus Trastuzumab acts as an antagonist of Her2, inhibiting the growth-stimulating properties of the over-expressed HER2 protein and can stimulate antibody-dependent, cell-mediated responses[2]. Trastuzumab has been shown to produce a modest response as a single agent and impressive efficacy in combination with cytotoxic agent[6].

The biology of HER2 and trastuzumab

HER2-positive breast cancer is usually associated with increased expression of the anti-apoptosis protein Mcl-1, a member of the Bcl-2 family and is associated with survival of haematopoietic stem cells and lymphocytes. ErbB2-expressing cells upregulate the Mcl-1 protein and so these breast cancer cells are less likely to undergo programmed cell suicide[4]. With trastuzumab treatment this HER2 expression is reduced, corresponding to an increased sensitivity in these cells to apoptosis.

Nagata et al. (2004) investigated the effects that trastuzumab had on PTEN, an important protein in tumour suppression. PTEN is a phosphatase enzyme that is crucial in the recruitment of Akt activity. Akt is constitutively activated in HER2 overexpressing cells and is involved in tumour growth; PTEN expression inhibits Akt activity and therefore acts to limit tumour formation and growth[6].

Trastuzumab activates PTEN in breast cancer cells and this leads to rapid Akt dephosphorylation, contributing to the drugs antiproliferative effects[6]. PTEN deficiency was associated with a poor response to trastuzumab-based therapies, and so may be a useful predictor for resistance to this treatment. PTEN deficiency has been found in approximately 50% of breast cancers[6].

Trastuzumab as a single agent

Trastuzumab was shown to benefit patients with HER2 gene amplification in early phase I and II trials. Phase I trials assess the maximum tolerated dose and toxicity whereas phase II trials look primarily at efficacy and further evaluate toxicity. The efficacy of a chemotherapy regime can be measured using objective response rates (ORR), a combination of complete responses and partial responses. A complete response is the disappearance of all known disease for more than four weeks, and partial responses are considered to be a decrease in the sum of the perpendicular diameters of the present lesions of greater than 50% for more than four weeks with no new lesions. It is important to note that efficacy is more than just ORR, it also involves important aspects such as overall survival, quality of life and progression-free survival.

Vogel et al. (2002) investigated the efficacy of trastuzumab as a single agent and found an overall response rate of 26%[3]. Trastuzumab was found to be well tolerated, and was most effective when used to treat tumours that were more advanced. HER2 status was evaluated by immuno-histochemistry (IHC); a strong positive result (3+) is when greater than 10% of cells have complete membrane staining, reflecting an over-expression of the HER2 receptor[3]. If at least a moderate result (2+ or higher) was seen in IHC, Fluorescence In Situ Hybridization (FISH) analysis is used to look for gene amplification, this is the "gold standard" and would be checked in women before treatment was given.

Trastuzumab in combination with other cytotoxic agents

Trastuzumab is more effective in killing the cancer cells when combined with drugs that promote apoptosis. Trastuzumab treatment combined with a chemotherapy agent, for example paclitaxel, has a synergistic apoptotic response that involves inhibition of cell survival signalling pathways such as the Akt pathway[4,5,6]. This inhibition leads to a decrease in the expression of Mcl-1 protein thus rendering the cancer cell more vulnerable to apoptosis. Using cell culture techniques, studies showed that trastuzumab could increase apoptosis to between 30-40%[4].

Slamon et al. (2001) carried out a randomised controlled trial (RCT) that compared standard chemotherapy alone with trastuzumab combined with standard chemotherapy. The chemotherapy was paclitaxel unless the patient had never had any treatment before in which case it was doxorubicin. The trial randomised 234 patients to the standard chemotherapy regimen and 235 patients to the combination group[4]. The results (see Table 1) showed a large difference in overall survival (OS): the standard chemotherapy group had a median overall survival of eighteen months whereas the combination group was twenty-five months[7]. The striking difference in OS highlights the benefits from combining trastuzumab with paclitaxel when treating HER2-positive breast cancer[7].

More recently, Robert et al. (2006) built on the research by Slamon et al. by combining trastuzumab with paclitaxel (TP) treatment and compared it to the combination of trastuzumab, paclitaxel and carboplatin (TPC). The combination of paclitaxel and carboplatin has been used previously to treat solid tumours but is not used generally as a standard treatment for breast cancer[8]. In a multicentre phase III RCT, 196 women with tumours graded 2+ or 3+ for HER2 through IHC were assigned to receive either six cycles of TP or TPC.

The overall response rate for TP was 36% whereas the TPC regime was 59%, suggesting that carboplatin, a platinum agent, has an additive effect[8]. The TPC treatment resulted in improved progression-free survival (PFS) of thirteen months compared to eleven months for the TP group (see Table 1)[8].

Docetaxel, like paclitaxel, is a taxane and disrupts the microtubule functioning of a cell, thus limiting cell division. Clinical trials have shown a synergistic effect between trastuzumab and docetaxel[9]. Marty et al. (2005) conducted a multinational RCT comparing the response to docetaxel-only treatment against docetaxel and trastuzumab. A total of 188 women were randomly assigned into one of the two non-blinded groups; after 2 women dropped out of the study there were 94 in the docetaxel only group and 92 in the combination. This study showed an overall response rate of 61% in the trastuzumab/docetaxel regime compared to 34% in the docetaxel group (for further trial results see Table 1). After sensitivity analysis there was still a significant difference between the two treatment groups, where median progression-free survival was 31 months for the combination therapy, 8.5 months longer than the single therapy regimen[9].

The increased benefit in combining trastuzumab with docetaxel for HER2-positive breast cancers is similar to combining paclitaxel and trastuzumab, which is expected given they have similar mechanisms of action. Results from the separate trials are not directly comparable as there were different specifications set on eligibility of the women participating and what prior treatment they had received for their cancer. The size of each study on the efficacy of various combinations of HER2-positive breast cancer treatment was relatively small; greater certainty about the effect of treatments can be achieved through larger studies. However it may be unethical to randomise women to an observation-only course of treatment when studies completed so far have shown consistency in their results with trastuzumab treatment. Meta-analysis can be used to pool results of small trials, accepting that these may have different methods and eligibility criteria.

Baselga et al. (2006) pooled the data from four major adjuvant trials with a total population of over 13,000 women with HER2-positive breast cancer. Adjuvant therapy refers to additional treatment, usually given after surgery where all detectable disease has been removed, but where there remains a statistical risk of relapse due to disease that is not readily detectable. The pooled data were from the Herceptin adjuvant trial group (HERA), National Surgical Adjuvant Breast and Bowel project (NSABP), North Central Cancer Treatment Group (NCCTG) and the Breast Cancer International Research group (BCIRG). The analysis carried out on this population showed that patients treated with trastuzumab had a lower rate of 46-52% in risk of an event; relapse of distant metastasis, as compared to observation only patients[10]. The overall analysis also showed that the benefit seen was similar over the trials despite differences in chemotherapy regimes, sequencing of agents and patient populations. In the HERA trial, the hazard ratio for the risk of death with trastuzumab compared with observation alone was 0.66, which means there was a decreased risk of death by 34%, also an absolute disease-free survival benefit of 6.3% was seen at three years[11].

Safety of trastuzumab

Trastuzumab is a generally well-tolerated therapy and is not associated with the typical adverse effects from chemotherapies such as alopecia, myelosuppression or vomiting[6,10]. On the other hand, adverse effects such as chills, pyrexia, fatigue and headaches have been associated with trastuzumab and are more common at higher doses6. Cardiotoxicity is one of the most serious adverse effects of trastuzumab and was reported in 2-5% of women who received this as a single agent, however this was not indicated by preclinical or phase I studies[2,5,6]. An independent cardiac review committee performing retrospective analysis on a number of phase II and III trials found that increasing age and the combination of trastuzumab with an anthracycline, such as doxorubicin (which inhibits DNA and RNA synthesis) lead to a higher risk of cardiotoxicity[10]. Many hypotheses have been proposed to explain the cardiotoxicity seen with trastuzumab. These have included interactions between drugs, immune-mediated destruction of cardiomyocytes induced by the chemotherapy or the fact that the HER2 receptor is expressed on myocardium[12]. Most patients who develop any form of cardiac dysfunction are asymptomatic and there is a high level of reversibility of symptoms and left ventricle dysfunction[3,6,13]. Rates of trastuzumab discontinuation due to cardiac effects have been found to be low, less than 5%[11] however this should be the course of action if a patient develops congestive heart failure (CHF).

The pooled analysis of the four major adjuvant trials also looked at the incidence of cardiac events and found that they remained within acceptable levels. However, there was a higher incidence of CHF, as high as 3.3%, though this mostly responded well to treatment[10]. In the HERA analysis, at a one year follow up symptomatic CHF occurred in 1.7% of patients in the trastuzumab group compared to 0.06% in the non-trastuzumab patients receiving observation[10]. There has been no evidence of an increase in cumulative cardiotoxicity over one year, which is encouraging[11].

Most studies that investigated the efficacy of trastuzumab excluded women with a history of many cardiovascular conditions. This means that the effectiveness of trastuzumab in women with a pre-existing heart condition is unknown and it would be inadvisable to prescribe trastuzumab to this group of breast cancer patients.

CONCLUSION

There is no doubt that trastuzumab has improved the treatment of HER2-positive breast cancer patients, even though they are a minority of the total number of women with breast cancer. It improves the efficacy of

Study	Therapy regimen	Study size	Overall Response Rate	Overall Survival (median)
Vogel et al. (2002)	trastuzumab	114	26 %	24.4 months
Robert et al. (2006)	trastuzumab + paclitaxel trastuzumab + paclitaxel + carboplatin	98 98	36 % 52 %	32.2 months 35.7 months
Marty et al. (2005)	trastuzumab + docetaxel docetaxel	92 94	61 % 34 %	31.2 months 22.7 months
Slamon et al. (2001)	standard chemotherapy standard chemotherapy + trastuzumab	234 235	32% 50%	20.3 months 25.1 months

Table 1. Results of clinical studies on trastuzumab efficiency as a single agent and in combination with other therapies.

chemotherapy in this patient group with little additional toxicity, and represents a highly significant clinical advance in the care of women with breast cancer, however, it may not be appropriate for all patients because of existing cardiac morbidity.

Trastuzumab is effective on its own but combining it with another form of chemotherapy appears to have a greater benefit. In particular, trastuzumab used in conjunction with a taxane chemotherapy agent such as paclitaxel or docetaxel produces increased efficacy. This is most likely due to the favourable interaction that occurs between trastuzumab and the chemotherapy agent used. Trastuzumab treatment for a twelve-month period has been proven to have survival benefits in a significant proportion of women. However, more research into shorter treatment regimes, such as is being offered to breast cancer patients in New Zealand, may need to be completed to evaluate its efficacy. Nevertheless, there is definitely evidence to suggest that effective use of new developments such as trastuzumab will further reduce breast cancer deaths in New Zealand.

When advising a patient about trastuzumab, every case needs to be considered individually, but for many patients it seems likely that the efficacy of the treatment will outweigh the adverse effects associated. Eligibility of patients for trastuzumab treatment depends heavily on their cardiac function i.e. patients should have a left ventricular ejection fraction of at least 55%. Careful monitoring of each patient's cardiac function is necessary when being treated with trastuzumab and care should be taken in the event of developing adverse reactions. It is important to take into account that the addition of a second agent such as docetaxel or paclitaxel to trastuzumab will most likely increase the adverse effects. These include the more traditional adverse effects linked with chemotherapy such as alopecia, nausea and vomiting and would need to be taken into account when discussing treatment options that involve trastuzumab combination therapy for effective patient care.

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A guide for medical students: examining the eye in infants and young children

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INTRODUCTION

Infants and young children can be difficult to examine and this is particularly true when trying to assess vision and look in detail at the eye! In this article a few basic examination techniques are described with the aim of helping you identify a problem with a child's vision.

Vision develops rapidly in the first two years of life and then continues to 'fine tune' until about the age of 7-9 years. Thus, early detection of visual problems is vital so that children have the best chance of achieving their maximum potential vision.

The timing of the examination of a developing child is important and dictates the type of assessment performed. Ideally, the child should be examined during the newborn period (before 6 weeks), at 3 months and at 6 months. Examinations outside of these times are also performed if there are any concerns regarding visual development. Formal visual acuity evaluations should begin at 3 years. However, this must be tailored to he child's level of co-operation. Children of any age seen in the eye clinic will have a formal visual acuity with kay picture cards or letter matching tests e.g. Sheridan Gardiner. From 5 years on most children will be able to cooperate with a recognition (letter) optotype test such as the Snellen Chart. Refraction (usually by an optometrist) and ophthalmoscopy should also be possible. After this children should ideally have an eye examination every 2 years.

Generally, all eye examinations should include an external inspection of the eyes, a test for visual acuity (which is dependent on age), assessment of ocular motility, muscle imbalance, stereopsis and ophthalmoscopy. At a specialist hospital eye service a refraction (test for glasses) is also performed.

You will get the best from children if they are comfortable, relaxed and well at the time of examination. Trying to deal with irritable, upset children is guaranteed to exhaust you by the end of clinic. Below, we discuss the methods used to assess children under 5 years of age.

AN AGE SPECIFIC GUIDE TO CLINICAL EXAMINATION

Newborns- 2 years

Firstly, conduct an external inspection of the eyelids and orbits - Are they symmetrical and structurally normal? Do the lids close properly? Can he/she open their eyes? Generally neonates/young infants open their eyes when held upright or leaned slightly forward. Is there any evidence of a lid mass, discoloration or proptosis? Are the lids droopy? If so, do they obscure the visual axis and risk the development of amblyopia.

Often most of this information is gained through observing the child whilst talking to the parents. It is also useful to note if the child is interacting with the environment, fixing and following and making eye contact. Most of the examination is usually opportunistic- often loosing the opportunity when you try to formally examine the eyes.

To test visual acuity use a toy to see if the child can fix and follow it (an interesting brightly coloured toy often helps). The smaller the toy the child can see, the better the vision (although this is a very crude test). Another gross test of visual acuity involves using 'hundreds and thousands'. If the child is able to see and pick up the small sweets at 33cm the visual acuity is at least 6/24.

There are other tests available which are usually performed by orthoptists e.g. preferential looking tests using Cardiff acuity cards/Lea Grating cards. These tests involve shapes with variable outlines and black stripes of varying thickness respectively. If the child looks up or down (depending on where the picture is placed on the card) it is apparent to the observer that the child can see the object. High frequency (thin lines) and shapes with a thin outline are harder to see and an assessment of visual acuity is made accordingly (see figures 1, 2 and 3 below).

Figure 1: Cardiff acuity cards. The figures illustrate the outlines of the shapes. The finer the outline the more difficult it is to see the shape.

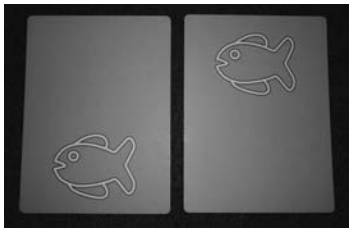

Figure 2: The cards also have images placed inferiorly so that the tester can be sure that the child has seen the image by tracking the child's eye movement.

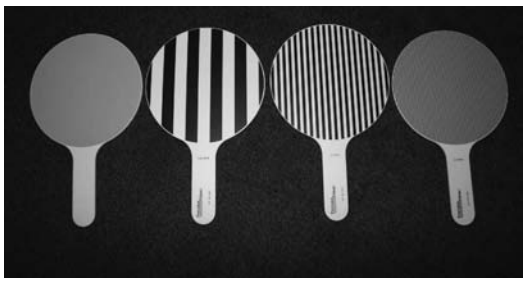

Figure 3: Lea grating cards

It is important to cover either eye with your hand (one eye at a time) to see if the child objects. Try to see if they can fix and follow the toy with the uncovered eye. If there is poor vision in one eye the child may try to pull themselves away when their good eye is covered. This is known as 'objection to occlusion'.

Use a torch and loupes (magnifier) to look at the conjunctiva, sclera, cornea and iris. Is one cornea larger or smaller compared to the other? Are they both clear? Cloudy corneas can be a sign of congenital glaucoma and also other ocular conditions. Look at the pupil and test the pupil reflexes- are they round? Are they equal in size? Do they react equally to light? (a good mnemonic to remember is 'PERLA': Pupils Equal and Reactive to Light and Accommodation).

In order to assess the alignment of the eyes you can shine a torch light onto the cornea and observe the reflections produced in both eyes. Asymmetry of the reflections may indicate a squint is present - this is known as the Hirschberg test.

Testing ocular motility and vision can be hard in young children! Ocular motility is tested by trying to get the child to follow a target such as a pen torch or a toy and moving into the different positions of gaze whilst keeping the head steady. This can be achieved by playing with the child and taking the opportunity to move the toy into different positions of gaze whilst keeping the head still.

Finally, see if you can obtain a red reflex with an ophthalmoscope and compare the reflex you see in each eye. The reflex should be red and equal in both eyes. If no red reflex is seen, this can be an indication to the presence of cataracts, retinoblastoma or other childhood eye diseases. You may be able to see if any obvious cataract is present with the ophthalmoscope.

2-4 years of age

A visual acuity should be obtained by 3 years of age at the latest. If this is not possible repeat again 4-6 months later. If this is unsuccessful then a referral to an orthoptist or ophthalmologist is warranted.

Many of the above principles also apply to this age group. A range of specialist picture-matching tests are available to test visual acuity (This is usually possible from around 2.5 years of age). Deciding which one to use depends on the capability of the child. Different tests are available for children who are older but unable to read letters or numbers. Examples include the tumbling E chart (see figure 4).

5 years and older

All the techniques previously discussed should be performed. Almost all children should be able to read a recognition letter chart and therefore have a formal vision test. Most children of this age are co-operative with ophthalmoscopy and refraction.

All children above the age of 6 months should ideally have an assessment of stereopsis. There are many different tests available to measure stereopsis, each varying in the degree of stereopsis they measure. These tests are usually performed by an orthoptist.

1. Never forget that a good history is vital and should include family history, consanguinity, birth history, information regarding the mother's condition during pregnancy and any problems encountered.

2. If a child wears glasses test their visual acuity and eye movements with their glasses on.

3. At the start of the examination introduce yourself, be friendly and try to 'win' them onto your side by, for example, chatting about their clothing/how old they are, where they go to school etc.

4. During the ophthalmosocpy examination make sure both eyes are kept open (this makes the examination easier as otherwise the open eye rolls upwards)

5. Try to keep them at ease by asking their age/favourite colour etc. Don't be afraid to be a little bit silly! Although too much noise may be somewhat distracting!

IMPORTANT EYE CONDITIONS

What are you looking for?

Carrying out the assessments well is important but it is important to be clear about what you are looking for.

Many conditions (a few of these are discussed below) need to be picked up early in order to ensure the child has the best chance of developing a 'normal' or near normal visual system. This not only means good visual acuity but also other visual functions such as using both eyes together to give good binocular vision and depth perception.

Congenital cataracts (see figure 5) - Many congenital cataracts are familial (Autosomal Dominant, Autosomal Recessive or X Linked). However, some congenital cataracts are associated with a variety of systemic disorders. Therefore, children with congenital cataracts usually need assessment by a paediatrician as well as an ophthalmologist. Cataracts may occur with some metabolic disorders. The infantile onset cataracts seen in galactosaemia may reverse with dietary manipulation. Other causes of congenital cataracts include chromosomal disorders such as Downs syndrome and congenital infections (Toxoplasmosis, rubella, herpes simplex/ varicella, Cytomegalovirus (CMV); a helpful mnemonic to remember these infections is TORCH). The finding of a cataract in a child requires prompt referral, for example a cataract found in the first year of life needs to be removed as soon as can be practicably achieved.

Strabismus ('Squints') - Strabismus is a misalignment of the two eyes so that the eyes are not looking in the same direction. This misalignment may be constant or intermittent. An esotropia or convergent strabismus (the most common type of strabismus in children) is an inward turn of the eye (see figure 6). Exotropia (Divergent Strabismus) is an outward turn of the eye (see figure 7). Vertical strabismus is less common but may arise in conjunction with a horizontal strabismus. (In hypotropia the non-fixing eye is lower than the fixing eye and in hypertropia the affected eye is higher).

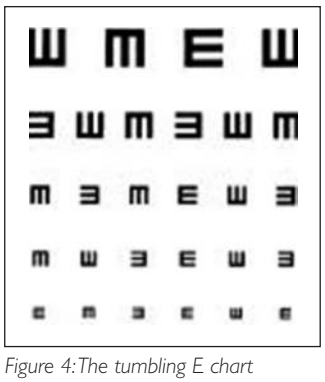

Figure 4: The tumbling E chart

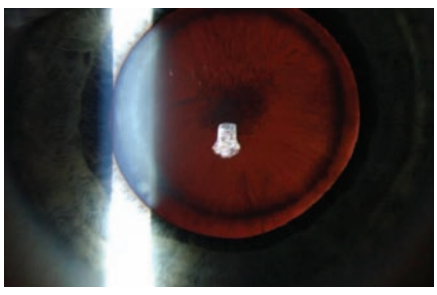

Figure 5: Congenital cataract

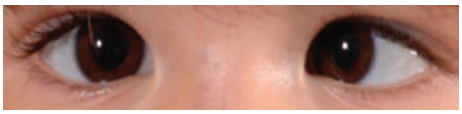

Figure 6: Left Esotropia (also note the epicanthal folds)

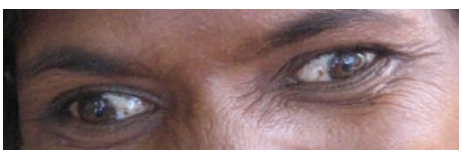

Figure 7: Left Exotropia (the fixating eye is the right eye)

There are many causes for strabismus. Refractive error (the need for glasses), either long-sightedness (hypermetopic accommodative) or a difference in focus between the two eyes (anisometropia) may cause strabismus. Other ocular pathology may lead to 'sensory' strabismus. This ocular pathology may affect any of the structures in the eye from the cornea through to the retina. Thus as strabismus may be a symptom of a more serious underlying cause, it is vital all children with a misalignment of the eyes have an comprehensive eye examination. However, most strabismus is not associated with serious eye disease, but this must be excluded.

If one eye doesn't see as well as the other, referral to the ophthalmologist is warranted. Treatment is often initiated in the form of occlusion or 'patching' (this treatment involves literally wearing a patch over the good eye) and/or wearing glasses. Patching the good eye encourages the eye with poorer vision to be used and therefore the visual function in this eye to 'catch up'. Regular orthoptic checks are done to ensure that the amblyopic eye improves. Loss of vision in the patched eye is very rare. It is important that parents understand this concept and thus encourage the child to wear the patch. The potential transferability of the visual system is greater the younger the child. The brain becomes more 'hard wired' as the child becomes older. Thus younger children have the best chance of gaining visual function after patching treatment is started.

Glasses - If a child has a visually significant refractive error they should be prescribed glasses and encouraged to wear them. The child's parents should understand the importance of this so they in turn can reinforce wearing the glasses as recommended. Not wearing the appropriate prescribed spectacles can itself lead to amblyopia. The need for glasses may be indicated by reduced acuity, onset of strabismus/squint or visual discomfort (asthenopia). A difference in the refractive error (need for glasses) between the two eyes (anisometropia) can also be an important cause of amblyopia.

Retinoblastoma - this is a rare childhood cancer of the retina. It can manifest in many ways, but most frequently as a white pupillary reflex, a squint, poor vision or rarely pain in the eye. This is a serious condition which requires urgent treatment. It has implications for the family should they plan further children and also implications for the child when they come to having a family. Children with this condition are managed in specialist units by a paediatric ophthalmologist, oncology and genetics teams.

The signs below should alert you that there is an ocular condition which needs further assessment.

Infants and toddlers (up to age 2):

- Jerky eye movements (Nystagmus) - you may be able to see fine movements of the eyes, these may be worse in a particular gaze.
- Eye turn, squint - this is very important and should not be overlooked. Any strabismus is abnormal after 3 months.
- One pupil larger than the other (or smaller)
- Droopy eyelid
- Closes or covers one eye
- Head tilts or head turn
- Red eyes/discharge
- Watery eyes
- Shies away from light/ keeps eyes closed
- No interest in visual stimuli
- Delayed development in other areas (speech, hearing, not grasping/reaching for objects)
- Poor hand-eye coordination

Children: 2-5 years:

- Eye turn, squint- again this should not be overlooked.
- Persistent rubbing of eyes
- Red rimmed eye lids
- Covers or closes eyes when looking at objects
- Avoids reading/puzzles (activities where clear vision is needed)
- Headaches

At risk children include:

- Premature babies
- Family history of glasses, patching, pre-school eye problems, lazy eye, surgery
- Low birth weight babies
- Special needs children

There are many other eye diseases manifesting in children that may cause poor vision or lead to blindness (such as childhood glaucoma) but due to the brief nature of this article they will not be discussed here. We recommend that a more extensive ophthalmology text is referred to, if further information is required.

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Observational study of the effect of elevated extra-cellular potassium chloride level on the differentiation of PC12 cells towards neuron-like cells.

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ABSTRACT

The nervous and endocrine systems are connected together. Chromaffin cells in the adrenal medulla display neuro-endocrine features as they secrete biological signals (hormones) in response to neuronal stimuli. Biological signals that stimulate the development of neuro-endocrine function have yet to be fully elucidated. This observational study tests the effect of depolarizing cellular membrane on the development of neuron-like cells from a population of undifferentiated PC12 cells. In this study the depolarization effect is achieved by elevated extra-cellular KCl which is a good inducer of PC12 differentiation towards neuron-like cells.

Key words

PC12, differentiation, KCl

INTRODUCTION

The human endocrine and nervous systems are interconnected and integrated together. Body organs which have both nervous and endocrine functions are the connection points between the two systems (nervous vs. endocrine) such as the adrenal gland. The adrenal medulla is thought to evolve from the nervous system and that explains why it retains some nervous functions[1] Thus, precursor cells of the adrenal medulla theoretically can differentiate into neuron-like cells or endocrine cells or a combination of both (neuro-endocrine cells). The Chromaffin cells of the adrenal medulla are neuro-endocrine cells that have they ability to receive nervous input and respond by releasing endocrine factors (hormones).

Better understanding of the complex biological mechanisms behind the development of cells from this type holds promise for future treatment of neuro-degenerative diseases such as Parkinson's disease and many other endocrine disorders such as phaeochromocytomas (tumors of adrenal gland). The factors that switch on Chromaffin cell development are not fully understood and the signaling pathways of Chromaffin cells are still to be filled. Research groups have used a cell-line from a phaeochromocytoma (PC12 cells) as a model to study neuro-endocrine cell development.

PC12 cells were derived from a rat phaeochromocytoma (adrenal gland medulla tumor) in 1976 by Greene and Tichler[2]. This line of cells is able to proliferate, divide limitlessly and avoid apoptosis untill they receive a stimulus that directs their differentiation and hence limiting their division and eventually inducing apoptosis. Furthermore, it has been used extensively in neural development studies because it has the ability to differentiate into neuron-like cells in response to external stimuli and its differentiation is detected by morphological changes. PC12 cells respond to external factors by differentiating either into endocrine-like cells or neuron-like cells. Many studies have shown that neuron-like differentiation of PC12 can be achieved by nerve growth factor (NGF) and forskolin[3]. On the other hand, endocrine-like differentiation occurs in response to glucocorticoids[3]. Morphological changes including neurite outgrowth index the differentiation of PC12 into neuron-like cells. Biological substances that control and initiate cellular differentiation of PC12 are still not fully recognized. It seems that most of these substances work co-operatively with other mechanisms in a network of pathways to switch on the cellular differentiation process. The broad goal of this research project is to examine the combinations of biological substances that will give optimal stimulation of PC12 differentiation into neuron-like cells. Many studies have suggested that elevated extracellular potassium chloride (KCL) is involved in neural differentiation via wide mechanisms and pathways[3-10]. Based on those studies, KCL is selected to be the start point biological factor that is examined in this short research. In other words, the main variable in this project is the extracellular level of KCL. Neurite outgrowth was used as an index to indicate the differentiation of PC12 towards neuron-like cells. This project provides the first step in formulating a powerful stimulant that drives PC12 neural differentiation and explores the role of KCL on neural differentiation.

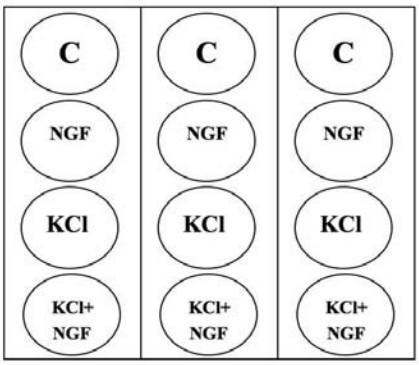
METHODS

Frozen PC12 stocks were used as a source of PC12 cells for this project. The cell culture medium was RPMI complete medium, which contains 5% fetal bovine serum (FBS), 10% horse serum(HS) and the antibiotics streptomycin and penicillin. Untreated PC12 cells were cultured in collagen-coated plastic plates for four days to allow the cells to double in number. During these four days, cells were incubated in a controlled environment with 37°C and 5% CO2 with regular removal of detached cells(dead cells). After this multiplication period, PC12 cells were sub-cultured into smaller collagen-coated wells and were treated immediately.

PC12 treatment

The first row of cells were treated with nerve growth factor(NGF) only, at a concentration of 50 ng/ml and the second row of cells with KCl only at concentration of 50 mmol/l and the third row with both agents. One row was left without treatment to act as the control. The treatments were added immediately after the subculture procedure. The treated cells were incubated for 96 hours with regular maintenance of the culture medium. This was done by the removal of 1ml of RPMI with detached cells and replaced with fresh RPMI in a daily basis.

On the 4th day of treatment, cells were processed for immunohistochemistry. First they were fixed using cold 100% methanol, then stained for total tyrosine hydroxylase enzyme using a specific monoclonal antibody (TH318 from Chemicon). In a replicated experiment, cells were stained for beta-actin protein. Immunohistochemistry enabled the visualization of the cells with microscopy and the evaluation of the morphological changes accordingly. The staining process clarified the difference between the KCl treatment and NGF treatment.



Observations

During the first 24 hours of treatment, there were not many noticeable morphological changes in the PC12 cells. However, one important observation was that the division process of PC12 cells with KCl only, NGF only and KCl/NGF treatment was reduced compared to the control cells. The culture medium became orange-yellow in colour indicating that metabolic activity was occuring. On the 2nd day of treatment, some neurite outgrowth appeared in these three treatments. PC12 cells treated with KCl appeared to be flat with undefined shape while PC12 cells treated with NGF were more spherical. During the third day, the difference in length of neuron-like processes of different treatments was very obvious. Cells treated with KCl and combination had web-like processes radiating in all directions. Furthermore, the number of processes from each cell treated with KCL and combination cells was far more than cells treated with NGF only. All the observations during the first three days were made using phase-contrast inverted-stage microscopy. Immunohistochemistry staining for TH and Beta-actin shows the clear difference between KCL treatment and NGF treatment in term of neurite outgrowth. Cells treated with combination of NGF and KCL had extensive neurite outgrowth ccompaerd to one treatment only(either NGF or KCL). In general, treated PC12 stained darker than untreated PC12.

DISCUSSION

This project supported many studies that have been done to investigate the key role of elevated KCL in neural development and PC12 differentiation. One possibility could be related to the depolarizing effect of KCl. That means the increase of KCl in the extra-cellular fluid encourages neuronal development of PC12 by triggering internal mechanisms that controls differentiation and neural development.

To begin with, scientific studies have suggested that elevated KCl exposure is time-dependant[5]. In this project, there was continuous exposure for three days which might explain the strong effect of KCL on cell differentiation. Other studies suggested that 6 hours daily exposure to elevated KCL for three days is sufficient to drive neural differentiation similar to the effect of continuous exposure[5]. In addition to exposure time, KCl effect is dependant on the stage of neural development. Experiments showed that neurons of petrosal ganglion (PG) developing during embryonic day 16 effected with elevated KCl more than neonatal PG[5]. It is hard to estimate at which stage the PC12 cells used in this project were first extracted to evaluate the observed effect. However, the response to elevated KCl indicated that they were more likely to be at early embryonic state.

One possible mechanism is the role of KCl in the control of trans-membrane calcium channels which are known for their differentiation and apoptotic effects by switching on the expression of genes that are involved in[5-9]. That means KCl controls the opening and closing of Ca2+ channels and thus the influx of Ca2+ to the cytoplasm of neural cells. The use of L-channels inhibitory molecules such as Nifedipine caused the loss of differentiation even with higher doses of stimulating KCL in the extracellular environment[9]. In another study, the use of selective K1+ blocker(Tetra-ethyl ammonium) which blocks Kv1.3 and Kv3.1 trans-membrane channels showed increased proliferation of neural progenitor cells(NPGs) and loss of differentiation process[8]. This gave first signs that KCl is a key controller of neural differentiation in many cell lines including PC12.

The genetic expression that is turned on by KCl induction involves very complex pathways and neuroscientists just start to appreciate its complexity.

One well established pathway is the Mitogen-activated protein kinase and extracellular signal-regulated kinase pathway (MAPK/ERK pathway). Both MAPK and ERK are activated by elevated KCL in the extracellular fluid. Activated MAPK and ERK drive the activation of G-proteins Ras and Rap1 via protein kinase (PKA)-dependant mechanisms[11]. The use of MAPK inhibitor (PD98059) and ERK inhibitor (H89) showed loss of KCL effect on the neural differentiation and disappearance of neurite outgrowth[6]. The end result of this pathway is the expression of genes that control neural differentiation.

The genes which are activated by MAPK/ERK pathway are not all known. One possible gene that is switched on by the KCL-sensitive MAPK/ERK pathway is NID67 which is discovered using representational difference analysis. This gene seems to be a differentiation primary response gene which is induced by elevated KCL[9]. The function of NID67 gene is not fully understood but it controls the expression of K-sensitive trans-membrane channels which controls Ca2+ ionic influx[9].

Another gene that is switch on by KCL-induced differentiation is Hst8Sia III. This gene controls the expression of Beta-tubulinIII which is a main component of neurite processes[12]. This might explain the longer processes induced by elevated KCL in PC12 cells.

One interesting point about KCL-induced neural-like PC12 is that, the cells stayed sensitized to subsequent exposure up to one week after the removal of KCL from the extracellular environment. Furthermore, a study used tyrosine hydroxylase (TH) expression as marker for neural differentiation of PC12 showed that pre-exposed PC12 cells showed four folds increased TH expression than 1st time exposed cells[5,6].

CONCLUSION

While this project was limited in scope, it gives a good starting point for further biomedical research. For future research, it would be useful to use biochemical analysis such as Western-blotting to test the effect of KCl treatment on neuron specific markers such as beta-tubullinIII, synapsin I and neuron-specific enolase (NSE). Also, it would be a future project focus to be able to culture PC12 on cover slips and use immune-florescent staining to visualize different proteins at one time.

Some limitations of this short project are the difficulty of growing PC12 cells and also the competence of PC12 to represent actual neuron-like cells is still in question.

There are many questions still to be answered about the role of KCl on cellular and tissue development and many neural differentiation pathways to be filled in.

ACKNOWLEDGMENT

I would like to thank Dr Stephen Bunn for this great opportunity to work in his laboratory and his continuous support. Also, I would like to thank Mrs Maureen Buchan and Mrs Shirley Douglas for their technical support.

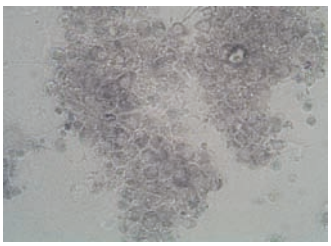


Figure 1: PC12 cells before treatment (phase contrast)

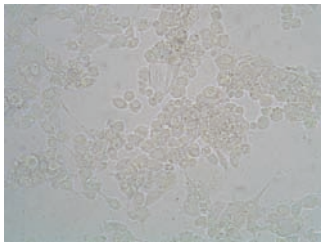


Figure 2: PC12 cells with NGF day two (phase contrast)

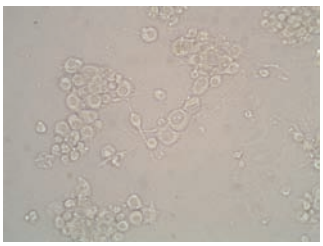


Figure 3: PC12 cells with KCL day two (phase contrast)

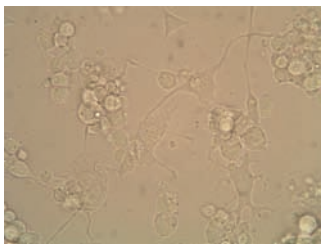


Figure 4: PC12 cells with KCL+NGF day two (phase contrast)

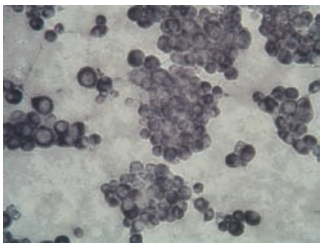


Figure 5: untreated PC12 stained for TH day four

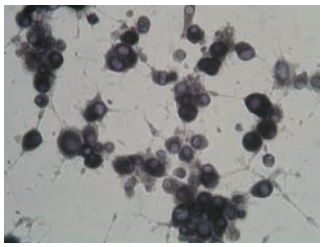


Figure 6: PC12 cells with NGF stained for TH day four

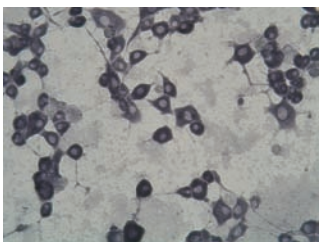


Figure 7: PC12 cells with KCL stained for TH day four

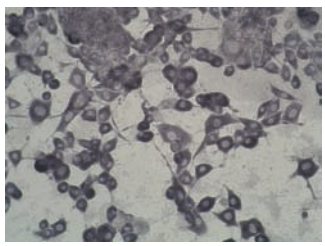


Figure 8: PC12 cells with KCL+NGF stained for TH day four

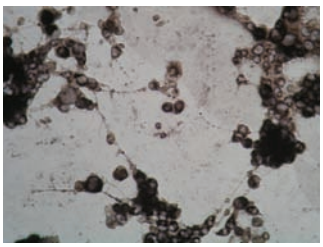


Figure 9: PC12 cells with KCL stained for beta-actin day four

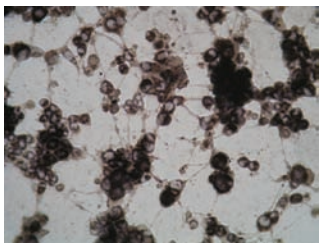


Figure 10: PC12 cells with KCL+NGF stained for beta-actin day four

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HealtheX

The inaugural exposition celebrating student research

Divya Dhar
Fifth Year Medical Student
Auckland School of Medicine
University of Auckland

Divya is studying medicine in Auckland was the chair of HealtheX 2007. She was also the driving force in organising this unique student research forum.

Event Synopsis

On Saturday 8th September 2007, over 90 students from the Faculty of Medical and Health Sciences at the University of Auckland got the chance to present their research in either oral or poster format to supervisors, family, friends and a panel of judges.

Vision

The vision for this conference went far beyond celebrating student research. It served to excite and inspire students in paving a pathway to revolutionise health care both in New Zealand and around the globe.

This event sought to pull together the multitude of threads involved in developing a truly world class health system, from developing the spatial configuration of a radical new drug, to formulating bold health policies that will shift the paradigm togiveyoung scientific minds the possibility to explore new passions and horizons.

HealtheX showcased discoveries, creations and innovations made by students from a diverse array of disciplines be it medical, pharmacy, nursing, biomedical sciences or population health. It presented a platform where both undergraduate and postgraduate students could gather under the same slogan of young budding researchers, providing opportunities for not only mentoring but, more importantly, camaraderie.

HealtheX is a celebration of the future face of health care and delivery.

In the next two to three years HealtheX hopes to expand by inviting student presenters from all around New Zealand.

Proceedings of the day

HealtheX was officially opened by the Dean of Medical and Health Sciences, Professor Iain Martin.

He was followed by the key note speaker Professor Robert Beaglehole who recently retired in his role as Director of Non-communicable Diseases and Health Promotion in the World Health Organization 2004-2007. Since his return to New Zealand he has been assisting the Parliamentary Select Committee on Obesity and Type 2 Diabetes acting as an international public health consultant. He is passionate about public health and especially the prevention of chronic diseases. Professor Beaglehole gave an inspiring address, encouraging students to examine the application and dissemination of research as a crucial, if not the most important part of research.

Over 50 students had qualified in the initial judging round to present their research in the oral format. These students then split into three morning and afternoon sessions run concurrently in the categories of Biomedical and Pharmaceutical, Population Health and Education, and Clinical research. At least two judges, both of whom were experts in that category of research were also present in the room. A moderator judge was asked to judge a couple of presentations in each session for scaling purposes.

Poster presentations were judged during the lunch hour where presenters were asked to stand by their posters in case judges had any questions.

The Roche Prizegiving ceremony was hosted by the Mayor of Auckland City, Dick Hubbard, who beganworking out of a small Onehunga factory with just two staff but is now the third biggest cereal company in New Zealand with a turnover of around $38 million per annum. Mayor Dick Hubbard gave an address on the 'Role of young

Key note speaker, Professor Robert Beaglehole.

Format	Place	Prize	Category and Winners		
Oral	1st	$750	*Biomedical and Pharmaceutical* Ursula Byrne	*Population Health and Education* Jennifer Utter	*Clinical* Amy Chan
	2nd	$250	*Biomedical and Pharmaceutical* Carthur Wan	*Population Health and Education* Serena Park	*Clinical* Catherine Bacon
Poster	1st	$750	*From all:* Group project: Megan Murphy, Hsin Yao Chang, Jae Young Han and Abir Ibrahim		
	2nd	$250	*From all:* Stefan Oehlers		
Grand Prize	Overall HealtheX Winner	$1000 additional	*From 1st prize winners in either Oral or Poster presentations* Amy Chan		

researchers in tomorrow's health' and presented HealtheX prizes including the Overall Grand Prize Trophy to Amy Chan.

Categories and Prize Winners

Presentations could be given in poster format, A0 size, or oral format, 10 minute Powerpoint with 5 minutes for questions. There were three categories for oral presentations: Biomedical and Pharmaceutical, Population Health and Education, and Clinical. Prizes were distributed accordingly.

Another 20 poster and 10 oral postgraduate presentations were selected to represent the Faculty of Medicine and Health Sciences at the university-wide postgraduate research competition, EXPOSURE.

Entertainment

All refreshments throughout the day were complimentary for presenters. Entertainment was provided by the Faculty of Medical and Health Sciences Strings music group which consists of staff and students from the FMHS 'self-contained' orchestra who played while the judges deliberated and the audience enjoyed a glass of wine and nibbles.

HealtheX Committee

The HealtheX committee convened a year ago consisting initially of a group of friends with a shared vision of hosting a prestigious conference which would enabled undergraduate students from all areas of health in Australasia to gather together. Early in the year of 2007 we went about seeking support for our proposal from the five Heads of Schools including Medicine, Pharmacy, Nursing, Biomedical Sciences and Population Health, as well as the Associate Dean of Research and Dean of Faculty of Medical and Health Sciences.

The vision for the conference evolved over this period to involve both undergraduate and postgraduate students in order to encourage mentorship, and to start small in the inaugural year by only involving University of Auckland students.

The committee consisted of both undergraduate and postgraduate students from all five schools and we werefortunate to also have the support of very passionate staff members of the FMHS - and a huge thank-you to the Committee!

Sponsors

HealtheX would not exist without the support of our sponsors. We would like to thank our Gold sponsors Maurice and Phyllis Paykel Trust, Roche Pharmaceuticals and Abacus ALS. Our silver sponsors Auckland Medical Research foundation and bio strategy. Our supporting sponsors Global Science online and Soar printing.

Conclusion

It is our hope that all medical students will have an interest in either conducting or being informed about research. It is undoubtedly an exciting pathway and as future leaders in health in our communities, we should constantly be seeking new hopes for our patients through research.

We received outstanding feedback and would like to thank everyone who helped make this event a spectacular success.

For further information or feedback please check out www.health.auckland.ac.nz/healthex or contact us at healthex-info@auckland.ac.nz

It has been encouraging to see the success of an idea that sprung from a conversation I had with a friend at the Australian Medical Students' Association's (AMSA) Leadership Development Seminar. Our shared passion led to the development of a research conference at our respective universities, University of Western Australia and University of Auckland and to witness its fruition was extremely rewarding. We would like to challenge you to follow your passions, wherever they may take you!

Mayor Dick Hubbard with Amy Chan, winner of the Grand Prize

The HealheX committee

Doctors creating change?

Aiming for prevention with small arms research

Jash Agraval
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National Co-ordinator
Medical Students for Global Awareness

Jash graduated from the University of Auckland Medical School at the end of 2007. Any correspondence about Medical Students for Global Awareness can be sent to jash_agraval@yahoo.co.nz or msga.nz@gmail.com

As medical students and future doctors, our role should not be limited to health related advocacy within our consultation rooms, but should be extended to social responsibility and awareness of both local and global issues. We have a powerful collective voice, a voice that is not seen to be politically biased or influenced by financial gain. Yet only a handful of practicing specialists seem to be using it. I represent a new group called Medical Students for Global Awareness. MSGA aims to foster interest and awareness about global health and peace issues amongst New Zealand medical students, creating a new generation of health professionals that collectively form a voice to better educate the public on global health issues and institute social change.

Our parent organization is International Physicians for the Prevention of Nuclear War, IPPNW. They are an organization that is dedicated to research, education and advocacy relevant to the prevention of nuclear war, demilitarization of conflict zones and creation of a climate of peace and stability. IPPNW is active in over 50 countries and has a strong network of members, which includes a global student arm. The organization was founded in 1980, inspired from the ashes of the cold war. In 1985 the organization was honored, and received the Nobel peace prize. It was commended for "considerable service to mankind by spreading authoritative information and in creating awareness of the catastrophic consequences of atomic warfare"[1]. IPPNW and its work is a great example of how doctors can create change. It is this spirit of awareness and action that MSGA promotes.

We aim to be an organization that is not limited to discussions of global health issues or how we can create change but one that actively involves students to make a difference. People may argue that small voices or small actions change nothing or create little difference, but we cannot continue to live in a world where people keep saying 'that's just the way it is'. The Tipping Point is a sociological term that describes this exact idea 'How little things can make a big difference'[2], the moment when something unusual becomes common due to a gradual increase in awareness and opinion. The Tipping point book[2] describes a 'bell curve' adaptation to new phenomena, in which one small voice becomes many and eventually tips to widespread social change. I recently heard a speaker who said "the next great superpower to combat the tyranny of some [unnamed] nations hold in the world, is the power of public opinion"[3].

The active participation of students is a key aim for MSGA, getting students involved in activities that have direct benefit to communities and have the potential to create social change. Whilst internationally we are isolated in geographical location, there is a strong culture amongst New Zealand medical students to go overseas for their electives. The kiwi spirit of adventure takes many of us to the third world and off the beaten track. Harnessing this elective travel experience gave birth to the small arms research project.

I am facilitating this project with the support of MSGA and IPPNW-Global. The project will enable New Zealand medical students to directly engage in preventing the harm caused by small arms.

Small arms, and the prevention of their use is a crucial objective for IPPNW[2]. Small arms warfare is rampant in many third world countries. The political unrest and instability in these countries makes it a necessary 'weapon' to use to get their respective governments to take notice and to incite fear in the population. Of the 49 major conflicts from 1990 to 2006, 47 of them involved small arms as the weapon of choice[4]. The problem is huge with 300,000 deaths a year and over 1 million injuries occurring as a direct result of small arms' use[5]. There are currently 639 million small arms in circulation, many of which are illegally held. Small arms trading is a lucrative business, the more illegal the transaction the higher the sums become and unfortunately in today's climate of violence, corruption and political instability the demand remains high. Annual global small arms trade is estimated at four billion US dollars[4,5]. Small arms and their illegal acquisition enable what is an otherwise small group of angry men to create devastating damage, incite fear in the population and hold whole cities at ransom. It was this exact situation that led to nine years of murder, conflict and fear in Bouganville - a country in our own back yard. This quote below is taken from a John Roughan a local NGO leader[6]. I believe he accurately describes this exact point.

"... A relatively small number of men are establishing a new way of acting.

An elective provides students with the unique opportunity to live and interact with peoples of different cultures in a way no tourist can ever do.

The gun and what is stands for - intimidation and power - is creating a society where the culture of violence rules."[6]

Corruption is a way of life for many government and other officials so the trafficking and supply of weapons into the country is often completely ignored. People are injured, maimed and killed every day, the issue becomes normal, and people come to accept small arms injuries and deaths as part of every day life often stating, 'it's just what happens'[5,7].

It is this attitude that we aim to change. The problem seems too big, too complex and too difficult to do anything about. Speeches, discussions, summits and protests often go unnoticed. What is needed is quantitative data, approaching the problem in a way that shows communities and leaders, both local and global, what small arms' warfare is doing to their people and economy.

The small arms project aims to look at the incidence of injuries, and to assess the health and economic impacts of them and the context in which they occur. I believe the application of this data can have far reaching consequences. Firstly, comparisons and contrasts can be made between different regions throughout the globe for example South East Asia with Eastern Africa, in terms of type of weapon available, their use and their respective supply. Secondly, I hope that the amount and quality of data present is powerful enough to lobby respective regional and local governments and make them aware of the burden small arms are creating. If they cannot be reached or convinced directly, then eventually with enough data international publications and medical journals can convey the message indirectly. Thirdly, the simple act of conducting the research at these hospitals increases awareness of the issue and may result in hospital based primary prevention strategies or the rise of community advocates. Lastly, the act of gathering data, meeting survivors and talking to their families increases the awareness of the individual student and their immediate network at home - creating the beginning of a small shift or 'tip'.

The project works by elective students taking with them simple survey forms that would be filled out with each small arms' trauma admission. These forms include basic demographics of the individual, information on the circumstances of injury, type of weapon used, context, injuries sustained, treatments applied and lasting health problems. There is also a small section on costs both directly to the individual and indirectly to the health system. The hope is that this becomes a continuing project within hospitals once the elective student has left - either with hospital staff or future elective students at that hospital. The data or raw survey forms would then be taken back to New Zealand, collated and placed into a database. It is a relatively simple idea that has the potential to easily generate large amounts of data. Considering the large number of students leaving New Zealand each year for third world hospitals, it would create a very large network of participants. Having a student at the hospital running and promoting the use of the survey forms is much more powerful then just sending forms via an email request. A typical elective period of approximately six to eight weeks is also a significant amount of time to get a snapshot of the area and to decide whether there is a problem within that region.

A 'pilot' or trial of the study is underway this year with University of Auckland, sixth year elective students in third and fourth quarters. Students attending third world country hospitals will be provided with information for the hospital and survey forms.

IPPNW-Students International also have another well established project called 'One-bullet stories'. These are personal case studies and stories about the injuries caused by one bullet, with the aim to put a human face on the campaign against small arms' violence. It works by students completing a case history on a 'bullet injury' patient, collecting the same information as for the small arms survey. A monetary value is then assigned to the cost of accessing healthcare, treatments and ongoing rehabilitation. A recent one-bullet story from a child shot in Kenya estimated the cost to that individual and their countries health system as US$6000, which is equivalent to one year of primary education for 100 Kenyan children[8]. Its application is powerful and was key in establishing the Land Mine Ban Treaty[8] - the process leading to this achieved its highest level of success and publicity by exposing the plight of its victims on a case-by-case basis. It is this sort of personal in-your-face exposure that causes citizens and governments to listen.

Imagine the Earth is a boat: millions of individuals' survival depends on a continuous base structure. We need to stop living in a bubble of privileged oblivion, as damage to one part of that structure will inevitably have flow on effects to the structure as a whole.

Medicine is not simply an occupation. It is and should be a way of life. Medicine is not only about mending wounds, but about preventing them. We are in a privileged position where society trusts and seeks our opinions, in domains not just limited to health. To first be able to give an opinion we need to be aware of what is happening in the world around us and the wider determinants of health. By taking part in these research initiatives during your elective experiences, discussing issues with your peers or joining organizations like MSGA we all become more 'aware doctors'. The projects described in this article are relatively simple in their collection of data but have potentially far reaching consequences in terms of their application. The exciting part of all this work is that we, New Zealand medical students, have an opportunity to be a part of it, to help in fostering awareness and creating real change. If you are interested in participating in either project or being involved in the work of Medical Students for Global Awareness, please contact either me directly, your local representative or via email, jash_agraval@yahoo.co.nz or msga.nz@gmail.com

"Never doubt that a small group of committed citizens can change the world; indeed, it's the only thing that ever has" - Margaret Mead.

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Examination Medicine: A guide to physician training. 5th Edition.
NJ Talley and S O'Conner. Publisher Elsevier

The certainty of death and taxes also holds true for medicine and examinations, but at least it is reassuring to know that Talley and O'Conner will be around to help. These authors have written Examination Medicine for junior doctors and the content includes discussion about sitting post-graduate examinations and long and short cases that are commonly found in hospitals. These cases are also relevant to medical students; after all, the goal of the medical student is to become a doctor. A complementary DVD adds value by demonstrating 10 systems-based physical examinations (PE) (NB: it is the same DVD that comes with Clinical Examination by the same authors).

A large proportion of the book is dedicated to covering 61 long cases that range from common cardiac diseases to pyrexia of unknown origin. Each disease has the following points discussed: the typical history and questions that should be asked, the relevant PE, a differential diagnosis if valid and then patient management. The management covers both the confirmatory investigations and treatments (with complications). Useful tables are scattered throughout the chapter summarising information such as the common causes of diseases, diagnostic criteria and typical investigation results. The only down-side is a lack of neurological and musculoskeletal type long cases.

The short cases are essentially systems-based PE and do include neurological

and musculoskeletal systems. There is an underlying assumption that the reader can adequately do all aspects of a PE (given that the book is written for a junior doctor). For each organ system, common PE findings are organised with relevant lists of possible explanations, clinical signs of severity and investigation results. These lists might come in handy when having to answer those annoying on-the-spot questions in the wards. The most recent edition concludes with an imaging chapter that serves as a quick guide for typical chest x-ray and CT results.

Overall this book is easy to read and relevant to medical students. The content is intended to be a guide, not a comprehensive reference, so students will need to go to other text books for more details. Also not every case found in the hospital is going to be covered in this book. Carrying around Examination Medicine on the wards may be useful, for example, when reminding oneself of the pertinent aspects of an eye examination or when comparing the pros and cons of peritoneal dialysis and haemodialysis. In addition, this book would be ideal for clinical years' exam study if the student likes having topics organised into diseases. One approach to buying and using this book might be to get members of a study group to chip in for a shared study resource and work through each case just like a real doctor.

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Crash Course Pharmacology Second edition.

Dawson, Taylor, Reide. Faculty advisor: Clive Page.

Medical science is in the midst of a knowledge explosion. Being a medical student in these changing and challenging times is difficult. Medical schools the world over are switching to an integrated, problem-based system of teaching and learning. The medical curriculum is being restructured to emphasize a core area of knowledge which every student is expected to know and knowledge which the student can access from text books, reference books and the internet. The crash course of pharmacology comes from the crash course series. This series tries to filter out the real necessary basics from the overwhelming pool of knowledge that is accessible to us

The crash course series consists of both Basic Science and Clinical titles. The series is written by medical students under the supervision of a faculty member. The book is primarily intended to serve as a quick and reliable reference and as a supplement to text books. The book is primarily written with the undergraduate medical student in mind but would also be useful to undergraduate dental and nursing students and students of other health professions.

The book is divided into three parts: Principles of Pharmacology, Clinical Pharmacology and Self-assessment. The various topics are covered in a concise and interesting manner. The main section is Part II. This is divided into eleven chapters. These are cancer, infectious diseases, inflammation, pain and immunosuppression, peripheral nervous system, central nervous system, respiratory system, kidney and urinary system, gastrointestinal system, endocrine system and eyes and skin. Comprehension check boxes test understanding of the topics which have been read. Hints and Tips boxes draw attention to key content and helps to remember important points. These boxes are very effective. Simple diagrams and tables help students to comprehend information easily. Each chapter ends with a list of short answer questions. The self-assessment section contains multiple choice questions (MCQs), Short Answer Questions (SAQs) and essay questions. The MCQs are in true-false format and the answers to the MCQs and SAQs are given.

The book has a number of advantages. The system-wise coverage facilitates system-integration across the various subjects. In addition the chapters are covered in a concise fashion and care has been taken to include the latestdevelopments, The index is comprehensive and helps to access information easily. The book is well produced and its compact size makes it portable. Furthermore the book also advertises an online resource, www.fleshandbones.com (a general medical resource) which will be useful to students and preceptors. The book is manufactured using paper obtained from sustainable forests. This book will be a useful addition to a students' bookshelf.

There are a few disadvantages. The tropical diseases section excepting malaria is not well covered. However, the book was primarily written for British students. The dose and regimens are not covered and will have to be obtained from text books. Cost may be a problem for students from developing countries. There is a tendency among students in South Asia to go in for guides and crash courses and neglect reading text books. This has to be guarded against.

The crash course series of books has been written by medical students under the guidance of faculty mentors to try to provide readers with the real necessary basic information. Though primarily written for the undergraduate medical student it would also be useful to undergraduates of other health professions. The compact, system-wise coverage facilitates system-wise integration across the various subjects. The index is comprehensive and accessible. However, the tropical diseases section excepting malaria is not well covered. The book may be expensive for students from developing countries. I would recommend the book to undergraduate medical and dental students as a supplement to regular textbooks to help the quick assimilation and mastery of information prior to examinations.

Dr Shankar reviews the second edition here but the third edition was published late last year so look out for it in the bookshop.

NZMSJ FEATURE Writing Prize ISSUE 7

An ambulance and a cliff

Medical student perceptions of population health

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Sarah

From 28th May - 2 June 2007, Auckland Medical School carried out an inaugural population health intensive week amongst a 5th year medical class. The week consisted of teams of medical students being assigned population health topics (injury prevention, oral health, mental health & obesity) and finding interventions for specific problems within a population based framework. Each team was given a hypothetical $500,000 and the opportunity to liaise with a variety of community based agencies to develop a population health strategy for their topic.

This article reflects on the attitudes of medical students towards population health in medical education and how these impact on future clinical practice.

An ambulance and a cliff

I am an ambulance at the bottom of a Cliff. Or so they tell me. I fix people when they're sick. Period. In two years I will be a doctor. By definition, I am the ambulance that catches people when they fall from the heights of good health. As for preventing them from falling in the first place? Well, that's someone else's job. After all, I'm a medical student not an epidemiologist, politician or public health agency, right?

When I was first told that I would be losing a week of precious lecture time in favour of a population health intensive week I felt somewhat resentful. The pervading feeling in my class was one of exasperation. Do we really need an entire week for a population health project? Wouldn't a simple lecture suffice? Even some lecturers lacked enthusiasm for the week which had usurped their lecture time. Cynicism was rife as we entered the inaugural population health intensive week.

Why do we have these attitudes towards population health?

• The historical context

Historically, these attitudes may be the result of the dichotomy created between public health and the institution that is medicine. Public health has often been regarded as the 'poorer cousin' to medicine, a 'soft science' and being "for med school drop outs". Several studies show that medical students' attitudes to public health have been extremely negative on the whole.[1-4] Medical students tend to perceive those who pursue public health to be more timid, less independent, less ambitious and less successful.[2-5] Even students who chose public health as a possible specialization reported feeling insecure about their standing in medical school.[2] While most of the literature describing these attitudes is now dated, anecdotal evidence overwhelmingly suggests they persist today.

• Resistance to change

Secondly, these negative attitudes are part of the wider phenomenon of medical students' resistance to change. Often medical students learn in a goal orientated manner - looking towards the immediacy of exams to structure their learning content. As an example, medical student attendance at non compulsory lectures declines towards exam time.[6] The type of mindset geared towards upstream causalities and thinking 'out of the box' is at times neglected in our curriculum. For example, visiting a refugee centre to research migrant depression can be out of the comfort zone afforded by daily hospital routines.

• Job insecurity

Outdated beliefs held that preventative medicine was contrary to the commercial interests of the practitioner. However, population based preventative medicine will not put doctors out of a job. Paradoxically, preventing people from presenting at the doctor's door in the first place may make doctors more popular with patients. This may mean patients are treated more effectively as people in the context of their respective communities. There will always be the need for individual one on one care since the "doctor's touch" and diagnostic skills cannot be substituted. Hence, the population approach is not a substitute for individualized care; rather it should be an integrated part of everyday clinical practice.

• Perception rather than ethical dilemma

It is important to note that the issue of medical student participation in public health is one of perception rather than ethics. Most medical students agree with the increasing importance of population health approaches but expect another colleague to fulfill this role rather than do so themselves.[5-7] It is not simply a case of today's physicians denying a place for public health but rather failing to personally analyze clinical data in a population based way.[7] Medical students do not need new skills to initiate commonsense interventions. Rather, they require new perspectives and a change in their frame of reference towards populations.[7]

Only recently an Auckland woman dependent on her oxygen machine died when her electricity was disconnected due to unpaid accounts. How can similar incidents be prevented in the community? What population targeted interventions can address poverty and the need for essential basics such as power?

What are the principal differences between public health and clinical medicine?

Traditionally medicine and public health have been viewed as separate entities; it is much more useful to regard them as different ends of a spectrum. The attractiveness of the individual approach is that there is instant gratification and less 'red tape' when implementing changes. Outcomes are direct and tangible. In contrast, a public health program requires more resources and co-ordination and the results of intervention

Public (Population) Health	Clinical Medicine
Focuses on populations	Focuses on individuals
Revolves around public service tempered by concerns for the individual	Revolves around personal service tempered by social responsibilities
Emphasises prevention. Cares for the whole community	Emphasises diagnoses & treatment. Care for the whole patient
Spectrum of interventions - environmental, behavioural, lifestyle and medical care	Predominant emphasis on medical care
Multiple professional identities with diffuse public image	Well established profession with sharp public image
Biological sciences central stimulated by threats to population health. Works between laboratory and field	Biological sciences central stimulated by patient needs. Works between laboratory and bedside

Modified from Harvey Fineberg, MD, PhD, Dean, Harvard University School of Public Health, 1990

can be harder to gauge. Initiatives like removing confectionary from school tuck shops may not have an immediately measurable effect on childhood obesity. Children will still have this confectionary available to them outside of school hours and it may take years before the health benefits of these initiatives are seen.

Why changing these attitudes will make us better doctors

• The raison d'être of the medical student

Why did we pursue medicine in the first place? If we cast our minds back to what we said at our medical school interviews, many of us wanted to improve people's wellbeing, save the odd life and give society back its basic human right of good health. Sound familiar? As we progress through medical school our initial idealisms wane and they are gradually surpassed by a cynical realism.[8] Public health serves to foster the genuine ethos that we want to have a healthy society made up of people with healthy, happy lives. Whether this is achieved by helping one patient at a time or helping thousands at once, that pre-medical school notion of changing peoples lives en mass remains.

• It works

The population health approach saves lives and prevents morbidity, simple as that. Maybe not with that instant satisfaction found in the resuscitation room but with comparable results. Treating the drowning infant who presents to you should trigger further thought about fencing pools and water safety. It is evidence based medicine. Just one mention of the word "vaccination" can appease even the harshest critic of public health. After all, it is more effective to address a cause than to temporarily fix an endpoint - it is like putting a band-aid on a gaping wound.

• Healing the masses

Population based medicine has the ability to change the health outcomes of many. Consider the successful eradication of polio or the subsidence of the Meningococcal B epidemic in New Zealand. Public health approaches have the advantage of improving the health outcomes for more people at any one time than a single doctor's consultation.

• Decreasing the burden on resources and minimising disparities

Case and point: the obesity epidemic. If we eliminated obesity we would half the number of diabetics we treat and this in turn would allow for a redistribution of resources. Obesity and its subsequent effects (including diabetes, hypertension and heart disease) are straining the health system and its scarce resources. Novel approaches to changing food habits and exercise are becoming increasingly vital to stem the obesity epidemic.

Public health also has the potential to lessen disparities by addressing particular populations. The Maori population, as an example, on average experience poorer health outcomes and poorer access to services. Examples of possible public health interventions include marae based initiatives to "grow your own" fruit and vegetables in order to overcome the barrier of healthy food being the most expensive choice.

• It is a way of thinking - collaterally and collaboratively

Thinking with a population based focus is a good way of thinking laterally and innovatively - skills essential for any problem solving profession. Public health is in touch with community agencies at a grass roots level and requires collaboration. Thus, public health encourages the team approach. Medical students can no longer be of the mindset "looking out for number one" as a good doctor works well in teams.

• It is keeping in touch with reality

Modern medical practice must be up to date and reflect the society we live in. We can't ignore what is happening right in front of us. There's an obesity epidemic looming and we have third world diseases in South Auckland. Population approaches just make sense. It is the 21st century. Today's health picture is a place where polio and measles are no longer acceptable parts of childhood and the daily reality of overeating and under excising is the norm.

CONCLUSION

A similar medical student rotation in public health was carried out at Columbia University. Population based thinking was brought about by allowing students to find solutions for real public health problems in a clerkship environment. The results reinforced that the first step in changing adult behavioural patterns is bringing about changes in perspective.[7] The authors noted that this way of thinking needs to be reinforced by continual use throughout medical training rather than being applied in a single course and subsequently neglected.

Doctors are effective yet, often underused public health tools. They are in a unique position with their specialist knowledge, access to clinical information and community standing. A Population Health Intensive Week is an opportunity that some may not fully appreciate until they enter into clinical practice. It is neither an inconvenience nor a dispensable blip in our timetables: it is what our community desires of us. It is why we are health care professionals. It is what will ultimately make us better doctors.

Am I an ambulance at the bottom of the cliff? Perhaps, but that doesn't mean I can't stop a few people from falling over the edge in the meantime.

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To treat or not to treat:
the 'medicalisation' of unhappiness?

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Anna is a fourth year medical student in Dunedin. She has an interest in both research and bioethics, particularly in the role doctors can play as a medium for social change, and hopes to get involved in international health policy. She has also been on the New Zealand Medical Student Journal Editorial Executive for the past two years and is currently head of the Features Editorial Board.

ABSTRACT

In recent years antidepressant use has risen significantly. As doctors are, for whatever reason, the gatekeepers of such drugs, we examined the attitudes of psychiatrists regarding the tension between preserving patient autonomy -- in this case, a patient's choice to be prescribed antidepressants regardless of the presence or absence of clinical symptoms -- and the role doctors may be playing in medicalising sadness/unhappiness. Questionnaires were sent to 40 Dunedin-based psychiatrists addressing three main issues: Do psychiatrists think depression is different to sadness? Do psychiatrists think society is medicalising sadness? Who should be responsible for the choice to prescribe -- the patient or the doctor? Our results show that there is a qualitative difference between a patient with clinical depression and a patient who is sad/unhappy, with identifiable characteristics distinguishing the two, and that there is a limit to a patient's autonomy when it comes to requesting antidepressants. And though respondents believed the medicalisation of sadness/unhappiness should be a concern for doctors, their justification for denying a patient's request for antidepressants lay not so much in any concerns over the possibility of medicalisation but in their professional obligation to treat only those with a diagnosable medical condition.

INTRODUCTION

In the past two decades antidepressant use has risen significantly and there continues to be debate as to why this increase has occurred. Are doctors now better educated and thus better at diagnosing clinical depression[1], or is it the work of the multi-billion dollar pharmaceutical industry?[1,2] Is it that the state of the world in which we now live - the demands, the expectations - is much more conducive to a general melancholy leading to an increased prevalence of clinical depression within the developed world?[1,3] Or, as explored in this research project, is the increased use of antidepressants part of a social trend in which painful emotions like sadness and unhappiness have become medicalised, as the boundary between the physiology of normal distress merges increasingly with the physiology of pathological distress?[1,4]

Doctors have long been the gatekeepers of drugs and other treatments[5], so if people are increasingly turning to antidepressants for whatever reason, we must examine the roles and responsibilities of the doctors. "Considerable debate prevails about whether unpleasant changes in emotional state associated with [stressful life events] should be defined as mental illness and be treated with drugs... but clearly drugs are not appropriate for the relief of the stress and 'blues' of everyday life... [However] the psychiatrist's judgment to withhold medication may be met with the patient's demand for the right to prompt drug relief."[6] Much of mental health remains a mystery and the boundaries between the normal and the pathological remain unclear, thus when it comes to what doctors should do the debate continues.

AIM

To examine the attitudes and beliefs of psychiatrists regarding the tension that may exist between preserving patient autonomy in the present day – in this case, a patient's decision to be prescribed antidepressants regardless of the presence or absence of clinical symptoms – and the role doctors may be playing in shaping our society into one in which painful emotions like sadness and unhappiness no longer exist.

METHOD

A questionnaire was developed containing 29 statements to which respondents specified their level of agreement on a five-point Likert Scale, one being strongly agree and five strongly disagree. These statements were divided into five sections: Depression vs. Sadness/Unhappiness; Prescribing of Antidepressants; Patient Demand, Need and Autonomy; Sadness/Unhappiness and Social Trends; and Doctors' Roles. At the end of each section additional room was given for any further comments. Ethical approval was then obtained from the University of Otago Ethics Committee.

A list of 40 Dunedin-based consultant psychiatrists was provided along with contact information found through public records. The questionnaire was mailed to each of these psychiatrists and an email reminder sent two weeks later to those who had not yet responded. No further demographic information was obtained through the questionnaire, although the respondent's gender and place of work was already known. Each questionnaire had a random number assigned which corresponded with the name of the respondent for administrative purposes. This information was destroyed before the data analysis began to preserve anonymity. Each statement was analysed individually and the percentages for each level of agreement for a statement were calculated. Any additional written comments were transcribed and analysed to help explain questionnaire

replies. Some correlation analyses were also performed to ascertain the strength of correlation, if any, that existed between various statements.

RESULTS

Twenty-five psychiatrists responded (response rate of 62.5%) of which 14 had written additional comments. We found that a significant majority of respondents believed there is a qualitative difference between a patient with clinical depression and a patient who is sad/unhappy (average Likert Scale score of 1.23). In addition, most disagreed with the statement that there are no identifiable characteristics distinguishing depression from sadness, with an average Likert Scale score of 3.96. One respondent stated that "there is a significant phenomenological difference between sadness and depression which relates to a sense of brokenness - despair - that NOTHING will allow an improvement, that life will now be without pleasure; this is akin to the Jasperian comment on un-understandability of psychosis," while another respondent commented that "sadness is limited to an area of a person's well-being; depression is global."

A significant majority of the respondents believed that to 'treat' sadness/unhappiness is not justified merely by the desire or will of the patient. As one respondent stated, "A doctor must take responsibility for prescribing the best and most appropriate medication. They should not prescribe merely on patient request." (Original emphasis) Most respondents disagreed with the following statements: when prescribing antidepressants it is not the doctor's responsibility to discern between patients with clinical depression and patients who do not have clinical depression (average Likert Scale score of 4.53); a patient should be given antidepressants upon request when they are not clinically depressed (average Likert Scale score of 4.57); and a patient's demand/desire for antidepressants should be met even when it is against the doctor's professional judgment (average Likert Scale score of 4.74). A statistically significant correlation was found between those who believed there is a qualitative difference between patients with clinical depression and patients who are sad/unhappy with those who believed that meeting a patient's demands/desires for antidepressants is not justified by the patient's fundamental right for self-determination (Correlation Coefficient = 0.619; P-value = 0.001).

When it came to questions regarding medicalisation/social trends, respondents were relatively more ambiguous in their beliefs. There was a wide-ranging response to the statement that the rise in antidepressant use is due to an increased prevalence of depression with an average Likert Scale score of 3.54, as well as to the statement that the rise in antidepressant use is due to the medicalisation of sadness/unhappiness with most respondents agreeing or neither agreeing nor disagreeing (average Likert Scale score of 2.74). One respondent stated that "psychiatrists seem to generally fall into two categories (from observation), either biologically-oriented or psychodynamically-oriented; there are few who have a good grounding in both. I believe this is influential in the medicalisation of sadness/unhappiness," while another commented that "most of this [medicalisation] may be driven from wider societal pressure and not originate within medicine (or maybe not), but medicine runs the risk of reinforcing medicalisation because it flatters our egos to be able to 'save' people."

The majority of respondents disagreed with the statement that doctors do not play a significant role in the wider social changes that occur over time (average Likert Scale score of 3.87), in addition to the statement that it is not the doctor's responsibility to consider the implications of their decisions, if any, to wider social changes that may be occurring (average Likert Scale score of 3.87). Most also disagreed with the statement that doctors do not have a professional obligation to be concerned with the possibility of the medicalisation of sadness/unhappiness with an average Likert Scale score of 3.96.

DISCUSSION

The results of this study have shown that there is a limit to a patient's autonomy when it comes to requesting antidepressants. Most psychiatrists who responded believe that there is indeed a difference between patients suffering from clinical depression and those who are feeling sad or unhappy. Therefore, like a healthy patient unjustifiably requesting antibiotics, they believe it is the doctor's responsibility to discern between patients with a medical, and therefore treatable, condition and those who do not, antidepressants being appropriate only for the former. Although it may not always be straightforward to diagnose, especially patients with mental health problems involving significant amounts of psychological and emotional distress without a diagnosable mental disorder[7], doctors must use their professional judgement to do what they believe is best for the patient. This could mean prescribing or withholding a drug against a patient's wishes.

Considerable debate exists in medical literature regarding the idea of the medicalisation of sadness/unhappiness. With the advances we are daily making in medicine, science and technology, the Huxlyean fear of the inevitable atrophy of human desires for independence and enlightenment in exchange for a pseudo-utopia echoes in the minds of many. A new world order in which, by the power of science and technology, the experience of pain and suffering no longer exist and the widespread distribution of the perfect drug called 'soma' is used by the totalitarian government to create and preserve this seemingly perfect society. And though the idea of a brave new world is worrisome for all sides of the debate, two very different perspectives exist regarding sadness/unhappiness and the current use of antidepressant: the moral and the medical.[3]

The moral perspective is rooted in the concept of depressive realism in which depression is considered a manifestation of truths necessary for any true philosopher, genius, and artist, bestowing upon the sufferer insight about their identity and about life.[3] Melancholia, sadness, and unhappiness are believed to be an essential part of what makes us human.[8] Therefore, by medicalising those experiences and 'treating' them with an 'artificial' psychopharmacological happiness we are losing bits of who we truly are.[9]

In contrast, the medical perspective sees depression as a purely medical problem, easily treatable and contained through prescription of antidepressants.[3] Those holding this perspective argue that it is not so much the character change itself that worries those holding the moral perspective (for who could blame a person for being happier?), but suspicion and mistrust of the 'artificial' method of change[10,11], as well as a cultural preference for the melancholic genius over the sanguine optimist.[10] However, they argue there is no prima facie obligation to suffer merely because it will bring about a better character, and although we do need to be careful to prevent the genesis of a Huxlyean state, we must, more importantly, avoid stigmatising those who seek help for their mental pain.[11] "It may be true that antidepressants are currently over-prescribed and that some who use the drugs do so for improper reasons. However, these facts must not deter physicians and patients from legitimate use of antidepressants, in cases where there is real suffering."[11]

The psychiatrists in our study generally seemed to hold more of a medical perspective of depression, though not enough information was obtained to infer support for any of the specific arguments made in the literature. What we do know is that our respondents do indeed believe the medicalisation of sadness/unhappiness should be a concern for doctors, however their justification for denying a patient's request for antidepressants was less to do with concern over medicalisation and more to do with non-maleficence and their professional obligation to treat only those with a diagnosable medical condition.

Thus the ethical issue highlighted by our research was the concept of professional integrity verses the doubtful and/or problematic demands of society[12], though this may have been somewhat inherent in the nature and setup of our study. The doctor, although a professional, is a social creature prone to bias, influenced by not only their socio-cultural context and personal and social biographies, but also their professional training, the scientific understanding of their discipline, and the economic and organisational constraints of practice settings.[13] Although most psychiatrists in our study currently believe that the mere desire of the patient is not justification enough to 'treat' unhappiness, as Chodoff points out, "the psychiatrist is particularly vulnerable to pressure from government and

cultural sources and instances that will inevitably arise when these come into conflict with professional convictions... On such occasions, a difficult ethical issue is whether genuine responsibility to society is discharged better by adhering to professional standards or by obeying the dictates of law and custom."[12]

It must be noted that there was one respondent who disagreed significantly with the majority on the larger issues of concern. This psychiatrist stated, "It is unfortunate that doctors are in the role of social controllers of [the] use of drugs. This is a fundamental denial of human rights by the paternalistic society in which we live. Doctors should be teachers, educators, advisors - not the present agents of control by the state." For this respondent it seemed that the limits to a patient's autonomy, as defined by the doctor, were more or less unjustified, although s/he still agreed that a patient's demand/desire for antidepressants should not be met when it is against the doctor's professional judgement. Therefore, although this respondent believed that the "doctor's role needs to be changed from controller to educator," the importance of professional integrity was nonetheless underscored.

CONCLUSION

Our research has suggested that the respondent psychiatrists may have been more hesitant to express strong opinions on social trends and the idea of medicalisation, however they were undeniably clear on what their role as doctors, and subsequently as the gatekeepers of prescription drugs, entailed. As one respondent commented, "The doctor also has autonomy and should not prescribe when that might be harmful for no benefit... A person may be free to take anything legal (ie. St. John's Wort) but a doctor is not bound to prescribe anything." In other words, yes there is a limit to a patient's autonomy when to deny their request is in the patient's best interest because "the psychiatrist... has a central role to play in ensuring that while the therapeutic potential of psychotropic drugs is fulfilled, the ethical factors are kept under close and careful scrutiny."[7]

LIMITATIONS

The main limitation of this study was our relatively small sample size and the possible inapplicability of our findings to other societies and cultures. Our findings may not apply to other New Zealand psychiatrists, as there may be various local cultural influences affecting the beliefs and attitudes of the psychiatrists in another region. Our findings may also not apply to other non-New Zealand psychiatrists (for example, psychiatrists in the United States) because the beliefs and attitudes of psychiatrists are, as explored above, affected by the context in which they live, train and work. Another limitation is the possible inapplicability of our findings to doctors of other specialities. For example, the beliefs and actions of psychiatrists examined in this study may differ significantly from those of other doctors like general practitioners who may experience more time constraints and other boundaries, as well as being more likely to have patients struggling to deal with the 'normal' stress and blues of everyday life as opposed to very serious and extreme clinical depression. It is also important to note that the scale used in the questionnaire was developed for the purposes of this study, so has not been rigorously validated. Therefore due to these limitations our results suggest certain hypotheses rather than presenting tested and validated conclusions.

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Beyond the scarlet door: Exploring palliative care in terminal illness

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The true story of an unforgettable patient, Mr S.B.,
to whom I owe the privilege of peering into his amazing journey.

Dedicated to the memory of my maternal great grandmother (1903–1992)
whose courage in the face of terminal cancer I will never forget.

Disclaimer: The names of all persons in this narrative have been changed in order to maintain the confidentiality of the patient and his carers.

"For death begins with life's first breath, and life begins at touch of death" – John Oxenham

I. First Impressions: The Scarlet Door

Scarlet: an unforgettable bright red, symbolic of living blood. We faced the scarlet door with anticipation and uncertainty, three curious medical students on our first palliative care home visit. An earlier attempt to meet our patient had failed for he had been acutely hospitalised, so I was eager to venture beyond the scarlet door.

The door opened to reveal a slightly thin, white-haired gentleman who greeted us with warm handshakes. We were ushered to an upstairs living room and then a hushed silence fell upon us. I marvelled at the remarkable interior design of his home: sliding glass doors, sleek metallic sculptures, warm illumination and bold colours contrasting with cool, dark tones. As we sat against a stunning hilltop view of the Wellington harbour by night, our patient revealed his story.

II. Joe Architect: His Story

Born in Wellington in 1952, Joe Architect, a 55-year-old European New Zealander, left college to carve his niché as an architect and builder. Following two failed marriages, he met his partner Shirley two years ago while he was battling colon cancer. They have since lived together. Joe's next-of-kin are an elderly mother and his eldest son from his first marriage who is now 23.

Joe was diagnosed with colon cancer in late October 2003. Previously well and active, he had developed symptoms of altered bowel habit, bloody stools and significant weight loss. Following surgery in November 2003 to remove a tumour from his sigmoid colon, he underwent six months of adjuvant chemotherapy. Despite having received a good prognosis, Joe suffered his first relapse in May 2005 with metastases to his paraaortic lymph nodes; he received chemotherapy and surgery with subsequent remission. By July 2006, the cancer recurred in his paraaortic lymph nodes with liver metastases. Within six months his disease progressed rapidly beyond hope of eradication and he suffered from significant breakthrough pain, nausea, episodic vomiting and jaundice due to obstruction of his stomach and bile duct by an enlarging epigastric tumour. The disease that was slowly consuming his body also took a psychological toll on Joe: he developed nocturnal hallucinations and spiralled into depression.

By January 2007 Joe was grappling with his treatment options. The side-effects of chemotherapy made him feel very ill and he did not wish to continue. Repeated biliary stenting had only lasted a month each time with recurrence of obstruction. Therefore with support from his GP and partner, Joe requested his oncologist to cease all curative treatment seeking instead palliative radiotherapy and medications for symptomatic relief. Joe's current medications are antibiotics (ciprofloxacin, clexane, omeprazole) for prophylaxis of infection; cyclizine for nausea; morphine via a syringe-driver for pain; bisacodyl and laxsol to relieve constipation; clonazepam for insomnia; and nortriptyline for depression.

III. Living with Terminal Illness: Joe's Perspective

Joe's journey through his illness has been an emotional rollercoaster ride. Upon his initial diagnosis, he experienced intense psychological shock for he was "too young to die of cancer." After his initial surgery in 2003, he was optimistic about his "85% chance of survival." However, his hopes diminished with each relapse. Faced with recurrent metastases, Joe began to channel his frustration into lifestyle changes like aggressive exercise and diet modification, with his zeal to "battle his cancer" manifesting as denial of disease progression. He continued to strive towards his hopes and dreams, throwing himself into his work and renovating Shirley's home into an architectural masterpiece. However, as he grappled with the reality of his deteriorating condition Joe sank into depression. The spectrum of emotions in his grieving process finally culminated as acceptance by early

2007 when he began to consider a palliative approach to his care. This significant development has enabled him to begin carrying out plans for "the rest of his life." Nonetheless Joe still vacillates between various stages of grief, triggered primarily by his concerns for the future.

Progressive terminal cancer has also taken a physical toll on Joe, manifest as intractable nausea and vomiting, cholestatic itch, worsening breakthrough pain exacerbating insomnia and fatigue, and the side effects of his increasing analgesic requirements. His weight has declined drastically as the very sight or smell of food causes nausea. In addition he is also prone to infections due to his immunosuppresion. Joe's main physical concerns at this time are adequate relief of his pain and nausea to ensure dignity, as well as comfort and quality of life for his last days with Shirley and his loved ones.

Living with terminal cancer also poses psychosocial concerns for Joe. Despite having accepted that he is dying, Joe appears to be facing tremendous existential pain. During the interview he broke down several times and wept in silence, uncertain of how much time remained for him to achieve his unfulfilled hopes and dreams, as well as anxiety and sorrow at the thought of saying goodbye to his loved ones.

Joe denied being spiritual, deriving support primarily from loved ones, particularly his partner and son, as well as his friends.

IV. The Impact of Terminal Illness on Loved Ones

Shirley shared some of her experiences living with Joe as he grappled with his terminal illness. As his partner of two years, she had initially faced disapproval from well-intentioned friends when she fell in love with Joe regardless of his uncertain prospects as he actively battled cancer at the time. She is now his constant companion and source of emotional support.

Shirley acknowledged the pain and frustration of witnessing Joe suffering physically. She also described the struggle in keeping up with Joe's unpredictable mood swings, especially since she often cannot adapt her mood quickly enough to buffer his. When Joe opted for palliative care Shirley was disappointed that he had given up the fight against cancer but supported him nonetheless. She has coped very well with his terminal illness, despite its physical and social toll on herself: she has given up her job indefinitely to spend with Joe his remaining days, accompany him to medical consultations and live in the hospice during his admission. Their quality of life and future plans are entirely dependent on changes in Joe's condition.

Joe's family and friends have yet to accept his terminal illness. He has faced pressure from them to continue curative treatment or seek alternative and complementary therapies. Joe's primary social concern is the well being of his loved ones, making financial arrangements for after his death and organising his mother's living arrangements. Regular meetings are held to update the family about Joe's condition and plans for the future.

V. Role of Health Professionals

Joe expressed great satisfaction with the care he received from his multidisciplinary team. Joe has received hospital care from both Surgery and Oncology, in close coordination with his GP. Following his decision for palliative care, Joe's transition towards hospice care has decreased his reliance on his GP.

At present, ongoing management is coordinated by a Palliative Care Coordinator (PCC) from Mary Potter Hospice. A specialist nurse who conducts fortnightly home visits monitors Joe's health and medications including pain management, diet plans and acute admissions. In so doing, the PCC serves as a source of continued external support and ensures liaison between all health professionals involved.

In grappling with recurring thoughts of death and dying, Joe expressed a strong desire for "a peaceful death that will not be unpleasant or messy," rather than burdening his carers. Aside from prescribing medications to relieve insomnia and depressive symptoms, Joe's psychiatrist has played a vital role in dealing with Joe's overwhelming anxiety and existential pain by empowering Joe to address his anxiety and actively plan how to live his remaining days.

Joe continues to live at home with Shirley. However, he intends to move into the hospice should his condition deteriorate suddenly in order to "avoid inconveniencing his family." He desires to preserve pleasant memories for Shirley of times shared in their beautiful home.

VI. Ethics of Palliative Care

Shirley is grateful to health professionals for including her in consultations, since the decisions made would impact significantly on both Joe and herself. The couple feel that excellent communication and rapport with the healthcare team is central to ensuring the best quality of care. Joe's autonomy has been respected in his medical decisions, which was facilitated by strong advocacy from healthcare professionals; informed consent through clear explanations of disease and illness progression; and integration of professional knowledge and opinions on appropriate management through a multidisciplinary approach.

In Joe's situation, the ethical issue of significance is the critical decision to accept the transition into palliative care. In other words, when should curative treatment cease? The question is raised whether it is justifiable to continue with curative treatment given his poor prognosis. Evidently, the opinions of healthcare professionals, carers, family and social contacts may vary distinctly from that of the patient. In any circumstance, Joe's perspective is undoubtedly critical and emphasis should be placed on ensuring his well being by respecting his autonomy as much as possible. From a public healthcare perspective, resource allocation issues for patients would also need to be justified, however, this does not appear to be a significant issue in Joe's care.

Upon careful consideration of Joe's transition from curative treatment to palliative care, ethical frameworks must be applied to weigh the benefits and disadvantages of both options. The ethical tenets of beneficence, non-maleficence, justice, autonomy, dignity and truth-telling may come into conflict with each other, thus need to be balanced in light of Joe's unique context. Factors supporting Joe's decision for palliative care include respecting his right to make personal decisions concerning his life's end (autonomy); maintenance of dignity through ensuring a comfortable, peaceful death by relieving his symptoms (beneficence); and avoiding the unpleasant side-effects of curative treatment such as vomiting (non-maleficence). At this stage, these factors appear to best fulfil Joe's desires and outweigh the disadvantages of terminating curative treatment, which include the loss of hope of remission (beneficence), and the inevitable outcome that Joe is likely to die from cancer (non-maleficence).

As such, Joe's decision for palliative care appears to be ethically justified, and it is vital that his decision continues to receive full support from his partner and healthcare team, as well as gradual acceptance by his loved ones.

VII. Personal Reflections: Beyond the Scarlet Door

My meeting with Joe and Shirley in their home has been a novel and enlightening experience. I was impressed by the scope and quality of professional care and support that Joe and Shirley have received in living with his terminal illness. Moreover, taking into consideration the ethical issues involved, it was heartening to acknowledge that Joe's well being and autonomy have been highly prioritised. Joe has been able to take an active role in decisions about his dying and the management of his care, and this has helped him regain a degree of control and 'normalcy' in living with his terminal illness.

I have a finer appreciation of Joe's struggle to accept his terminal illness and transition into palliative care. It is apparent that his emotional and psychological struggles are likely to persist in the remaining days of his life, even as his body succumbs to physical disease, highlighting the crucial

role of psychosocial support fromhis social contacts, as well as his personal and professional carers.

Furthermore, the role of psychiatric assistance should not be undervalued in palliative care. Aside from the significant effects of his perceived degree of breakthrough pain, Joe's mental and emotional status is key to determining his perceived quality of life. In addition to addressing physical symptoms of anxiety, insomnia and depression, a vital issue that should not be overlooked is the 'existential pain' that terminally ill patients inevitably experience including recurrent thoughts and concerns regarding their death and the dying process. Eventual acceptance and contentment is the elusive ideal that almost every human being seeks when faced with their mortality or that of their loved ones, and psychiatrists are vital in this process.

From a philosophical perspective, accepting one's own mortality and grappling with the dying process is the final, most challenging journey in life. In the words of the writer John Oxenham, "For death begins with life's first breath, and life begins at touch of death." The tragic disempowerment of one's personhood that begins at the very instant one's life is touched by the dying process often causes us to forget the fact that a dying person is nevertheless a living person, every day until their death. There should be no compromise on a dying person's comfort or enjoyment, nor should we in any way relegate their pursuit of personal hopes and dreams. Only then can life truly begin. Only then will the sweetness of quality living counter the bitter self-discovery of mortality.

FEATURE : CONFERENCE REPORT

Clinicians Medical Education Convention Aotearoa

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Kerryns Blurb

The Medical Education Convention Aotearoa (MECA) is an annual weekend-long convention held in Dunedin for medical students. MECA aims to enhance the education of future doctors by exposing them to a wide range of ideas and opinions whilst developing practical skills and strengthening collegiality. MECA relies on the generous support of our sponsors so thanks must be extended to Clinicians, ACC, Best Practice New Zealand, Otago Faculty of Medicine, Otago University Medical Students' Association, Tyco, Syneture, Austin Medical Centre and Mobile Surgical Services.

MECA 2007 went off without a hitch and was by all accounts a huge success. The following report will highlight the key features of the weekend of September 28th to 30th.

The opening ceremony was kicked off with a piped entrance of the official party into Glenroy Auditorium. This was followed by addresses from MECA'07 Convenor Kerryn Harlow, Dunedin Mayor Peter Chin and the Deputy Chair of NZMSA Dr Paul Ockelford. Following this, the Honorable David Benson-Pope officially opened the convention. With formalities concluded, the participants of the Bpac Emergency Medical Challenge took to the stage. The challenge participants included past MECA convenor, Jared Kilday, medical students, lecturers, professors and respected Doctors: a mix which ensured entertainment. Due to the absence of one of our participants, Professor Mike Ardagh was welcomed to the stage only to be defeated by the opposition!

Saturday saw the beginning of the academic content of the weekend. Highlights from Saturday included inspiring presentations from Professor Mike Ardagh (who knew Spice Girls could play a role in medical ethics?), Rae Lamb, the Deputy HDC Commissioner who spoke on patient-centered care and Professor Des Gorman, the Dean of Auckland University Medical School, who presented the complications of diving and submarine medicine. Saturday also included a presentation by Shawn Riley who had traveled from the Mayo Clinic in America to address the MECA delegates.

Delegates also participated in workshops throughout the weekend. The Tyco Suturing Workshop was the highlight with delegates practicing and mastering their skills on pig skin. Other workshops included an acupuncture demonstration, public health and integrative medicine.

On Saturday night the much anticipated Dinner and Dance took place. The ultimate highlight of the weekend saw delegates and honoured guests enjoying a three course buffet dinner and an energetic dance floor. The food was excellent and the band superb, ingredients sure to produce longtime memories and friendships. Our dinner keynote speaker was Dr Murdoch Herbert who recounted memories of his long-standing and remarkable medical career.

The academic content continued on Sunday with presentations from Dr Stuart Gowland and Dr Tim Ewer. The highlight for the day was a presentation by Dr Glenn Colquhoun, an award-winning New Zealand poet and a highly respected GP working in Maori Health. His presentation consisted of readings and poems from his works and was greatly moving, causing a great number of delegates to 'tear-up'.

MECA'07 was an extremely rewarding experience and an event 'not to be missed'. I look forward to MECA'08 and the development of this fantastic initiative in the future. "Here's to the Future…"

A discussion of the contribution of complex genetics to the aeteology of osteoporosis based on a clinical case

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Janar is a graduate of the University of Auckland Medical School currently working as a first year house surgeon at Auckland City Hospital. He has research interests in cardiovascular and general medicine and wrote this case study as a Trainee Intern.

CASE

Mr AM is a 29 year old Fijian-Indian male who presented to the endocrinology clinic after a low trauma fracture to the neck of his left femur earlier in the year. The injury was sustained after he fell to the ground while carrying a chair and he has no previous history of fractures. The patient was screened for symptoms suggestive of a secondary cause of osteoporosis such as Cushings, hyperprolactinemia, hyperthyroidism, hypogonadism, chronic malabsorptive conditions, alcohol excess, and other chronic diseases, all of which were negative.

The patient is normally fit and well with no significant past history, and no regular medications. He works as a store salesman, and is a non-smoker with minimal alcohol intake (two standard drinks per week).

Mr AM's brother also recently had a low trauma fall without sustaining a fracture and a DEXA scan showed decreased bone density at the spine. However Mr AM could not recall the exact T-score of his brother's scan. There is no family history of fractures.

Physical examination was normal other than a slightly low BMI of 19.9.

Investigations:

1) 25 hydroxy vitamin D: 37nmol/L (Normal range: 50-150)

2) Normal liver function tests, thyroid function tests, B12/folate, serum cortisol, full blood count, antinuclear antibodies, gliaden/gluten sensitivity, neutrophil cytoplasmic antibodies, iron studies, testosterone, LH, FSH, HIV antibodies, calcium, crp, albumin, creatinine and rheumatoid latex test.

3) DEXA scan: T score: spine -2.4 and right hip -2.6

Problem list:

1) 'Idiopathic' osteoporosis

2) Vitamin D insufficiency

Summary:

Mr AM is a 29 year old Fijian-Indian man who sustained a left hip fracture following low trauma. He has no previous fractures, no family history of fractures and his general health has been good. His DEXA scan confirms osteoporosis. He is lean (BMI: 19.9) and is Vitamin D insufficient with a level of 37nmol/L. This may contribute to his osteoporosis by increasing parathyroid hormone bone turnover which can lead to a low grade loss of bone density. However these low levels are commonly seen in patients of Indian ethnicity and are unlikely to be the primary cause of his osteoporosis. A complete screen of possible secondary causes of osteoporosis was negative. Therefore the diagnosis of 'idiopathic' osteoporosis was made, with a possible genetic component considering Mr AM's brother's low bone density.

DISCUSSION

Osteoporosis is a disease characterized by low bone mineral density (BMD) and micro-architectural deterioration of bone tissue. This subsequently leads to an increase in bone fragility and increases fracture risk, particularly of the spine, hip and wrist.[1] Osteoporosis is mainly a disease of the elderly and is generally a multifactorial disease process due to a number of risk factors such as ethnicity, gender, age, glucocorticoid therapy, low body mass index, Vitamin D deficiency, environmental factors and coexisting diseases. It has also been shown that a positive family history is also an important risk factor in the pathogenesis of osteoporosis.[2,3] Considering Mr AM's young age at the time of diagnosis and the lack of any other significant risk factors, the cause of his osteoporosis is likely to have a genetic component, especially considering his brother's low BMD.

Research in the genetics of osteoporosis has focused mainly on two separate areas: (1) genetic factors associated with peak BMD and rate of loss of BMD, and (2) family history of fractures. These two variables have shown to be independent risk factors of osteoporosis. Two separate studies in women have demonstrated a heritability of wrist fractures of approximately 25 per cent and 54 per cent. In both studies this was independent of patient BMD. This demonstrates that identifying genes which affect BMD does not necessarily correlate to a family history of fractures.[4] In this case study there is no family history of fractures, therefore it is probable that Mr AM's genetic risk factor is related to BMD.

Genetic factors in osteoporosis are believed to be polygenic in nature and are influenced by the polymorphisms of certain genes.[2] The effect of these genetic factors in the pathogenesis of osteoporosis is still unclear.[4] Research has mainly focused on female osteoporosis and a large number of genes have been identified which may affect BMD and thus increase risk of fracture. Certain genes have been identified which may contribute more specifically to male osteoporosis: Lipoprotein receptor related protein 5 (LRP5) Vitamin D Receptor Gene (VDR), Collagen Type I Alpha I gene (COL1A1), Insulin growth factor I (IGF-1), Estrogen receptor, Androgen receptor and Aromatase genes.

LRP5 is a receptor that functions as a co-receptor for canonical Wnt signaling, which plays a role in osteoblast and chondrocyte differentiation. Several studies have shown that LRP5 is related to BMD and/or osteoporosis fracture. Subtle polyporphisms of the LRP5 gene have been shown to regulate BMD. In addition a strong association has been seen between LRP5 and male osteoporosis.[4]

VDR is a specific hormone receptor that is responsible for the action of the bioactive form of Vitamin D, 1,25-(OH)2D3. Studies have demonstrated correlations between VDR and male osteoporosis particularly relating to peak bone mass, bone size, skeletal growth, fracture risk and intestinal calcium absorption.[3,4]

COL1A1 encodes Collagen type 1, a major structural protein of bone which has clear implications for osteoporosis. Mutations in this gene cause the syndrome of osteogenesis imperfecta. Polymorphisms of the COL1A1 gene have been associated with osteoporosis in both men and women. In addition to BMD, COL1A1 has also been associated as a marker of bone fragility. However there is limited research regarding the relationship of COL1A1 with male osteoporosis.[3,4]

IGF-1 may be a significant genetic factor in male osteoporosis. Low IGF-1 levels have been demonstrated in idiopathic osteoporosis in men. Studies have shown that certain allelic configuration of the IGF-1 gene (CAn dinucleotide repeat polymorphism) is associated with lower BMD. In addition this polymorphism also appears to be gender specific affecting mainly male patients.[3]

Oestrogen deficiency is a risk factor in both male and female osteoporosis. Oestrogen receptor, androgen receptor and aromatase genes all have an effect on sex steroid metabolism which ultimately affects BMD. Case studies have shown that mutations in any of these genes can lead to male osteoporosis.[3]

Current research has demonstrated that the genetics of osteoporosis is mainly mediated by a number of genes and their polymorphic variants which contribute collectively to both BMD and skeletal integrity. Some case studies have demonstrated that single gene defects can contribute to osteoporosis. For example, mutations in aromatase and estrogen receptor genes have been shown to result in osteoporosis. However these cases are rare and also tend to have a strong family history, usually inherited as an autosomal dominant trait.[3,4] Considering his lack of a positive family history it is unlikely Mr AM's osteoporosis is due to a single gene defect. The most plausible causative explanation of his osteoporosis is probably due to multiple genetic variants, which may possibly include some of the genes discussed above. Therefore it is not possible to definitively determine the genetic cause of Mr AM's osteoporosis.

Mr AM was placed on long term alendronate treatment and calciferol tablets, with clinic review every two years. Alendronate is a potent bisphosphonate that is an inhibitor of osteoclast-mediated bone resorption. It is most commonly used for the treatment and prevention of osteoporosis. Research has shown that alendronate significantly increases BMD and reduces the incidence of osteoporotic fractures in post-menopausal women and patients with glucocorticoid induced osteoporosis.[5] While it is a proven therapy in women, there have only been a few large controlled trials analysing the effectiveness of alendronate therapy in male osteoporosis. This is an important issue to address as this is Mr AM's primary treatment.

While research in men is limited compared to women, large trials have been conducted that demonstrate alendronate significantly increases BMD and decreases the incidence of osteoporotic fractures. One double-blinded trial compared alendronate versus placebo in 241 men with osteopororsis over a two-year period. Men who had alendronate had a mean increase in BMD of 7.1±0.3 per cent at the lumbar spine, 2.5±0.4 per cent at the femoral neck, and 2.0±0.2 per cent for the total body. Men who took alendronate had a significantly higher BMD in all areas compared to placebo ($P<0.001$).[5] In this particular trial all patients were given calcium and vitamin D supplements. A recent study comparing the effect of alendronate with and without cholecalciferol showed that patients who took cholecalciferol and alendronate reduced the relative risk of vitamin D deficiency by 91 per cent.[6] This has clear implications for Mr AM. His investigations revealed a slightly low vitamin D level, and based on the above trial he will benefit from Vitamin D supplements in combination with his alendronate therapy.

In addition it has also been demonstrated that the magnitude of benefit in BMD in men, is also similar to that seen in post-menopausal women after two years of therapy. The reduction in the incidence of vertebral fractures is also similar between men and women on alendronate therapy.[7] The benefit of alendronate in patients who have long-term therapy has not been discussed. Mr AH is a young man and it is likely he will need to remain on alendronate for a minimum of 5 years. The long term ramifications and benefits of such prolonged alendronate therapy in men have not been discussed as there are currently no major trials which address this issue.

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New England Journal of Medicine. 1995;333:1437-43.

NZMSJ author guidelines for submissions

Format requirements

Use Microsoft Word

Include figures, legends and tables

Save as a word document (*.doc)

Photographs are to be included as separate files

Types of Submission

Original research articles (<3000 words)

Feature articles (<3000 words)

Case reports (<1500 words)

Book reviews (<500 words)

Letters (<500 words)

Criteria for Submission

Submissions are of interest to medical students

Written approval from research supervisors is required

Author's email address for correspondence is necessary

Short blurbs about authors should be included

Style

The British Medical Journal house style is to be followed.

This is available at:

http://resources.bmj.com/bmj/authors/bmj-house-style

Use the Vancouver referencing style, insert numbers within the text using superscript, do not use brackets around the numbers

Abstracts are required for research articles

Delivery

Email articles and authors' blurb to:

nzmsj@otago.ac.nz

with "article submission" in the subject header

Download an article cover sheet from:

www.otago.ac.nz/nzmsj

complete and post it to:

New Zealand Medical Student Journal
c/- Medical Teaching Support Unit
Dunedin School of Medicine
PO Box 913
Dunedin
New Zealand

Process

All submissions will be subedited for spelling, grammar and clarity. They will then be sent for expert reviews. Authors will be required to revise their articles during this process.

Final article selection for publication will be made in conjunction with our academic advisors and editorial board once the review and revision process is completed to a professional publishing standard.

Acceptance of an article into the review process does not constitute a guarantee of publication. It is the intention of the NZMSJ to provide authors with the benefit of external review and revision processes that are standard internationally for published journals. This is in keeping with our educational aim to assist medical students in making the transition from writing for medical school to writing as a graduate

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Submissions
received before March10
will be considered
for issue 8

In keeping with the NZMSJ's ethos of encouraging students to submit articles, we are proud to offer prizes to acknowledge excellent work. Under the category of academic submissions, **a first prize of $350 and a second prize of $150** will be awarded.

The best feature article and letter to the editor will receive **medical book prizes.**

Submissions for the next issue are due **10th March 2008.**