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NZMSJ

New Zealand Medical Student Journal

Te Hautaka o ngaa Akongaa Rongoaa

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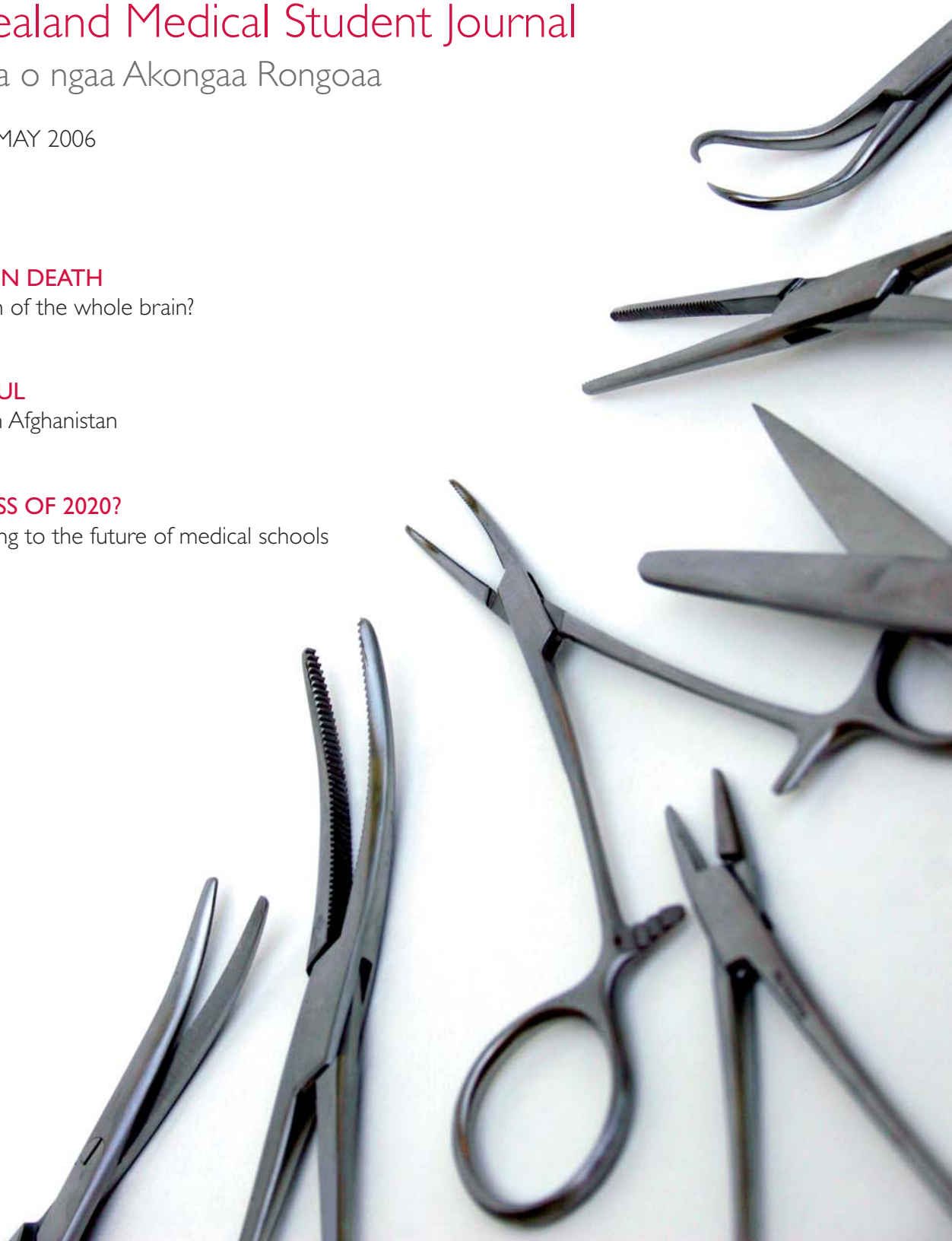

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EDITORIAL

2006 represents an exciting time for the NZMSJ, with an establishment of a branch of the executive committee at the School of Medicine at the University of Auckland. Associated with this expansion, we are delighted to announce that this issue's NZMSJ Writing Prize is provided by the University of Auckland's Dean of the Faculty of Medicine, Professor Iain Martin. The winner of this prize was an excellent piece written by an Auckland trainee intern, Matt Wheeler. His article titled "Is Death the Death of the Whole Brain?" can be found on page 7.

The amalgamation with the University of Auckland has also resulted in an improvement to the NZMSJ's peer review system by increasing the number of high quality reviewers it uses to assess submissions. All articles accepted by the NZMSJ go through peer-review by an expert in the relevant field. This process has now been expanded to include feature articles. We would like to take the time to thank the academic staff members of all four New Zealand's schools of medicine who have volunteered to make a contribution to medical education. The recent high profile Hwang fraud case, involving stem cell research, has created some misconceptions about the value of the peer review system. Peer review relies on trust and is not designed to detect false reports. It is invaluable however to use experts in the field to evaluate the robustness and credibility of submitted works. Publication of research, including that undertaken by students in this journal, allows current medical practice to be continually challenged and improved. This process provides the evidence base that differentiates modern medicine from mere witchcraft and wizardry.

The NZMSJ provides another important role in medical education. As the only peer-reviewed medical student journal in Australasia and the South Pacific, we not only encourage publication of quality academic work by students but we also facilitate public debate of issues that affect students, by students. Premjit Gill's opinion article in our last issue regarding the Advanced Choice of Employment scheme stimulated some interesting feedback (see pages 5 and 6). Similarly, Brad Stone's opinion piece in this issue regarding our current medical education "Where to from here for Medical Schools" (pages 24-26) opens another forum for informed debate. Response in the form of letters to the editor, or further opinion pieces are welcome.

We look forward to continuing our roles, with an expanded executive, from issue 5 and beyond.

The NZMSJ Executive

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

Credits

To the editors,

The opinion piece, "Advanced Choice of Employment: Friend or Foe?" on page 28 of your November edition contained two ambiguities. The article suggests that ACE is biased on ranking NZREX graduates and international students lower than local students. This is inaccurate. ACE welcomes applications from all suitably qualified people, but preference for the 1st match is given to applicants with New Zealand citizenship or residency. Likewise, the article infers that DHBs are told what rank they have been given by a student. This is not the case and DHBs do not know how they have been ranked by applicants. The ACE process uses a computer algorithm to best match applicant's preferences with DHB preferences; the higher applicants rank DHBs, the more likely they are to be placed with them and vice versa.

For more information, ACE can be contacted on 0800 223236 or via email at ace@nctn.co.nz.

Our web-site address is www.newdoctors.co.nz.

Yours sincerely,

Andrea Evans
PGY1/ACE Co-ordinator

To the editors,

I read with interest the featured opinion piece, "Advanced Choice of Employment: Friend or Foe?" in your last issue, however I was disappointed to notice a number of misleading factual errors. I have been involved with the Advanced Choice of Employment (ACE) scheme in various capacities over the last few years, including as a DHB ACE co-ordinator, and as a presenter at the NZMA ACE Information Evenings around the country. While it is certainly valuable to debate aspects of the scheme, I think it is crucial for such debate to be accurate given the importance of the scheme in the lives of trainee interns.

The most glaring error is the author's assertion that "applicants who miss out on their first job choice will not be awarded their second". This is not the case. In each of the last three years, more than 72% (and as high as 86% in 2004) of applicants got their first choice, with a further 7-14% gaining their second choice. This leaves only 7-14% receiving their 3rd choice and below*. Clearly, while most candidates get their first choice, those who do not are more likely to get their second than their third and so on.

Next, the ACE scheme does not prioritise New Zealand graduated trainee interns ahead of NZREX graduates. Further, it is not the design of the ACE scheme that discriminates against international students. ACE does, and must, operate within New Zealand Immigration Law which states that New Zealand residents and citizens are given preference ahead of non-residents. NZREX graduates, as residents, are treated the same as New Zealand trained, resident trainee interns with international students coming below both groups. Any discussion around the 'fairness' or otherwise of this situation should be directed to the Government and not levelled at the ACE scheme. The author also asserts that "a great deal of this system is based on luck" which is also inaccurate. The ACE scheme operates to a strict computer algorithm with no room for the operation of chance or luck! Other more minor errors included:

1. The Resident Medical Officer (RMO) job fair is not organised by ACE, it is a joint-DHB initiative at which ACE is represented

2. The Overseas-Trained Doctor Bridging Programme no longer exists.

Advanced Choice of Employment is still in its infancy and debate on its function is to be encouraged, as only through free and frank discussions can we identify any problems and generate solutions. While peoples' opinions and experiences are an important part of the debate, the role that ACE plays in the lives of every new graduate New Zealand doctor makes it vital that the debate is informed by the facts, and not clouded by inaccuracies. For people wanting more information, there is an excellent article by Pole, O'Grady & Adams that summarises the scheme and its results, that was published in the New Zealand Medial Journal in 2004[1].

Yours sincerely,

Dr. Andrew Old
Chairman, Doctors-in-Training Council
New Zealand Medical Association

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NZ Med J 2004;117(1204) U1120.

* Statistics provided by ACE and available from www.newdoctors.co.nz

To the editors,

I am writing in response to the article "Advanced Choice of Employment: Friend or Foe?" published in the last NZMSJ. This article has raised many issues that are faced by our international medical students and NZREX graduates.

New Zealand has a doctor shortage crisis. We rely on a high number of overseas trained doctors. In 2003, 34.1% of doctors obtained their basic medical qualification outside New Zealand[1].

The ACE scheme was introduced in 2003 after years of work and lobbying by medical students' associations and other organisations to improve the system for first year job applications. Prior to the ACE scheme there was a long process that offered little certainty for employees and employers. It has been suggested that we lost many New Zealand graduates to Australia during this period[2].

The ACE scheme does group applicants for PGY1 into four categories:
1. NZ graduate (TI)
2. Non resident/overseas student, NZ graduate (TI)
3. NZ REX (NZ resident)
4. Other overseas doctors

In 2004, there were 299 first-year house officer positions available in New Zealand and there were 413 applications[3]. Quite clearly there were going to be unsuccessful applicants due to the major shortage of first year jobs and that no matching scheme, including the ACE could prevent this.

New Zealand, like the majority of other countries does not want to lose its new graduates. Each year we lose approximately 25% of third year New Zealand graduates[4]. One New Zealand graduate costs approximately $200,000 to train[1]. At least $150,000 is paid by the Government, which represents a major investment by the New Zealand tax payer.

In 2004, 99% of NZ graduates and 19% of NZ REX graduates were successfully matched under the ACE scheme. There were no successful applicants from non resident/overseas students that had graduated from a NZ medical school and doctors applying from overseas[3].

This current predicament is distressing to many international students and NZ REX applicants. This situation is only going to get worse with the increase in medical students in 2004 and since 1996 the number of full-fee-paying international students has risen sharply. In 2002 there were 163 out of 1370 students[1]. This situation has been labeled the "PGY1 (post graduate year one) bottle neck," as we have too many applicants for first year places, but a shortage of advance trained doctors. The District Health Boards, NZ Medical Council and the Health Workforce Advisory Committee are currently looking at options to address this problem. In some respects, New Zealand medical schools must also take responsibility to adequately inform international students that they may not be able to gain NZ registration if they choose to study in New Zealand.

It is very easy to blame the ACE scheme for the shortage of first year jobs and the low amount of successful applicants that are not NZ resident graduates. We must look at the underlying problem of solving the PGY1 bottleneck and the issues faced by international medical students and NZREX graduates.

Yours sincerely

Xaviour Walker
President
New Zealand Medical Students' Association

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Editorial response

It is interesting to note the debate which has been provoked by the feature opinion piece "ACE: Friend or Foe?" which appeared in Issue 3 of this journal. The New Zealand Medical Student Journal (NZMSJ) editorial board wishes to clarify that the article in question was an opinion piece. The purpose of the article therefore was not to give our readers factual information about the Advanced Choice of Employment (ACE) scheme; instead it represented the author's perception of the ACE scheme.

However, the NZSMJ editorial board accepts that this opinion piece contained statements with the potential to mislead our readers including a number of factual errors. Therefore, we would like to thank the writers of the above letters to the editor for highlighting these statements and clarifying the issues raised for our readers.

The NZMSJ editorial board has made substantial changes to the review procedures for the features section of the journal in order to prevent the publication of such misleading statements in future issues. These changes have taken effect from Issue 4 of the journal.

The NZMSJ editorial board would like to highlight the fact to our readers that Issue 1 of the NZSMJ contained a feature article on the ACE scheme titled ""ACE coming up trumps?" which represented a different perspective from the article published in Issue 3 of the NZMSJ. As an independent medical journal, the NZMSJ will always strive to publish an array of articles with different viewpoints.

NZMSJ Writing Prize 2006 FIRST PLACE

Is Death the Death of the Whole Brain?

Matt Wheeler
Trainee Intern
Faculty of Medical and Health Sciences
University of Auckland

The author is currently a Trainee Intern in Auckland. Next year he wants to work at Tauranga Hospital. Matt is interested in whitewater kayaking and enjoys the outdoors.

Technology currently allows support of the body to keep people alive beyond what was previously possible. This has brought about the existence of states that cause confusion. The 'irreversible coma' (and others) is the closest thing to middle ground between life and death. "Are people in such a state alive?" If so, withdrawing life support would be tantamount to murder. Are they dead? In that case, the body is being kept in a state of suspended animation, which may prevent the family from moving on and starting the grieving process. This has brought about a second type of death, which has been poorly called 'brain-death'. Does this mean there are two ways in which to die? In this essay I will examine the history behind these developments, the definitions of the three standards of death and some of the debates surrounding death. Finally, I will show that the only way that death should be defined is by a Higher-Brain Standard of death.

In the past 50 or so years two events ignited the debate that still rages. The first was the invention of the first ventilator in the 1950's. It was designed when polio was still prevalent and 'iron lungs' were in use. These were giant iron chambers where afflicted people, who were too weak to breathe, were placed. A Dutch doctor, who was observing the nurses and medical students at Copenhagen Medical School working the bellows of the iron lungs, wondered what would happen if the manual labour could be replaced by a machine. Hence the first ventilator was born. This great invention allowed extra respiratory support when patients temporarily needed it in cases such as drug overdose, diabetic comas and the like. However, it created new problems when people were being sustained on them. As the definition of death at the time was cardio-respiratory, it would have meant killing the person if this treatment was withdrawn. As life-sustaining treatment cannot be removed, neither could the ventilator. Another factor was that those patients on ventilators would require specialised nursing care. "They [Directors of Intensive care units] began to have nightmares about wards filling up with permanently unconscious patients, each one needing not only a respirator and a bed, but also skilled nursing care".[1]

The second event began circa 1967. At this time, the first heart transplants were being performed. Although generally unsuccessful the operation did have promise. It focused new attention on those who were permanently on ventilators as "the thousands of permanently unconscious patients filling hospital wards around the world suddenly appeared in a new light. Instead of being an increasingly intolerable burden on a hospital's resources, they could become a means of saving the lives of other patients"[1] "every hospital has patients stacked up waiting for suitable donors"[1] and led to the formation of 'The Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death'. The committee was made up of ten doctors, a lawyer, historian and theologian. Their results were published in August 1968 in the Journal of the American Medical Association. They made two controversial statements:

1. People attached to ventilators were not recognised in law as dead, so they cannot be removed from the ventilator. Not, that these people were actually dead, they were being kept in a state of suspended animation by the ventilator.

2. One of their intentions is to clarify criteria for obtaining organs for transplant.

What makes someone dead?

Who decides who is dead? The obvious answer to this would be: the doctor. Right? But is that actually the truth? Doctors decide that a person is dead by a set of criteria that are set down for them, usually by leaders in that field. As shown by point one above, in this case they did things in an interesting manner. When the law does not recognise someone as dead can you actually say this? However, I believe that if you wish to change the law, you first need to say that they are dead and then change the law to reflect this.

The second point was about the need for transplant organs. Before this time, people were taken to court for their somewhat overzealous removal of organs because by law it was not entirely clear if the person was dead or not. An example of this was the shooting of Pamela James. Her assailant was charged with aggravated homicide for shooting her in the head but when his lawyer discovered that "the time of death listed by the coroner was virtually to the minute coincidental with the time [the transplant team] removed the heart"[1] the charges were reduced in a plea bargain and the case never made it to court.

Despite the above problems, this led to the 'Uniform Determination of Death Act' in 1981, which made every state of the US adopt the same brain-death definition. Indeed, 15 other countries had already done so,

including Britain, where the medical profession had just taken on board an extra set of criteria for certifying a patient dead. What this did was set the definition of death for the whole of the United States of America.

"[Determination of Death]. An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards."

All this change went through with very little opposition. Indeed, many welcomed the change. Euthanasia activists (on both sides) welcomed it because it gave a more definite standard of death.

Three definitions of death

Below, I explain the cardio-respiratory definition, the whole-brain definition and the higher-brain definition, the latter two being at the centre of the controversy.

The cardio-respiratory standard was the traditional way of looking at death prior to 1967. Once the heart stops beating and the lungs stop taking in oxygen the person is said to be dead. One of the good things about this standard is that it is very easy to tell that death has occurred. You can measure pulse (or not), blood pressure, even the fogging of a mirror when placed over a person's mouth! By ignoring the fact that the hair and nails keep growing for a time after death by the cardio-respiratory standard you can say that the organism is dead. The main problem with this standard is that when a patient will not survive off ventilation you enter a halfway point. They are not counted as dead because they are still breathing, yet you cannot disconnect them as this would take away life sustaining treatment.

The whole-brain standard of death is defined as 'the permanent cessation of the critical functions of the organism as a whole'. It is called whole-brain because in order to be counted as dead by this standard one needs to have both the brain stem and the cerebrum non-functioning. This is demonstrated by the loss of the functions described below. 'Critical' has only been added recently due to evidence of patients considered dead under the whole-brain standard still maintaining secretion of anti-diuretic hormone (ADH) and although this is a function of the brain it is not essential for life. James L. Bernat gives us the critical functions of an organism as a whole in three distinct but complementary biological categories:

1. Vital functions of spontaneous breathing and autonomic control of circulation;

2. Integrating functions that assure homeostasis of the organism, including the appropriate physiologic responses to baroreceptors, chemoreceptors, neuroendocrine feedback loops, and similar control systems;

3. Consciousness, which is required for the organism to respond to requirements for hydration, nutrition, and protection, among other needs.[1]

All of these functions must be lost, permanently, for the organism to be classified as dead. If any one of these three functions is clinically present the organism is considered alive.

The higher-brain standard of death can be described as "irreversible cessation of only cerebral and thalamic function." That is to say that once a person has lost all capacity for consciousness and higher function then they are no longer alive. This standard means that it would also include those in irreversible coma, patients who are in a persistent vegetative state (PVS), and ancephalic infants. The cerebrum is what occupies most of the cranial cavity and as such is in charge of sensory, motor and so called higher functions as well as their overall integration. These include: thought, reasoning, judgement, emotion and memory. The thalamus is the way station of all of the impulses travelling to the cerebellum and so modulates the sensory signals going to and from the cortex. In conjunction with this the thalamus is said to have some more complex roles, which include blood pressure, instincts, emotions, and intuitions.

The 'irreversible coma' is the closest thing to middle ground between life and death. Are people in such a state alive? If so, withdrawing life support would be tantamount to murder.

Here I would like to continue with some thought exercises. Look within yourself. Do you see yourself as a whole or as two parts? Now look at someone else, a hypothetical Mr A and tell me if you can separate him into any parts. Say for instance the old adage of the body and the mind? Whereas I see myself as a whole, when I look at someone else I would say that there is definitely a body and a mind or organism and person (respectively). Although philosophers count the brain as part of the body, as distinct from the mind, I think that actually giving the brain some sort of substance makes this separation easier. Now, imagine the situation of a 'brain switch' operation – if you switched the brains of two separate people, who is who? Is it the body (the organism) that makes the person or is it the string of memories, the personality or any number of things that you would consider makes up a human being? The brain (person) is the powerhouse of the body (organism). You could even take this one step further. If you could transplant a person's memories, behaviours, quirks, attitudes *etc* (*i.e.* someone's mind) into a robot would this robot be a person? Would they still continue to be the person that you knew? What if the operation to do the transplant went wrong and you lost the person. You would be left with just the organism. Devoid of the person that inhabits it. This is an example of what higher brain death is.

Finally try this. Imagine the hypothetical person Mr A underwent surgery in which he was decapitated. At the same time the now separate head was put on a bypass machine to keep the blood oxygenated and flowing. Then the head goes through a second stage of surgery where all parts of the head are removed leaving only the brain, the eyes and larynx while the rest is replaced on the body (this includes the brainstem which is keeping the body's functions going). Mr A's brain portion still has full awareness of his surroundings, his capacity for thinking and experiencing and he also is able to communicate. The body on the other hand is still breathing, it still digests the food that it is given through a feeding tube, and it produces urine. Is the organism dead? According to the higher-brain death standard this person is but under the whole-brain death standard, it maintains one of the three criteria for brain death, *i.e.* it has control over vital functions of spontaneous breathing and autonomic control of circulation. It also has permanent cessation of cerebral and thalamic function. If one were to maliciously harm the organism in such a way that it did enter a cardiac arrest and it was no longer maintaining these vital functions, is it murder?

What distinguishes us from other species in this respect? Why is it that we can have such confusion surrounding death of humans when there

is no such confusion about death of a carrot, cabbage, dog or cat? The functioning that we are talking about is of extreme importance. It is what defines us as human. Why do you think the term 'persistent vegetative state' came about? It may leave the organism functioning but the person inside is dead. Robert Veatch says "death may be formally defined as the irreversible loss of that which is considered to be essentially significant to the nature of man".[2]

The above experiments show support for a higher-brain standard of death. Although hypothetical I think that it shows profoundly what it is that we consider being alive and that if this is not present then the affected organism is dead.

There are other reasons why there should be a higher-brain standard rather than whole-brain. They are allocation of resources and organ harvesting for transplant. In the public health system as we know it there are so many health dollars with an ever growing pressure to make them stretch as far as possible. As we have shown above there are more people who would be considered dead if they had a higher-brain standard. Before we adopted a whole-brain standard there were a few hospital managers that were getting a little 'hot under the collar' as hospitals were not allowed to withdraw any life-sustaining treatment. A patient on ventilatory support was considered alive whereas previously they would have pronounced dead. The issue then arose that these patients then required full-time medical care, which is a huge drain on limited resources. As such it would be more beneficial to the health system to adopt a higher-brain standard. The resources saved could be put into other areas that show more positive outcomes. Of course ideally we would like to keep people on life support for as long as possible. We have heard reports of people waking from comas after 10 or more years but it is not feasible unless we adopt a 'user pays' system. If we were to liken life support to medication it would be unlikely that Pharmac would allocate funding for it.

The second reason to adopt a higher-brain standard is organ transplant. There is no doubt that there was a second standard for death introduced in order to help facilitate the procurement of organs for transplant. Indeed the chairman of the ad hoc committee was himself a transplant surgeon! With more people being pronounced dead with still functioning organs there would be more to transplant. There would be a greater ability to harvest all of the usable organs in the body. There could be one central theatre for the donor and theatres surrounding for the recipients of the heart, lungs, liver, kidneys, corneas *etc.*

There are problems that exist for the higher-brain standard. The first is that we do not have a definitive test to tell us exactly how much or how well the brain is functioning. We do have ways of looking at the brain. A CT or MRI can show us the structure of the brain. We also have ways of looking at the individual cells within the brain. We are able to do an electroencephalogram, which looks at the electrical activity of the brain, or look at a cerebral blood flow study. Where we have serum creatinine for the kidney or liver function tests for the liver, we have no equivalent test for the brain. We can look at the individual cells but how much can we lose before there is loss of consciousness, loss of integrated function or higher function? However, in the definition of the whole-brain standard of death if any of the three functions are clinically present then the person is considered to be alive. But as one of the whole-brain criteria is loss of consciousness, and that can be tested for. Why can the higher brain not when its only standard is for the same thing?

I have one more point to make. Although this does not differentiate between the brain-death standards it does show why we are yet unable to move towards a higher-brain standard. I think no one yet is adhering to the concept of brain death on an educated level. There have been studies conducted on doctors and nurses who work consistently with brain-dead patients and in organ transplant teams. The findings all show that there is a discrepancy between what the law states and what the subject thought, with a small but significant majority believing that a person in a persistent vegetative state was dead. "Only 35 percent of physicians and nurses who were likely to be involved in organ procurement for transplantation correctly identified the legal and medical criteria for determining death".[3] When asked why it was that they thought that this type of patient was dead some replied that they were terminally ill anyway and that their quality of life was so poor. Another issue raised by the studies was that the terminology that the medical staff used suggested that they thought the patient was still alive: 'the machine is the way that he will have to live the rest of his life'; 'the machine is basically what's keeping him alive', *etc.* I believe that the reason for this is that these people still hold to the cardio-respiratory standard above brain death. When you see the heart beating and the lungs taking in oxygen and putting out carbon dioxide it is hard to take that that person is dead at face value. An EEG could be broken or miscalibrated. However your eyes do not lie. If we as educated professionals cannot put into practice the theory then how can lay people? If we were to try and move things along faster than lay people can accept there would it be construed as doctors playing god? As a result of this we must take things slowly, one step at a time. Whole-brain death today, higher-brain death tomorrow.

The final problem I think is that we are using non-technical terms that allow some interpretation in situations where educated people will be dealing with the lay public. An example of this is how we use the term myocardial infarction to mean that the patient has had a heart attack, whereas a phrase that possibly could be used is end-stage cerebral failure. Here I am likening it to renal failure but the concept is still the same. The brain is no longer working at a sufficient level to sustain the person and it is at a point where transplant or dialysis is needed (for the kidney at least). Creating such a term would make medical professionals overcome this. There would not be such confusion and the transition could take place faster.

Conclusion

Is death the death of the whole brain? In this essay I have attempted to show that it is not. I have shown that metaphysically we are able to think in terms of higher-brain function. What is holding us back is rather society's acceptance of a change and the consequences that it would bring. It is simply a matter of time before we start to take on higher-brain standards of death?

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Kabul, Afghanistan 2005-6

[Name withheld]

The author is originally from Auckland where he trained to be an architect and an optometrist. During the last three years he worked as an optometrist in South Dunedin and at the Dunedin Public Hospital in the Ophthalmology Section, School of Medicine, University of Otago.

I'm a New Zealander working for a Non-Governmental Organisation (NGO) in Kabul, Afghanistan. My NGO works in health, education and development in Afghanistan. I work in their eye hospitals and normally repair hospital equipment, make stuff they need and design some of their media. The NGO I work for runs almost all the eye hospitals in Afghanistan, and in 2004 saw over 240,000 patients in 20 of the 34 provinces. The common eye problems are trachoma, cataracts, and conditions associated with malnutrition, but we're also starting to get untreated diabetic retinopathy because of the diet change here in Kabul. We run 3-year training programmes for local ophthalmologists and optometrists. Eighty percent of all Afghan ophthalmologists have been trained by my NGO. Our HQ is very close to the parliament buildings so it is not unusual for armoured vehicles to ring our block. A big boom I heard two nights ago turned out to be a rocket attack on the nearby Intercontinental Hotel. Yesterday morning there was a suicide bombing on one of the main roads. We drove past it twenty minutes after it happened, and didn't see anything at all. Weird. To maximise our safety we receive daily security updates from the Afghanistan NGO Safety Office (see box over page).

There's a side of me that quite enjoys the kudos of working in a confusing place like this. This country has become a large part of who I think I am. When I'm miles away from here I reminisce about this weird, horrible, fantastic place with a quiet smile. Recently the Red Cross flew me over to repair some equipment at the eye hospital in Herat, near the border with Iran. I felt like a complete fraud when I found that most of their equipment was irreparable. One of the hospital workers had more than enough honesty when he answered my question about what had happened to the $15,000 auto-refractor, "Well we were running it without a voltage stabiliser, and it kept blowing fuses. So we put some bigger fuses in. Now it doesn't work". I did make the hospital laundry-man happy by repairing his old washer and dryer.

In Autumn I went on a two week trip into the mountains of Nuristan. Nuristan is a province between Kabul and the border with Pakistan; you can drive there if you don't mind the nearby war; the road goes through Al Qaeda and Taliban territory. We decided instead to try to hike in over the mountains from the north. It took four days of driving and five days of hiking to get over the 15600 foot pass. We stayed a day and a half, and then left by the same route. Lost five kilos, gained 500 photographs. Brilliant.

Now is winter, friends are a continent away, and the grind of living here beats the novelty. The snowline has descended fast on the nearby mountains. There's a foot of snow in our yard and our dog's water bowl now has an inch of ice in it. Almost all foreigners keep dogs as alarms, along with 10-foot high walls. You never answer the door; you have a guard for that.

In mid-winter, life here can be extremely sapping. Anything that can bring you a smile is to be savoured. I usually enjoy shopping; cruising the second-hand bazaars is one of my favourite Thursday activities. My weekend here is on the Muslim calendar; Thursday and Friday. I'm fortunate to be with my particular NGO. Most foreigners are not allowed to walk around the streets, especially if they're female. My UNHCR friends were until recently only allowed to travel in conveys of two armoured cars. Even then they only had two armoured cars for fifteen expat staff.

Finding weird stuff in the bazaars makes me smile. English muffins and blue cheese, cast off from the military bases, sold at what we've started to call the 'Used-food bazaar'. Leathermans and iPods (new and used) from the bazaar outside the Bagram airbase. A broken

Italian espresso machine from the local bazaar. US$30, five hours fixing-time, before it was putting a big smile on my friend's face. The beautifully pale grey Sony stereo I'm listening to, I may have paid too much for it, but I'm enjoying it, and I had a great chat with the guys in the shop where I bought it. They also had a broken telescope; they didn't know how to use or what it was for. We sat and I drew diagrams of solar systems, lunar orbits, moons with craters. "Like rocket?" they asked. "Yeah, crater is like a rocket."

I want to buy some thin tissue paper to make some papier-mâché floor lamps. My Dari (one of the Afghan languages) is pretty thin; I'd be stoked if I could make this request understood. To try, I'll walk 10 minutes through the mud to one of the guys who sells stationary from a dim shop that really specialises in Bollywood posters and plastic flowers. I'll ask my language teacher tomorrow if paper like this exists; if he doesn't know then I'll negotiate a taxi and search the scattered stationary bazaars. This will likely take all day and I will share the streets with pickpockets and guys who want to 'bump' into any females they see. Maybe I'll discover some new bazaar selling some weird stuff like last week when I found one that sold single bore shotguns being made by an elderly gunsmith, and fur coats, one made entirely of cat-skins. Incredible. Matching cats.

A doctor friend of mine, angry and frustrated by the ossifying speed that everything seems to move with says with his voice cracking just a little, "Amazingly, some people are helped". It's a funny old place. Sometimes you're convinced you're doing nothing but hinder. That is how life often is here. Sometimes I give up. Often I'm angry and frustrated. My friend can only offer a hug with sign-language. The culture prevents her from doing otherwise.

But sometimes you have the sneaky feeling that you may actually be doing something worthwhile.

ANSO North – Security Incident – Armed attack on NGO – Faryab Province.

Incident report: ANSO N201005-095

Location:	Faryab Province, Shirin Tagab district, main north-south route in the vicinity of Qara Shaikhi village near Bai Moghli.
Incident type:	Armed attack.
Date/Time of incident:	20 October 2005, approximately 1330hrs.
Report status:	Confirmed.
Information:	At approximately 1330hrs a NGO vehicle was engaged by small arms fire while travelling south on the main route in the vicinity of Qara Shaikhi village near Bai Moghli. When the vehicle stopped and the occupants disembarked, they were attacked by two armed persons, resulting in four occupants being shot. ANP responded to the incident and an investigation is underway.
Casualties:	1 NGO staff member killed, 3 injured.
Arrest:	None.
Assessment:	The incident appears to be a deliberate attack against the NGO persons given that the vehicle was displaying identifying insignia. As nothing was stolen from the scene, it is assessed that robbery was not the motive for the attack.
Advisory:	ANSO advises NGOs operating in the region to postpone all movement through Shirin Tagab district, and ensure all staff exercise extreme caution. ANSO will continue to monitor the situation and forward additional information.

Above: excerpt from an ANSO (Afghanistan NGO Safety Organisation) report. Non-governmental organisations have provided assistance to the people of Afghanistan for many years while working in many remote and dangerous areas of Afghanistan. Since 2002 civilian aid workers have paid the price of over 45 murders. ANSO aims to maximise the safety of health workers in Afghanistan.

Outcome after Percutaneous Coronary Intervention (PCI)

Is a shortened (14-day) course of clopidogrel after successful coronary artery stenting appropriate?

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ABSTRACT

This study aimed to retrospectively investigate the outcome of 1000 patients after a successful coronary artery intervention and evaluate the appropriateness of a 14-day clopidogrel therapy after the procedure. Participants' data was obtained using two hospital databases, 'Oracare' and 'Cardiobase' and analysed using Microsoft Access and Excel. This study found that there was not a significant increase in clinical event occurrence after a 14-day clopidogrel therapy. As part of this study, a database containing demographic and clinical details of 1000 patients who had PCI with stenting was created. This database will provide the base or comparison for future research.

Ever since the first percutaneous coronary intervention (PCI) was done in 1977, there have been many advances in PCI technology and it was postulated that one day it might extinguish the need for coronary artery bypass surgery. PCI is a minimally invasive interventional procedure that unblocks narrowed coronary arteries through balloon dilatation or other instruments in the artery. While interventional treatment will vary from patient to patient, currently the majority of PCI procedures involve coronary artery stenting. During stenting a small, latticed, metal tube is placed against the artery wall by balloon expansion to scaffold it open following plaque disruption. Stents substantially increase procedural safety and success and reduce the need for emergency coronary artery bypass surgery by reducing restenosis to very low rates (with the latest generation of drug-eluting stents).[1]

The coronary plaque disruption, which follows PCI, activates platelets and coagulation pathways, which play an integral and complex role in the process of thrombosis. Platelets adhere to collagen and von Willebrand Factor at the site of disruption and result in an initial platelet monolayer. After activation, secondary agonists like thromboxane A2 (TXA2) and adenosine diphosphate (ADP) are released. Combined with thrombin generated from the coagulation cascade, these molecules mediate the stimulation and recruitment of more platelets. Because of this, it is not surprising that anti-platelet therapy is vital to the management of patients undergoing PCI.[2]

Aspirin is an anti-platelet agent which inhibits the production of TXA2 by irreversibly acetylating cyclooxygenase (COX). Despite the efficiency of aspirin in reducing adverse events in a variety of ischemic heart disease states, many patients still experience adverse events. Thus, more potent anti-platelet agents have been developed and used. Clopidogrel is an oral anti-platelet agent of the thienopyridine class, which selectively and irreversibly inhibits the platelet ADP receptor. By blocking this receptor, clopidogrel interferes with platelet activation, degranulation and aggregation. When it is given with aspirin, the anti-platelet effect is synergistic.[3,4] A proportion of these patients, for whom clopidogrel did not achieve its pharmacological effect, are classified as having 'clopidogrel resistance'. Patients who are resistant to clopidogrel are more likely to develop complications after PCI.[5]

Following PCI, continuation of dual anti-platelet therapy (aspirin and clopidogrel treatment) for at least nine months instead of two to four weeks, leads to a reduction in major thrombotic events. [4,6] Apart from that, further platelet inhibition can be achieved by increasing clopidogrel dosage beyond currently recommended loading and maintenance doses.[7] These findings may be useful in the management of diabetic patients, who have a higher mortality and adverse event rate following PCI compared to non-diabetic patients.[8]

Worldwide, four weeks of clopidogrel treatment has been accepted as the mainstream management of patients who had a successful PCI with stenting. However, this costly drug is not funded in New Zealand. In Dunedin, the local health board subsidises the use of clopidogrel for two weeks following PCI. While the proposed study was observational and does not compare outcomes following four weeks of clopidogrel treatment with two weeks' treatment, our aim was to retrospectively explore whether there is a significant increase in event occurrence rates after two weeks of clopidogrel therapy in patients who have had a successful stent implantation. We hypothesised that there will be an increased event occurrence rate two weeks after PCI. Since no literature to date documents the outcome of patients who went through a successful PCI with stenting in New Zealand,

we also hoped to create a database through our analysis, which future research can be based on or compared with.

METHODS

The outcome of 1000 consecutive patients who had a successful PCI with stenting done in Dunedin Public Hospital from February 2000 to October 2003 were reviewed. The participants resided in Otago and Southland and were under the care of the Cardiac Department of Dunedin Public Hospital. They came forward for PCI due to problems with coronary artery disease.

Utilizing the clinical database system Cardiobase used in the Department of Cardiology in Dunedin Public Hospital, a list of patients who had a PCI from 2000 to 2004 was generated. From the list, the first 1000 patients who had a successful PCI were selected. To be included in the analysis, participants had to have one or more successful stent implantations in the PCI procedure. However, it did not have to be the patient's first stent implantation or PCI procedure. An additional hospital patient management database, Oracare, was used to find out more about the participants' demographics and readmission details after their PCI procedure. Patients were not identified through their name but through their National Health Index (NHI) number.

From the Oracare database, information about the gender and ethnicity of the 1000 participants was collected. The Oracare database was also used to ascertain whether the participants were deceased, had risk factors (hypertension, diabetes, hyperlipidaemia and smoking), had an event following PCI (time of event and what it was) and whether they had a previous myocardial infarction (MI) or coronary artery bypass surgery (CABG). An event is classified as cardiovascular-related death, myocardial infarction, sub-acute stent thrombosis or urgent target-vessel revascularisation through a repeated PCI or CABG. The Cardiobase database was used to identify the participants' primary indication for the PCI procedure, body mass index (BMI), procedural details (number of diseased vessels, number of treated vessels, complications), drug regimes (dosage of clopidogrel, heparin and Gp IIb/IIIa receptor antagonist), time from the PCI procedure to November 2004 and whether they had clinical restenosis.

The information collected about the 1000 participants from the Oracare and Cardiobase databases was recorded using Microsoft Office Access 2003. Microsoft Office Excel 2003 was used to analyse the data. The angiographic data for patients who had an event within the first 70 days was reviewed to exclude database errors and to establish further information (detailed clinical outcome and coronary vessel details).

Table 1: Baseline demographic, clinical and procedural characteristic

	Timing of event (days after PCI) (n=1000)				
	Group 1 (0-14) n=17	**Group 2** (15-35) n=3	**Group 3** (36-70) n=11	**Group 4** (>70) n=169	**Group 5** (None) n=800
Age (years)	67.8 ±'b1 12.8	64.1 ±'b1 10.9	62.1 ±'b1 8.8	68.9 ±'b1 11.9	66.1 ±'b1 11.2
Men	13 (76.5%)	1 (33.3%)	7 (63.6%)	114 (67.5%)	552 (69.0%)
White	16 (94.1%)	3 (100.0%)	11 (100.0%)	160 (94.7%)	759 (94.9%)
Previous CABG	3 (17.6%)	0 (0.0%)	4 (36.3%)	27 (16.0%)	70 (8.8%)
Previous MI	2 (11.8%)	0 (0.0%)	6 (54.5%)	53 (31.5%) (n=168)	244 (30.5%)
Systemic Hypertension	7 (41.2%)	1 (33.3%)	8 (66.7%)	98 (58.0%)	423 (52.9%)
Diabetes	2 (11.8%)	0 (0.0%)	2 (18.1%)	36 (21.3%)	103 (12.9%)
Smoking - Current	1 (0.1%)	0 (0.0%)	3 (27.2%)	24 (14.2%)	188 (23.5%)
- Ex-Smoker	11 (64.7%)	0 (0.0%)	5 (45.4%)	79 (46.7%)	333 (41.6%)
Hyperlipidaemia	7 (41.2%)	2 (66.6%)	9 (81.8%)	109 (64.5%)	524 (65.5%)
BMI	28.9±'b14.1 (n=10)	28.1±'b10.6 (n=2)	31.9±'b16.1 (n=6)	27.9±'b14.8 (n=105)	29.4±'b111.7 (n=407)
GP IIa/IIIb Inhibitor use	10 (58.8%)	3 (100%)	5 (45.4%)	75 (44.6%) (n=168)	304(38.1%)(n=798)
Heparin Units (1000's)	7.6±'b12.4 (n=16)	6.6±'b12.1	6.4±'b12.3 (n=10)	7.7±'b12.3 (n=166)	7.4±'b12.2 (n=798)
Clopidogrel (weeks)	1.9 ±'b1 0.4	2.0 ±'b1 0.0	2.1 ±'b1 0.3	2.1 ±'b1 0.8	2.1 ±'b1 1.1
Later CABG	2 (11.7%)	0 (0.0%)	4 (36.3%)	35 (20.7%)	0 (0.0%)
Clinical Restenosis	2 (11.8%)	2 (66.6%)	5 (45.4%)	72 (42.6%)	18 (2.3%)
Years from PCI to Nov 05	3.3 ±'b1 1.3	3.9 ±'b1 0.6	3.3 ±'b1 1.2	3.2 ±'b1 1.0	3.0 ±'b1 1.0
No. Deceased at Nov 05	7 (30.4%)	1 (33.3%)	5 (45.4%)	43 (25.4%)	0 (0.0%)

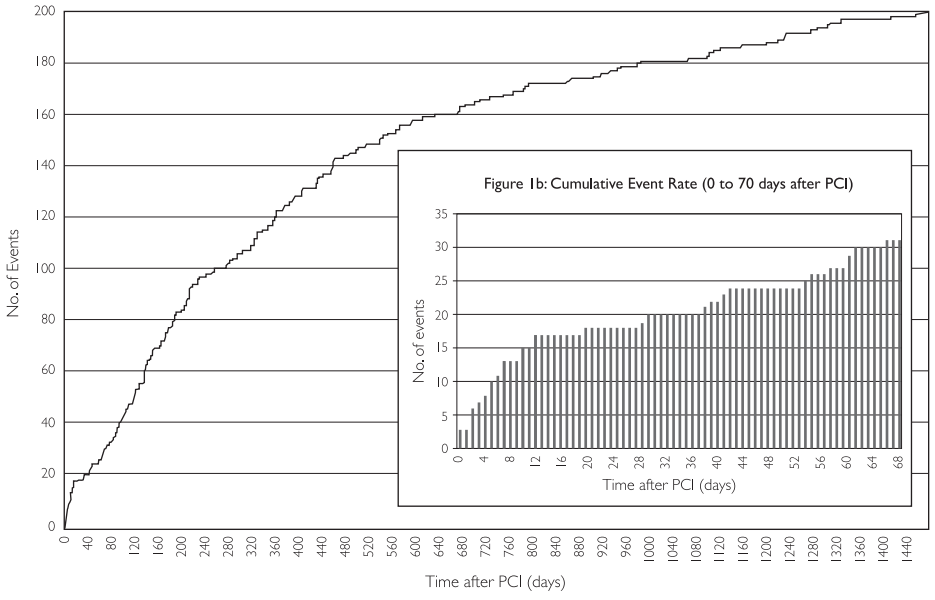
RESULTS

After the demographic and procedural data of the 1000 participants was obtained, it was sorted into five groups: patients who had an event in the first two weeks, an event in the third to fifth weeks, an event in the sixth to tenth weeks, an event after the tenth week and patients who had no event following PCI. The demographic and procedural characteristics of the participants are listed in Table 1 according to their groups.

Of the 1000 patients included in the study, 31 (3.1 per cent) had an event within the first ten weeks. 800 (80 per cent) of the patients did not

Since clopidogrel is a costly drug, more resources could potentially be allocated to other services to provide better patient care if a 14-day therapy is sufficient after PCI.

Figure 1a: Cumulative Event Rate (0 to 1470 days after PCI)



have an event after their PCI procedure. 68.7 per cent of the patients were men and 94.9 per cent were of European descent. The mean BMI of the study participants was 29.1 (n=530). The mean time between the participants' PCI procedure and the time of data collection was three years. All of the participants were given aspirin therapy indefinitely and clopidogrel therapy for at least two weeks after their PCI procedure. Some of the patients had more than two weeks of clopidogrel because they were in another study or were privately funded. Statistical analyses comparing the different groups were not carried out because of insufficient patient numbers in groups 1, 2 and 3. All the patients underwent PCI with stent implantation following initial angiogram.

Originally, 39 patients were found to have had an event in the first 70 days. However, after revision using angiographic data, it was discovered that eight out of the 39 patients did not have an event. Thus, they were transferred to Group 5. All the events within the first 70 days were either death, myocardial infarction or an acute coronary syndrome. There were 12 deaths in the first 70 days (nine deaths caused by cardiovascular factors, one because of chronic renal failure and two patients did not have an identifiable cause of death). In the first 70 days, nine patients had a myocardial infarction and ten patients had an acute coronary syndrome. Six out of the 31 patients (19.4%) had later coronary artery bypass surgery done on them.

Based on Figure 1a, patients were more likely to have an event within the first few days following their PCI procedure. The risk of them having an event diminishes as time goes by. Figure 1b shows that there is an increase in event occurrence in the first 14 days, which reduces after that for the remainder of the 70 days following PCI. Clopidogrel therapy for most patients ends at 14 days after their PCI procedure. However, no significant increase in event occurrence was documented 15-35 days (n=3 in Group 2) after PCI.

DISCUSSION

The results of the study failed to support the hypothesis that there will be a significant increase in clinical event occurrence after a 14-day clopidogrel therapy. Only three participants (Group 2) had an event 15 to 35 days after their PCI procedure. The initial sharp rise in occurrence rate displayed in the first 14 days following PCI (Figure 1b) suggests that most events resulted from complications after PCI (thrombosis, dissection) or possibly resistance to clopidogrel or aspirin therapy.[2,5]

In the present study, 20 (two per cent) had an event between 0 to 35 days after PCI (Table 1). The CREDO trial, which compared a clopidogrel loading dose versus placebo prior to PCI, showed that at 28 days, 6.8 per cent of patients in the clopidogrel pre-treatment group had an event (death, MI or urgent revascularization) and 8.3 per cent of patients in the placebo group had an event. Patients enrolled in the CREDO trial had 28 days of dual anti-platelet therapy (aspirin and clopidogrel) after PCI.[6]

While it is recognisable that the event occurrence rate is lower in the present study, it is important to note that the CREDO trial was a randomised controlled trial and thus is more conclusive than the present study. It is also important to note the limitations of hospital databases such as Oracare and especially Cardiobase. The information recorded in the Cardiobase database in the Cardiac Department was not complete, not entirely accurate and not reviewed by cardiologists. Angiographic and clinical outcome review showed that 8 out of 39 (20.5 per cent) events in the initial analysis were false. This mistake was corrected.

The present study showed that a 14-day clopidogrel therapy after PCI did not result in a significant increase in event occurrence rate 15 to 35 days after PCI, which supports the decision by the local health board to only subsidise a 14-day clopidogrel therapy following PCI with stent implantation. However, further prospective studies must be done to confirm this finding, such as a randomised control trial comparing the outcome of patients on a 14-day clopidogrel therapy versus a 28-day clopidogrel therapy after PCI. Since clopidogrel is a costly drug, more resources could potentially be allocated to other services to provide better patient care if a 14-day therapy is sufficient after PCI.

By doing the present study, a database containing demographic and clinical details of 1000 patients who went through PCI with stenting was created. Using this database, we can determine the platelet response to clopidogrel treatment in the patients who had an event in the first 35 days through platelet function assays. By doing so, we hope to provide better care to patients who do not respond well to clopidogrel by using other anti-platelet agents, such as oral Glycoprotein IIb/IIIa inhibitors, with the hope that event occurrence rate following PCI will be reduced.

ACKNOWLEDGEMENTS

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Prescribing of Antiepileptic Drugs (AEDs) during pregnancy

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ABSTRACT

This article combines the results of literature reviews conducted for two separate but related topics, namely "General principles of medication use during pregnancy" and "Anti-epilepitc drug use during pregnancy". This has allowed the provision of a more comprehensive coverage of this important topic i.e. the general principles and a demonstration of these principles by a specific class of drugs.

KEYWORDS

Pregnancy, Epilepsy, Anti-epileptic Drugs (AEDs)

INTRODUCTION

A recent survey has shown that 83% of mothers took medicines throughout their pregnancies.[1] Most medicines given in pregnancy are for the benefit of the mother and the foetus is the unintended recipient. All drugs diffuse across the placenta to some extent and many can have harmful effects on the foetus.[2] This review aims to provide a broad overview of medicine usage during pregnancy and to focus specifically on the management of epilepsy during pregnancy.

GENERAL PRINCIPLES OF MEDICATION USE DURING PREGNANCY

What is a teratogen?

A teratogen is any agent which when administered to a pregnant mother directly or indirectly causes structural or functional abnormalities (*i.e.* teratogenic effects) which present both in the foetus and congenitally.[2,3]
Examples of teratogenic effects are [2]:

- Chromosomal abnormalities
- Resorption or abortion of the early embryo
- Structural malformations
- Intrauterine growth retardations (IUGR)
- Death of foetus
- Functional impairment in neonate *e.g.* Deafness
- Behavioural abnormalities
- Mental retardation

Medications and the foetus: how do medications reach the foetus?

Medications taken by pregnant women reach the foetus by crossing the placenta which is the same route taken by oxygen and nutrients, which are needed for the foetus' growth and development.[4, 5, 9.]

Nearly all medications, except those with a very high molecular weights such as insulin and heparin, cross the placenta to the foetus. Lipid soluble, un-ionised medications cross more rapidly than polar medications. All medications have the potential to affect the foetus.

Factors influencing teratogenesis: timing of medication exposure

How a medication affects a foetus depends on the foetus' stage of development and the dose of medication given.[2] (refer to Table 1).

During the pre-embryonic period, which lasts until 14 days post-conception (Table 1), exposure to a teratogen has an all-or-nothing effect. Damage to all or most of the cells results in death of the foetus. If only a few cells are injured then normal development is likely.

The foetus is most vulnerable to teratogens during the embryonic period *i.e.* 3-8 weeks after conception, when the major organ systems are formed. Some medications have a specific time period of highest risk for a particular defect *e.g.* exposure to sodium valproate during the time when the neural tube closes *i.e.* 17-30 days after conception, may result in spina bifida.

From week nine post-conception to birth (foetal period) the foetus is less susceptible to teratogenic effects, although some organs such as the cerebellum and some urogenital structures are still forming. A medication given during this time is more likely to cause general growth retardation or interfere with the functional development within specific organ systems. For example warfarin may cause intracranial haemorrhage in the foetus after exposure in the second and third trimesters of pregnancy.

Medications taken close to term can cause predictable pharmacological effects in the neonate. For example, non-steroidal anti-inflammatory drugs (NSAIDs) taken in the last six weeks of pregnancy can cause premature closure of the ductus arteriosus giving rise to neonatal pulmonary hypertension.[2, 3]

Dose-response relationship and polypharmacy

Teratogenic effects are usually dose-dependent. Studies have shown a significant relationship between the incidence of neural tube defects and total daily dose of sodium valproate.[3, 6]

Exposure to multiple medications is more likely to result in abnormalities than exposure to a single medication. A study of malformations among babies born to women with epilepsy found that the incidence of birth defects increased with the number of anit-epileptic drugs (AEDs) taken. There was a 4% incidence of birth defects in babies born to women taking one antiepileptic medication and a 23% incidence in babies whose mothers took four or more medications. Further evidence of such synergistic teratonergic effects is lacking but polypharmacy should be avoided whenever possible.[3]

Genetic factors

Risk of teratogenicity can differ among individuals. There is increasing evidence from studies involving AEDs that genetic factors are an important determinant of teratogenic effects.[3,7] Most AEDs are converted by hepatic microsomal enzymes to epoxide intermediates which are then detoxified by the enzyme epoxide hydrolase. Studies suggest that malformation rates correlated with high levels of epoxide intermediates. Phenytoin teratogenicity can be linked with high levels of these metabolites occurring in individuals with low activity of the enzyme epoxide hydrolase, the activity of which is genetically determined.[7]

Pregnancy induced pharmacokinetic changes

The following pharmacokinetic changes occur during pregnancy affecting the way the body handles medications:

- Renal function increases leading to renally eliminated medications such as gentamicin and digoxin being eliminated faster.

- Body water increases by about 8 litres and plasma volume may also increase. As a result, there is a decrease in the serum concentration of many medications, especially those with a small distribution volume.

- Protein binding of medications falls due to a decrease in serum albumin concentration. This leads to an increase in the unbound (free) fraction of the medication. The protein binding of several antiepileptic medications such as phenytoin and sodium valproate has been shown to decrease in the last trimester of pregnancy.

- Some medications have lower serum concentrations during pregnancy. This can

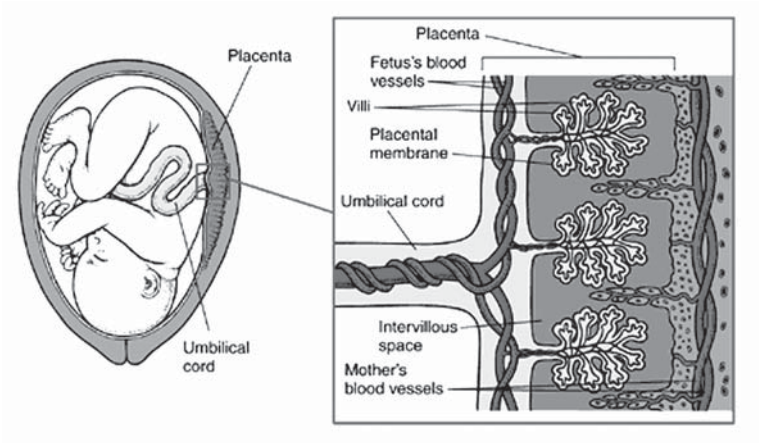
Table 1: Summary of Foetal Development during pregnancy[5]

Weeks	Development	Organs vulnerable to drug effects
0-3 After conception	Limb buds and a primitive central nervous system forms. Heart develops and starts to beat.	Brain and skeleton are sensitive to teratogenic effects from week 3 until the end of pregnancy (week 40 post conception). Heart is most sensitive to teratogenic effects during 3-4 weeks.
3-8 Embryonic period	Cell division is rapid. Major organ system formation occurs. Head and facial features develop. Foetus shows early movements. External genitalia are present but sex is not distinguishable. From 6 weeks onwards the foetus is visible on ultrasound.	Foetus is very vulnerable to birth defects during this period as major organ formation is occurring. e.g. neural tube defects and spina bifida occur during this time.
8-12	Eyelids fuse and sex is apparent. Fetal circulation starts functioning. Sucking and swallowing begins and the foetus moves freely. Kidneys begin to function – foetus passes urine from 10 weeks.	External genitalia are most sensitive to teratogenic effects during 8-9 weeks.
12-16	Rapid skeletal development. Nasal septum and palate fuse. Lanugo (a fine downy hair) appears on body.	
16-20	Mother feels fetal movements. Fetal heartbeat can be heard with stethoscope Fingernails can be seen and skin cells begin to be renewed.	
20-24	Most organs are capable of functioning. Foetus goes through periods of sleep and activity and responds to sound.	Medications taken after organ development is complete may alter growth and function of normally formed organs.
24-28	Eyelids reopen and there are respiratory movements. Survival may be expected if baby is born prematurely.	
28-32	Foetus begins to store fat and iron. Skin becomes paler and less wrinkled.	
32-36	Fat storages makes the body more rounded. Nails reach the tip of the fingers. Lanugo disappears from the body and head hair lengthens.	
36-40 post conception	Baby's contours are rounded and its skull is firm. Term is reached and birth is due.	

Adapted from: Every M, Hallam C. **Overview of Pregnancy.** *Pharmaceutical Journal*. 2003;270:194-196.[5]

Figure 1: How drugs cross the placenta

Some of the foetus' blood vessels are contained in tiny hairlike projections (villi) of the placenta that extend into the wall of the uterus. The mother's blood passes through the space surrounding the villi (intervillous space). Only a thin membrane (placental membrane) separates the mother's blood in the intervillous space from the foetus' blood in the villi. Drugs in the mother's blood can cross this membrane into blood vessels in the villi and pass through the umbilical cord to the foetus.



Reproduced with permission from Merck Manual – online edition[4]

be important for medications showing good correlation between plasma levels and therapeutic effect e.g. phenytoin, carbamazepine, lithium and digoxin. Women taking these medications should have their serum concentrations monitored and dose adjusted during and after pregnancy.[3]

FDA Classification of risk in pregnancy

The United States of America (USA) Food and Drug Administration (FDA) has developed the most widely used system to grade the teratogenic effects of medications. FDA assigns a safety category for use of medications in pregnancy using a 5 letter system: A, B, C, D and X. Category A indicates no demonstrable risk, B to D indicate increasing level of risk while category X indicates extreme risk [8] (see Table 2).

Table 2: FDA Classification of risk in pregnancy[8]

Category	Definition
A	Controlled studies in women fail to demonstrate risk to the foetus in the first trimester (and there is no evidence of a risk in later trimesters) and the possibility of fetal harm appears remote.
B	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester (and there was no evidence of a risk in later trimester).
C	Either studies in animals have revealed adverse effects on foetus and there are no controlled studies in women, or studies in women and animals are not available.
D	There is positive evidence of foetal risk, but the benefits from use in pregnancy may be acceptable despite the risk.
X	Studies in animals or humans have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of use of medication in pregnant woman clearly outweighs any possible benefit. The medication is contraindicated in women who are or may become pregnant.

Evaluation of studies

Data on human exposure to medications during pregnancy is limited because drugs are not tested in the pre-marketing phase on women of child bearing age or pregnant women. Many drug companies and independent agencies have established pregnancy registries which prospectively collect information on drug exposure during pregnancy. Some examples of pregnancy registries are listed below:

• Australian Pregnancy Register for Women on Antiepileptic Medication – reports on pregnancy outcomes for women taking AEDs.

• Northern American Epilepsy and Pregnancy Registry – women with epilepsy taking AEDs who are pregnant are encouraged to contact the registry voluntarily and pregnancy outcomes are then reported.

• Lamotrigine Pregnancy Registry – set up by the manufacturer of Lamotrigine to monitor pregnancy outcomes in women exposed to lamotrigine.

• EURAP – Central Registry of Antiepileptic drugs – an international antiepileptic drugs and pregnancy registry. A number of health professional groups world-wide with an interest in AED use during pregnancy contribute information on pregnancy outcomes to this registry.

• Motherisk programme (Hospital for Sick Children, Toronto, Canada) – prospectively enrol patients who contact their teratology information service and follow the pregnancy. The pregnancy outcome data is then compared to non-exposed cohort and the results are published as prospective cohort studies. The Motherisk programme has a website, containing useful information and abstracts of studies undertaken by their organisation, available on URL: http://www.motherisk.org/drugs/index.php3

Table 3 outlines the possible study types used to investigate the teratogenic properties of drugs and their advantages and disadvantages.

Table 3: Evaluation of study types used to investigate teratogenic risk[10]

Study type	Advantages	Disadvantages
Animal/ in vitro	Can provide clues concerning safety of drugs in humans	Extrapolation of findings to human pregnancy is questionable
Case reports	Have been useful indicators in proving the teratogenicity of certain drugs	Findings may be due to chance or influenced by a combination of factors e.g. genetics, environment, other drugs taken, recall bias
Case control studies	Cost efficient, fast, allows analysis of rare malformation	Retrospective exposure assessment Recall bias
Prospective cohort studies	Prospective exposure & outcome assessment Allows analysis of rare exposures Temporal relationship between drug exposure and gestational age can be accurately determined No recall bias Results can be extrapolated to a defined population	Time consuming More expensive than case-control studies Loss to follow-up Low numbers obtained
Retrospective cohort studies	Less time consuming than prospective cohort	Retrospective exposure assessment Loss to follow-up
Randomised controlled trials	Most reliable methodological approach	Not ethical Rarely used for the evaluation of teratogenic properties of drugs
Systems based on voluntary or spontaneous reporting	Possibility to investigate drugs in a real life setting	Incomplete data, the outcome assessment often retrospective Potential for under-reporting

MANAGEMENT OF EPILEPSY DURING PREGNANCY

Case

Mrs R is a 27 year old pregnant female who presented to the Women's Health clinic for prenatal care at 15 weeks gestation. This is her first pregnancy. She has been an epileptic since the age of 8 suffering from tonic clonic seizures. Her epilepsy has been well controlled over the past five years during which she has been taking Phenytoin at a dose of 100mg twice daily. She has no other medical problems and is not using any other medications.

Mrs R has voiced her concerns about phenytoin use during pregnancy and wants to know:

"What are the risks associated with taking phenytoin during pregnancy?"

Continued on page 36

Tanzania – more than an experience

Aoifé Kenny
Third year student
Dunedin School of Medicine
University of Otago

Aoifé Kenny is a third year medical student at the University of Otago Medical School. Her ultimate goal is to use her medical training in emergency and/or development settings.

A friend of mine invited me to "write about your trip to Tanzania". With so many stories and experiences I wanted to share I believed that penning a short piece would be reasonably straight forward. I didn't realise how difficult it would be for me to put my thoughts into words. It is not an experience that I had; it is a part of who I am now. It is in me. Like the persistent red dirt that remains in the stiches of my clothes, Africa will never leave me.

Currently I am reading a book called "Emergency Sex (and other desperate measures)". One of the authors is a young doctor called Andrew from New Zealand. At the moment in the story he has been working in Cambodia with the Red Cross for so long he thinks the Medical Council has removed him from their records. He wanted to get away from academic medicine and hospital hierarchy. He wanted to be a "real doctor", in the middle of nowhere, where he was desperately needed. Other people admire him for making a difference "with his bare hands". He is also respected for knowing the people of Cambodia, living with them, being their friend. Andrew reminded me a lot of the couple that we lived with in Tanzania. Tom and Fiona Gibson are a doctor and nurse team doing a two year Volunteer Service Abroad (VSA) assignment. They are stationed in Huruma Designated District Hospital and live in the village

of Mkuu in the district of Rombo, 1500m up Mt Kilimanjaro. Their assignment is focused on the development of the local hospital and the skills of healthcare workers. This is on top of their clinical work. Although hailing from New Zealand, they speak Swahili, shop in the local market like everyone else, and seem to understand the real situation of the people. They are admired and deeply respected. To a certain degree, I can also relate to Andrew. I want to make a difference, and chose Medicine as my means of doing so. Maybe I am being naïve, or even arrogant, thinking that it is possible. Whatever the case, I am going to try and Tanzania concreted that goal.

Thanks to Tom and Fiona I gained a lot of clinical experience and knowledge. Having only just finished my second year at Otago medical school, I had no 'hands on experience' with patients. Just weeks after finishing my second year exams, here I was, examining people at the HIV clinic, seeing births, and all scrubbed up helping drill a pin through a man's tibia! Ward rounds, x-ray discussions, weird and far progressed conditions. It was a great experience for me and the other two medical students. The lack of diagnostic 'machinery' showed us that we rely on it far too much in the Developed World. Developing good clinical skills, always making time to think clearly, confidence, and trust in your judgement were just some of the lessons gained.

What we learnt about the local people and society in general was invaluable. The majority of those living on the mountain are subsistence farmers, meaning that they eat what they grow. There is some trading done, however most people would not have any money. Forget about living "under $US1 a day". And yet they were the happiest people I have ever met. The women especially amazed me. They worked on the shamba (small plot of land), carried loads as heavy as themselves up the mountain and raised large families without complaint. They lived for their children. They were so strong. To look in their eyes was to be inspired. Such a simple connection helped me to understand that we are all in essence the same. I watched a mother caress her child's head as her husband was told that his child was dying. The one-year-old's twin was gazing at the nurse, then at her sister. In that moment I saw the value of life and the fight for it. I once heard the phrase "life is cheap in Africa". Life is always precious.

My hosts' assignment was based around development and not aid; this is in line with all VSA projects. It's not just the "giving a man a fish vs. teaching him how to fish" concept; it's more than that. We cannot, as people wanting to help, go into a place and try or expect to change everything. That is very self-righteous. Why is it that we think we have it all spot-on? I believe now that development is about sharing ideas and methods with the sharing going both ways. We all have much to teach each other. The people I met taught me the strength of the human spirit, to relax and take things slowly, and how vital it is to look after one another. I saw pure compassion, true fear, and the real meaning of empathy. They even have a word expressing empathy "pole" (pol-ay); there is no English translation, not surprisingly.

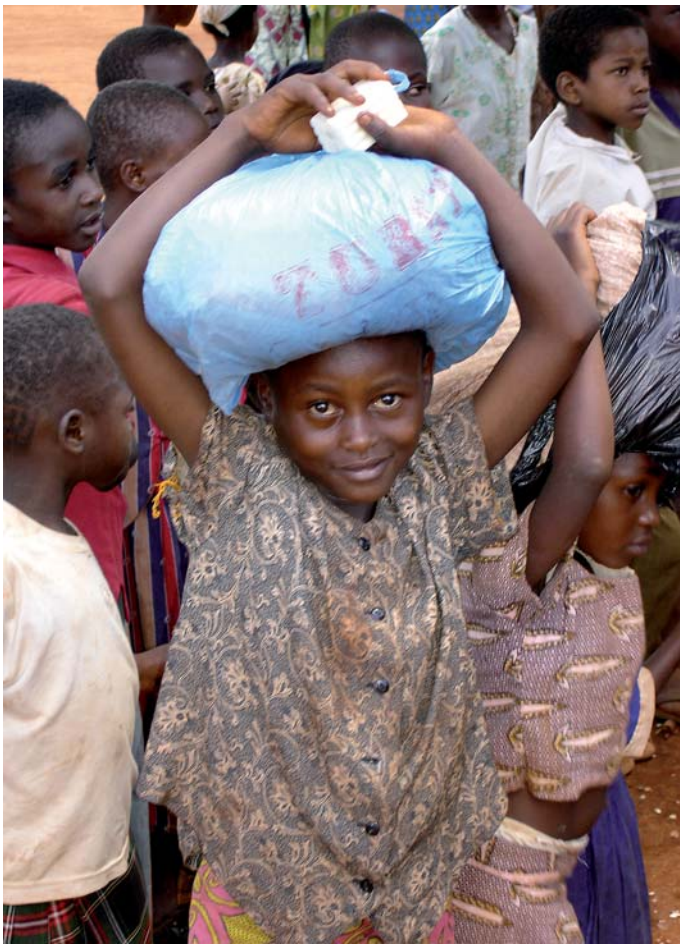
The smallest children also had a boiled egg. We could only find 120 eggs in the village the evening before, so only the neediest children got one.

We can all do our bit. As Mother Teresa said "Do not wait for leaders; do it alone, person to person". My partner, Tim, and the other 'non-medics' spent their time teaching children in the hospital English, tutoring nursing students on how to use computers, and creating a data base for the funding of the Tumaini centre for orphans. Although this group was young with all of them in their early twenties, even their limited time in the area resulted in a tangible difference

The most inspiring moment of my time in Tanzania was a Christmas food delivery to 200 plus Tumaini children. They all received 6kg of maize and a bar of soap as a present from us. As they waited patiently and quietly in line we gave them a doughnut-like snack to munch on. And the smallest children also had a boiled egg (we could only find 120 eggs in the village the evening before, only the neediest children got one). Such simple gifts, and so greatly appreciated. I have never felt so humbled. The children had nothing, some slept in trees, and yet they were well behaved, kind, and happy. We played in the church's dirt courtyard before they headed off with their precious load atop their beautiful heads. I have so many amazing memories of that day, ask me some time.

'Tumaini' means 'hope' and that was the children's gift to me. Nothing is a lost cause. And if we try, really give it all we have, who knows what we can achieve in friendship and partnership.

[For more information on the Tumaini Project please contact me on aoife.kenny@myself.com]



Going back to the Pacific

Report of the Pasifika Medical Association Conference

Xaviour Walker
Trainee Intern
Dunedin School of Medicine
University of Otago

"Collective creation of our future; The Plight of the modern Pacifician"
21-24 August, 2005 Nuku'alofa. Kingdom of Tonga

Xaviour Walker is of Tongan and Northern Irish descent. He is currently a Trainee Intern at Dunedin School of Medicine. He is the president of The New Zealand Medical Students' Association and past president of the Otago Medical Students' Association. He has interest in Pacific Island health, rural health and global health issues.

Representing the University of Otago

Dr Faafetai (Tai) Sopoaga, Xaviour Walker, Shekhar Sehgal, Shivani Shilam, Sina Barrot, Charity Vagai, Luseane Raratabu, Noela Dugu, Vaaiga Autagavaia, Emily Giblin, Rachel Dyer, Rachael Wilkinson

In August last year I was fortunate enough to travel with nine other Pacific medical students from the University of Otago to attend the Pasifika Medical Association Conference (PMA) in Tonga.
The PMA was formed in 1996, providing a forum for, Pacific doctors, medical students and other allied health professionals. The PMA alternates its conferences between New Zealand and one of the Pacific Island

The number one health risk in the Pacific island is obesity. Type 2 diabetes is 3-4 times more common in Pacific Islanders compared to New Zealand Europeans. Pacific people have less knowledge about their disease and are more likely to be receiving sub-optimal treatment.

countries. This conference attracts health professionals, politicians and leaders from throughout the Pacific to discuss the current issues facing its people in New Zealand and the Pacific.

The Kingdom of Tonga has a population of 112,000 people and is composed of 169 islands, 36 of them inhabited, and is divided into four main island groups – Vava'u, Ha'apai, the Niuas and Tongatapu. We stayed on the largest island Tongatapu in the capital Nuku'alofa which is home to His Majesty King Taufa'ahau Tupou IV.

Our visit was in the middle of a civil service strike, which was highly publicised in the New Zealand media. On the NZ news it seemed that the country was in anarchy, though in reality we only saw peaceful sit down protests beside the parliament.

Day 1: Church Service and Conference opening

On the Sunday before the Conference, we attended a church service at the great Saione: Centenary Wesleyan Church. This magnificent church is also His Majesty's church, though unfortunately he was away. We, however, were treated to the beautiful voices of the Fasi Free Wesleyan Church Choir and going to church in the islands is an experience that everyone should have. The conference was opened by the Honourable Princess Nanasipau'u Tuku'aho and the welcome address by Mr. Viliami Ta'u Tangi, who is the not only the chief surgeon in Tonga, but is also the Minister of Health.

Day 2: Theme: Non Communicable Diseases

Non communicable diseases (NCD) are the leading cause of morbidity amongst the Pacific People. The number one health risk in the Pacific island is obesity. Type 2 diabetes is 3-4 times more common in Pacific Islanders compared to New Zealand Europeans. Pacific people have less knowledge about their disease and are more likely to be receiving sub-optimal treatment.

In the pacific it has been described as the "double burden" with a decrease in infectious diseases and an increase in NCD. The effects of westernization lifestyle – globalization and urbanization are having a major impact on the Pacific with aggressive marketing from the tobacco, food and motor industry. Confronting the problem has been difficult with the political, financial and geographical barriers. Culture and social acceptance has to be taken in high consideration as food has a high status and is an integral part of hospitality.

We heard from many top researchers, leaders and medical professionals from around the pacific and New Zealand. The common themes were that there is a need for:

- Long term investments in funding and policies to control NCD,
- social change fundamental for sustainability, and a
- NCD strategic plan.

Many of the Pacific islands are leading the fight against NCD, including the Tongan Ministry of Health who is building a diabetes programme with partnership with the Prince of Wales Hospital in Sydney. The World Health Organisation (WHO) is spending 60% of their 2006/7 budget on NCD control in the Pacific.

One of the most exciting investments in research is the $6.5 million Pacific OPIC (Obesity Prevention in Communities) project. This is a collaborative study including Fiji, Tonga, Australia and New Zealand which will be run over 5 years looking at:

- National, Community, Individual levels of obesity,
- multiple strategies (e.g. education, policies, environments, social marketing), and
- all community settings (e.g. villages, churches, schools, sport & recreation, food outlets).

Day 3: Theme: Injury Prevention and Research

Road traffic accidents are a hidden epidemic in the Pacific. This is due to the increase of cars, the need for road infrastructure, lack of legislation with drink driving and seat belt use. In Tonga the number of registered cars had increased by 58% since 2000.

There are economic implications of road traffic injuries including the direct costs involved in hospital admissions, with complicated cases transferred to New Zealand. Considering the limited financial resources available these are costs that restrict money spent in other areas of health. The indirect costs include time off work, or school, and time spent for caregiving by families.

The key to address this neglected problem is prevention through legislation on drink driving, seat belt use and cyclists wearing helmets. There is a need for speed control, road maintenance and planning, strict vehicle inspection and driver licensing with tougher penalties.

Day 4: Oral Health and Mental Health

Oral health is an important and often neglected aspect of health in the Pacific. The cost of training oral health care workers for the pacific has always been a problem, with previous graduates sent to the Otago Dental School for training at significant costs. In 1993 the Fiji School of Medicine set up a dental school. It was a delight to hear about the successful training of pacific dentists and oral healthcare workers specific for the Pacific.

One of the most exiting developments in mental health is a WHO report which has a detailed analysis of the mental health needs and resources in Pacific Island countries. This is the preliminary phase in the development of a technical support programme for the organisation of mental health services in countries in the Western Pacific region.

Summary

The opportunity to attend this conference allowed us to hear first hand of the problems currently faced by Pacific health. As doctors in training it was a chance to speak and make contact to our Pacific role models and Pacific health providers. We are extremely grateful for the funding provided by our sponsors which enabled us to attend the conference. Compared to the general New Zealand population, Pacific people have a poorer health status, are exposed risk factors to poor health and experience barriers accessing health services. It is a major credit to these organizations for investing in the future Pacific health professionals.

Information about this year's conference

Pasifika Medical Association of New Zealand: 8th Annual conference

Theme: "Women – Strength of the Pacific"

Dates: 24th-26th August 2006

Venue: Waipuna Hotel & Conference Centre, Mt Wellington, Auckland

Website: www.pacifichealth.org.nz

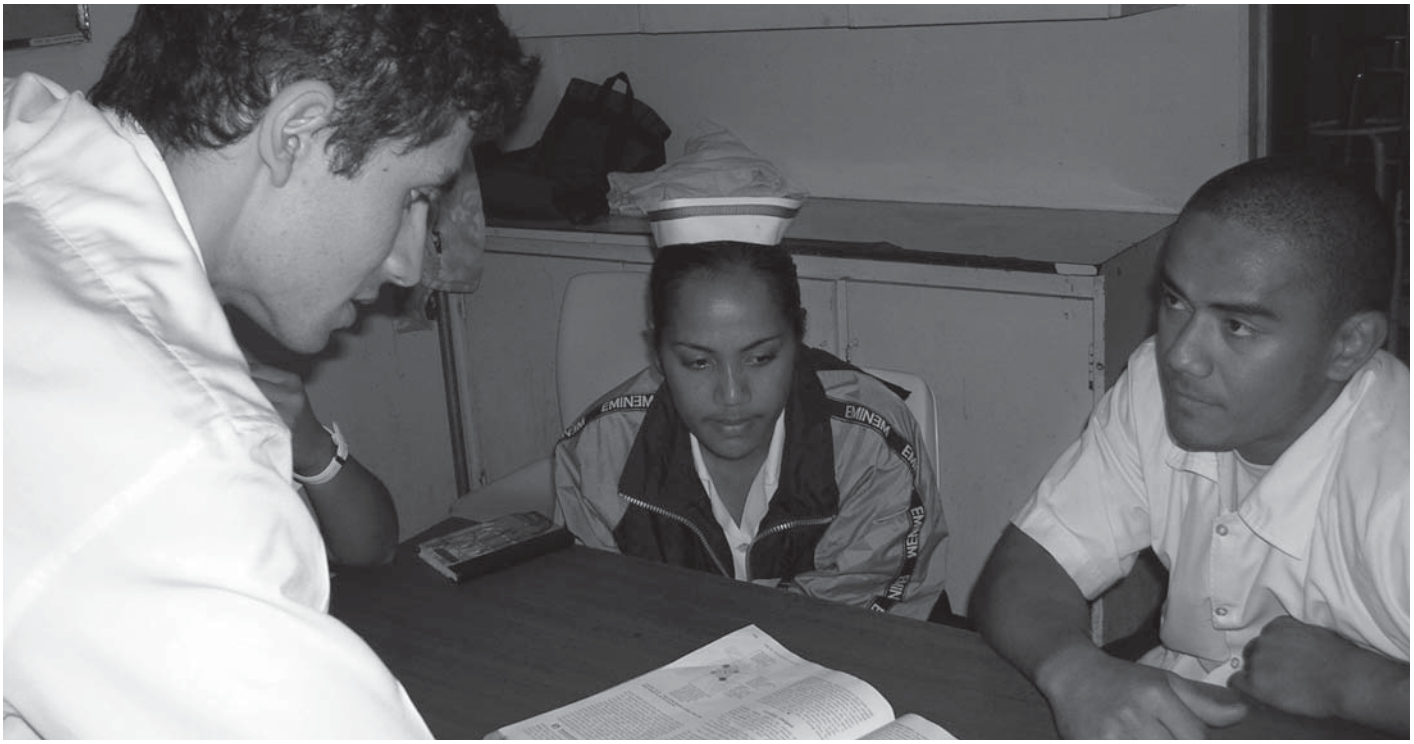
Contact: pma@pacifichealth.org.nz

Sponsors

Royal College of General Practitioners
Otago Pacific Peoples Health Trust
University of Otago School of Medicine

Acknowledgements

Tongan Medical Association
Pasifika Medical Association
Presenters and speakers at the PMA conference



Where to from here for Medical Schools?

Brad Stone
Third year student
Dunedin School of Medicine
University of Otago

Prior to beginning medical school, Brad studied commerce at Otago University and worked in the financial services sector in Europe. He has become involved with the NZMSA since beginning his medical studies, and continues to be interested in the delicate balance of health provision and scarce financial resources, as well as where the profession is heading in New Zealand. He hopes that he might be involved in addressing some of these issues in his future career.

Is medical health still a public good?

The provision of a countries' health care is the most fundamental of socialist notions. Taxpayers provide to their central government revenue that is used to, amongst other things, choose, educate, train and employ those members of society who take the responsibility of maintaining the overall good health of a nation. But is this public good indeed just that any more in New Zealand?

The most damning implication of all is that the provision of medical education itself is becoming less associated with providing Aotearoa with a future wave of health providers. Tertiary fees are increasing across the board, but to lump education of junior doctors into the 'investment in their future' argument, as we might well do with accountant, lawyers, architects and other private sector professions, detracts greatly from the idea that medical health is, and will continue to be, a public good. Even the most clumsy of financiers are aware that financial investment should reap financial reward. Offshore jobs, highly paid specialties, maverick junior doctors holding out for locum wages – the downstream workforce effects of medical students treating their education as an investment in their fiscal security, instead of an investment in improving national health across the board, paints not a pretty picture. With no likely immediate appeasement to increasing fees and the prospect of full-fee paying students entering the medical student ranks, the cost of a students financial 'investment' is becoming so exorbitant that the expectant rewards are forcing both the overall cost of medical health provision through the roof, and those same medical health providers out of NZ, in some cases indefinitely. Recent surveys of the career and emigration intentions of Christchurch Clinical School students after graduation confirm that the net effect of increasing student debt levels is that the NZ medical workforce is suffering, both in terms of numbers of doctors in certain specialties (GP, psychiatry) and numbers of doctors in general[1]. In the best interests of NZ's general health, future medical students should not be forced into a situation that they consider their degree as an investment in their career, but an investment in the future of their country. Although funding is an issue that should be addressed by the central government, there is also plenty that can be done by the medical providers to ensure that medical health remains a public good, and is delivered in the most optimal fashion.

Medical School Intake

The winds of change are whispering in the breeze of NZ's major medical education providers. The most influential western countries – America, the UK, Canada and Australia are all usurping their traditional methods of medical education, and opting for inspired new methods of not only teaching, but selection of medical candidates. Is it about time NZ followed suit?

Demographic Structure

From a solely holistic point of view, if medical care is to be perceived as a public good, surely the demographics of those souls lucky enough to gain admission to medical school should accurately reflect the demographics of the entire population. Ideally, those same students should be academically capable enough to handle the rigours of such an arduous course, compassionate enough to make those who are ill feel less self conscious and scared, and sufficiently well dispersed in their vocational interests and residential preferences to take up the relevant medical posts that require filling. Oh, and if they remained in the country to practise for a while, that'd be just dandy too.

Let's consider those being granted the privilege of being educated as the countries future doctors. Despite a population that is nearly 20% Maori or Pacific Islander[2], less than 3% of graduating medical students had this ethnic background in 2003[3]. Despite the fact that nearly 10% of our GDP is derived from agricultural, horticulture, forestry or fisheries[4], and over 40% of the nation live in settlements of 200,000 or less (including over 15% in a settlement of 1,000 or less)[5], rural students are still underrepresented in medical class intakes. Currently there are a number of initiatives being followed up by a variety of groups to encourage an increase in those underrepresented demographic groups into medical education. The medical schools make a number of places available to those persons that meet the criteria for entrance as a member of those demographic groups. But medical entrance and financial support only solves part of the problem. It cannot be expected to accurately bring medical school demographics into line with the population demographics. And it definitely will not ensure that the areas of the medical workforce being addressed (rural, Maori, Pacific Island health) will be catered for by those they have granted entrance to under the given scheme in the future when they graduate[6].

Other countries have displayed innovative ways of addressing the very same issues that New Zealand is presented with at the current time.

In response to improving demographic representation amongst medical students, Australia have introduced rural entrance places, funding, ongoing training and bonding schemes to encourage persons of rural origin (or those interested in working rurally) to train and return to an area of workforce shortfall. Maastrict University in the Netherlands applies a minimum academic achievement level, and then draws successful candidates from a ballot, reasoning that as long as the candidates are of sufficient academic aptitude to cope with the course, then a fair demographic dispersion of students' best serves their future workforce. While this may be harsh on those individuals who have done sufficiently well to distinguish themselves from the pack, it does improves diversification, and the question begs asking: Is it any less likely to produce a capable, compassionate workforce than other measures (such as solely academic grades or UMAT) which research suggests cannot conclusively assess a students aptitude for the career[7,8] and can almost certainly not be relied on to resolve current specialty shortfalls? With current workforce shortages in the areas of rural practitioners, GP's and psychiatrists, should the medical admissions board be inclined to focus less on the fairness of entry to the individual, but more on the future workforce implications of those who are selected?

With current workforce shortages in the areas of rural practitioners, GP's and psychiatrists, should the medical admissions board be inclined to focus less on the fairness of entry to the individual, but more on the future workforce implications of those who are selected?

Graduate Entry

But what about other aspects of medical entry? There are many positive arguments for New Zealand changing their entrance protocol to a completely graduate entry stance. Research in the UK has been inconclusive in determining whether the age of entry to medical school results in better or worse performance, and higher or lower rates of dropout[9]. However, interestingly, some research has shown that prior study, particularly of humanities, correlates with better clinical performance[9].

As such, Australia has recently opened Flinders in Brisbane, its first exclusively graduate entry medical school, which also allows for prior study in areas outside health sciences. This correlates well with the American system, which has been operating under graduate entry medical schools for some time. Making a career decision at a young age, which can be based on romanticised notions, or as a result of a desire to simply prove they can win the health science rat-race, is not necessarily an optimal way to make a decision that has significant implications on a persons future life, and the livelihood of those they are to care for. This can cause despondency further down the track, and result in increased drop out rates. Furthermore, some research and personal attestation from lecturers has pontificated that graduate entry students are easier to teach and get more benefit from teaching[9,10] In turn, it would be reasonable to assume this would have a positive effect on recruiting and maintaining academic staff (another problem likely to require addressing in the not-too-distant future).

Studies have shown that those students with a rounded educational background, such as in the sciences AND humanities (or even humanities alone), often correlate to better clinical practitioners[9,10]. If this is so, would introducing post-graduate entry only to medical schools in NZ therefore reduce the need to spend such a large portion of undergraduate teaching on non-biomedical subjects, those subjects aimed at bringing a PC, smiling health workforce through the ranks? Not to say that this isn't an important element of healthcare, but can anyone really tell me that person-to-person interaction, empathy and compassion is really something you can uncork and serve up in 3 lectures and 2 tutorials a week? Perhaps the excellent clinical practicing of graduate students is as a result of that commodity that cannot be bought sold or stolen; life experience. If we allowed only graduate school medical entry as they do in the States and increasingly in the UK and Australia, maybe we could reduce the hours devoted to the 'Psychosocial Theory of Change', and instead focus on such things as the seemingly insurmountable amount of anatomy that should be learnt as an undergraduate.

Should NZ change the way it provides medical education?

So how do we go about teaching these graduate-entry, demographically-accurate students we have decided to inundate our medical schools with? The current method of spending a number of pre-clinical years studying textbook theory in an academic environment appears to be under threat. At least one medical school in Australia (Newcastle) has already moved to a syllabus of entirely problem based learning (PBL). Because lets face it, the academic criterion set for entry into med school means that pretty much all successful entrants are capable of interpreting, sorting and feeding back knowledge garnered from a text book or lecture (at least for the duration of the exam period). But the real beauty of medicine is its inherent art. The ability to take minute pieces of information, some relevant, others maybe not, with inconclusive test results and varying patient backgrounds, and to turn these into accurate, timely diagnoses. To treat stricken individuals with compassion and respect. To know your own limitations, but still be able to believe in your own ability. These intangibles are not taught in any classroom, but on the wards. Wizened old doctors talk of the need to see cases, and more cases, to build clinical skills and knowledge. Why not start straight away? The theory can be learnt by students on the go and those attributes that make good doctors, rather than the ability to regurgitate information easily garnered these days from ones' palm pilot, can be instilled immediately. Not only that, but theory applied to practical situations has far more relevance than purely theoretical pre-clinical years can hope to create, despite the excellent quality of teaching received in this country.

Problem based learning, and earlier exposure to ward based teaching are extremely teacher-intensive methods of providing medical education, but the continuing pursuit of excellence has always been the mantra of the medical profession, as it strives to best serve the public good.

Conclusion

The selection of medical students, and the provision of medical education to these students, are but two cogs in the supply of medical healthcare as a public good to a nation. But in creation of the best quality medical graduates and optimal health care to a nation, all elements of the machine must be working in an optimal fashion. A team is only as good as its weakest member, and medical providers have a vital role to play in maintaining the provision of New Zealand's health care as a public good.

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Treatment of Sprains and Strains

Do Non Steroidal Anti-Inflammatory Drugs Have a Role?

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KEYWORDS

NSAIDs, Sprain/Strain

INTRODUCTION

Sprains and strains of the ankle are the most common sporting injury and ankle strains alone are reported to account for 15% of all sports injuries.[1-4] While these types of injuries are usually considered minor, they can be significant due to their frequency and symptoms and should be taken seriously due to potential to cause chronic pain, swelling and functional instability.[2-5] Measures such as rest, ice, and compression are crucial to aid healing and health professionals are often approached to suggest and provide drug treatments to reduce pain and inflammation. The inflammatory response is a part of the body's natural healing process, and healing cannot occur without it.[6,7] Inflammation acts to limit the amount of damage (i.e., haemostasis to prevent bleeding), protect from further damage (i.e., swelling to immobilise the joint) and initiate healing (via macrophages to remove debris and growth factors to promote regeneration). This acute inflammatory phase is usually transient lasting 24-48 hours,[7-9] and soon after it is initiated, muscle or ligament repair begins.[10]

Currently there is controversy as to whether non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and diclofenac, provide the best treatment due to their analgesic and anti-inflammatory effects, or if the anti-inflammatory effects impair the healing process.

METHODS

A Medline search was conducted in March 2005 and keywords used included non-steroidal anti-inflammatory drugs (NSAIDs) (and variations), sprains, strains, soft-tissue injury. Both review articles and experimental articles of potential interest were obtained, and further references cited in the articles were included. The aim was to find clinical evidence that either supports or does not support the use of NSAIDs in acute ankle sprains and/or strains immediately after injury.

Strains and Sprains

A sprain is when a ligament within a joint is stretched or torn[3,4] and is caused by a sudden forceful movement (such as a sudden change in direction when running), which results in pain and swelling. The swelling occurs soon after the injury due to an inflammatory response, and this can lead to some loss of joint function.[9-11] Sprains usually occur in the ankle, knee and wrist joints.

A strain is when a muscle or tendon is overstretched or torn[3,4](such as when lifting a heavy object), which results in pain and swelling due to the inflammatory response. Strains commonly occur in the muscles of the back and extremities.[3] It is hard to differentiate a sprain from a strain but both initiate an inflammatory response and are generally treated in the same manner. It is most important for pharmacists to first determine if referral is needed. A good history and observation of a patient's ability to ambulate or use the affected limb may give an indication of the severity of an injury. Pharmacists should refer if there is the possibility of fracture, dislocation, or complete tear or if there is any doubt as to the seriousness of the injury.

Inflammation

When an injury occurs the body responds with an initial influx of inflammatory cells and blood.[6] The cells act to remove debris and recruit other inflammatory mediators to the injured area.[6] When inflammatory mediators are present the enzyme cyclo-oxygenase 2 (COX-2) (which is not normally found in healthy tissue, but produced by inflammatory mediators) converts arachidonic acid to inflammatory prostaglandins. Prostaglandins in inflammation include PGF2, PGD2, PDI2 and PGE2, which are responsible for pain, vasodilation and oedema.[12] This conversion also attracts other inflammatory cells to the injured site and leads to the release of bradykinin which acts to 'sensitise skin pain receptors'.[6] It is during this inflammatory response that cytokines, proteins produced by many cells, which are involved in the regulation of the growth and maturation of 'particular cell populations'[13], are recruited. Growth factors are also recruited and together these form the proliferative phase of healing.[14]

NSAIDs in inflammation

The inflammatory response can be reduced by the use of NSAIDs. The dosage of NSAIDs needed to achieve an anti-inflammatory effect is usually twice as high as that needed to achieve analgesic effects.[8]

NSAIDs work by inhibiting the COX-2 enzyme (as well as COX-1, necessary for normal physiological processes[6]) thereby inhibiting the conversion of arachidonic acid to prostaglandins. This decreases pain and swelling but may also block the recruitment of cytokines and growth factors, which will slow the early phases of healing.[14] This idea is supported by a clinical study by Reynolds et al. showing that in patients with more severe injuries a placebo group actually had lower pain scores than those taking NSAIDs indicating that healing may have been delayed in this group.[15]

NSAIDs also inhibit thromboxane A2 on platelets which may lead to increased bleeding into the injury site, increased swelling and further tissue damage or delays in healing.[14] Other effects include the suppression of neutrophil migration and cytokine production[16]. Proteoglycans, components of the extracellular matrix which regulate the 'connective tissue structure and permeability' also have decreased production.[12-16]

However, the inflammation process is not completely stopped by NSAIDs, as the arachidonic acid can still be converted to leukotrienes via the lipoxygenase pathway.[8]

To use or not to use?

Concern has been raised over the use of NSAIDs early in therapy because the initial inflammatory response coincides with muscle repair, regeneration and growth.[7] As inflammation is a necessary component, decreasing inflammation may impair the healing process and result in a delay of tissue repair.[3] Current evidence suggests that if these medicines are used too early following injury, they will reduce the inflammatory response and may actually delay acute healing, slow muscle regeneration and compromise long-term healing.[2,6,8] There is also potential for increased bleeding and swelling at the site of injury due to NSAIDs decreasing platelet aggregation.[14]

Clinical studies have shown that NSAIDs are effective in decreasing pain and swelling associated with sprains and strains.[3] As a result of this, the range of motion is increased and pain is decreased.[14] Conversely, one of the roles inflammation and pain play in healing is to limit movement to prevent further damage and returning to activity faster may increase the risk of recurrence.[17,18] A study performed on Australian army recruits strongly recommended the routine use of NSAIDs in the management of acute ankle sprains, as they allowed a more rapid return to activity and reduced the overall morbidity. These effects may be caused by the analgesic effect, which enabled patients to return to normal activity prematurely. However, the study also found treatment with NSAIDs produced greater instability, a decreased range of motion and an increase in the amount of swelling.[19]

It has also been noted that in some subacute injuries, inflammation is no longer present but instead a degenerative process, tendinosis, is occuring.

Current evidence suggests that if these medicines are used too early following injury, they will reduce the inflammatory response and may actually delay acute healing, slow muscle regeneration and compromise long-term healing.

In this case, there is no benefit in using NSAIDs as there is no inflammation and patients are being put at risk of the possible side-effects of these drugs e.g. gastrointestinal (peptic ulcers, bleeds), renal (fluid retention, renal failure), cardiovascular (arrhythmias) and respiratory systems (worsening of asthma symptoms).[6]

RECOMMENDATIONS

The inflammatory response exceeds what is needed for repair, therefore it is desirable to limit both bleeding and swelling as soon as possible after a soft tissue injury.[11] The non-pharmacological intervention RICE has shown to be an appropriate treatment of sprains and strains for the first 48 hours after the injury. RICE comprises [3,11,20]

- Rest - reduce the length of time spent moving the affected joint, preventing further damage.

- Ice - apply for up to twenty minutes every two hours for the first 2-3 days. The effects are to relieve pain and minimise blood flow to the area. The combination of pressure and ice is more efficient than ice alone at controlling swelling.

- Compression - minimises swelling and limits joint movement, reducing further damage.

- Elevation - decreases oedema at the site of the injury.

RICE is important as it acts to minimise bleeding and inflammation without stopping the influx of key factors needed for healing. Pharmacists should consider whether an NSAID is really necessary. They should avoid their use in minor conditions, and not recommend their use in "at risk" patients, such as the elderly and those with a history of peptic ulcers or asthma. Alternative options such as paracetamol or a topical agent should be considered.[11]

Currently in New Zealand, the Accident Compensation Corporation (ACC) recommends RICE for the first 2-3 days after the injury occurs, combined with the use of paracetamol, if required, for pain. ACC recommends the use of NSAIDs (if indicated) after 2-3 days, but advises against using aspirin, as this can increase bleeding and swelling.[20]

Self Care Cards available in many pharmacies provide information about particular conditions. The "Sprains and Strains" card recommends RICE for the first 1-2 days and, contrary to ACC's recommendations (and current evidence), states that anti-inflammatory drugs can be used immediately to reduce pain and swelling.[21]

CONCLUSION

Currently, while NSAIDs may be used to reduce pain and inflammation, there is little evidence regarding the impact of their anti-inflammatory effects on the healing process of sprains and strains. While NSAIDs have been used as first-line treatment, their use needs to be evaluated given current evidence suggesting potential for problems. With the additional risk of NSAID side-effects and their potential to blunt the normal healing process, it is important to consider whether their use is appropriate for treating sprains and strains and particularly whether they should be avoided in the first 24-48 hours after injury. The optimal treatment appears to be RICE for the injury and paracetamol for pain. Use of NSAIDs immediately after injury should be discouraged. If the patient insists on using NSAIDs within three days of the injury, they should be informed of the risks: predominantly impaired healing, possible long-term effects to the joint, and recurrent injury due to premature activity.

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Emergency Peripartum hysterectomy

A review of the current literature

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ABSTRACT

Emergency peripartum hysterectomy (EPH) is one of the most risky operations performed in modern-day obstetrics[1]. This review aims to illustrate international trends in crude rates, indications, and the risk factors for EPH across several centres worldwide.

Rates of EPH have remained stable over time, and are reported at between 0.3 and 2.7 per 1000. The only centre which has reported data in two time periods noted no significant change in rates over time.

The main indication for EPH has changed over time from uterine atony to uncontrolled placental site haemorrhage. This has been attributed to the rising rate of caesarean section. The main risk factors for EPH are abnormal placentation, previous caesarean delivery and uterine curettage, increasing parity, and possibly caesarean section as the current mode of delivery.

Studies looking at differences in outcomes found no distinction between women who underwent subtotal hysterectomy and those who underwent total hysterectomy, although it is not clear why a decision for subtotal hysterectomy was made. Overall morbidity remains high at around 50% for the majority of the studies. Mortality is rare.

The consensus of studies supports further use of conservative management to preserve the uterus.

KEYWORDS

Peripartum hysterectomy; maternal foetal medicine; emergency obstetrics; epidemiology

INTRODUCTION

Emergency peripartum hysterectomy (EPH) is a potentially life-saving procedure, usually performed when conservative measures to control haemorrhage have failed. EPH carries significant risks of mortality and clinically significant morbidity. It is one of the highest risk procedures performed in modern-day obstetrics.[1]

This review is a summary of international trends in EPH from the current literature. It compares crude rates, indications, and the risk factors for EPH across several centres worldwide.

Definition of EPH

EPH is defined as hysterectomy performed either at the time of delivery or in the immediate postpartum period, due to complications arising from the delivery.[2-5] Hysterectomy planned prior to delivery is not considered EPH[4,6-7.] Studies have used varying definitions of the peripartum period; the majority define the immediate post-partum period as up to 24 hours after delivery.[3,6,8-13] The majority of studies excluded cases where the gestation of the pregnancy was under 28 weeks.[3,8,11,14]

Rates of EPH

Rates of EPH are under three per cent of the population at risk in reviewed papers after 1992. However, most current series reported a rate of 0.3-0.7 per cent.[2-4,8,10,12-13,15] Table 1 shows a range of rates of EPH across different countries from the largest studies reviewed.[2-5,8-11,15-19]

There are no appreciable differences between rates of EPH in developed nations and developing ones.[14,18-19] However, there were fluctuations in rates even within the same country.[9,11]

Many studies were performed at secondary and tertiary centres,[3,6,10,14,18-20] and did not include in their denominator, the number of deliveries in centres from which there were transfers. In one study, 14 such transfers accounted for 28.7 per cent of the total number of EPH performed. Some of the studies with the highest crude rates also had the longest post-partum time periods and the least exclusion criteria.[5,19]

Two studies reviewed rates of EPH by year.[8,5] The Turkish study[8] showed a decrease in the rates of EPH, and suggested better obstetric care as the reason. The US-based study showed no change in rates over time.[5] Only one pair of studies compared rates in the same institution over different time periods. Clark et al[7] had reported a rate of 1.02 per 1000,

Table 2: Rates of EPH reported in papers published since 1993

Reference	2	3	4	5	8	9	10	11	14	15	16	17	18	19
Rate per 1000	0.5	0.5	0.6	1.6	0.3	1.3	0.7	1.4	2.3	0.5	1.2	2.2	2.3	2.7
Country	Jordan	Turkey	USA	USA	Turkey	USA	Hong Kong	USA	South Korea	Canada	South Africa	India	Nigeria	USA
Study period	Jan 1994 - Aug 1998	Jan 1996 - June 2001	Jan 1989 - Feb 2000	Oct 1983 - July 1991	Jan 1985 - Jan 1994	Jan 1985 - June 1990	May 1984 - Dec 1994	Jan 1991 - Dec 1997	Jan 1986 - April 2001	1988 - 2000	Jan 1993 - June 1998	1994 - 2001	Jan 1986 - Dec 2000	Jan 1990 - Jan 1995
Number of months studied	56	66	144	94	120	66	127	84	183	156	66	96	180	60
Number of EPH	19	38	79	117	67	123	52	48	101	76	71	50	46	39
Number of total deliveries	41,221	142003	122025	75,656	208772	94,689	73,819	34,241	31,044	142634	59,380	23,187	20,344	14,220
Number of caesarean sections (% total)	3,586 (8.7%)	19,882 (14%)	Not stated	Not stated	23,941 (11%)	13,996 (15%)	Not stated	Not stated	11,924 (38%)	Not stated	Not stated	Not stated	Not stated	4,149 (29%)

(n=70) between 1978 and 1982, while Stanco et al reported a rate of 1.3 EPH per 1000 deliveries during 1985 to 1990.[9] Although there appears to have been an increase in the rate of EPH, this difference was not statistically significant (chi-squared test p=0.10).

Indications

In the past, the most common indications for EPH had been uterine atony and uterine rupture.[7,21] Recent literature shows uncontrollable haemorrhage due to morbidly adherent placenta (accreta; increta, or percreta) is the most common indication.[2-3,5,9-11] Clark et al. had reported uterine atony as the most common indication in 1983[7], while Stanco et al. found placenta accreta was the main indication at the same institution, in 1993.[9]

Several studies attribute this phenomenon to the rising incidence of caesarean sections and uterine curettage. [7,11] There is a strong association in the literature between previous caesarean delivery and/or uterine curettage and placenta accreta.[2,9,11-12,17,20] Moreover, management of uterine atony has improved through advancements in pharmacology (ie prostaglandins), reducing its incidence as the primary indication.[5,11] Studies stratifying by parity showed uterine atony as the main indication among primiparous women, [3,11] but accreta was the main indication amongst multiparous women.

Risk factors

The majority of recent studies suggest abnormal placentation is now the major risk factor for EPH.[1,4-5,9,19,21] Several studies documented previous caesarean delivery and/or uterine curettage as an important risk factor.[2-3,4,9-11,13,15,19] Kastner et al. noted the increased incidence of abnormal placentation in women with previous caesarean delivery.[11]

Abnormal placentation is now the major risk factor for EPH.

Caesarean section as the current mode of delivery was also suggested as a risk factor.[9,11,19] Two studies suggested the proximity of the operating theatre as a major reason,[4,14] but did not compare delivery-to-decision times between modes of delivery, or adjust for associated abnormal placentation.[4] Increasing parity was also noted as a risk factor. [5,17,18]

Morbidity and mortality

The majority of studies reported no maternal mortality.[2-6,9-11,15] Mortality associated with EPH appears to be confined to developing nations.[16,17,18] Nevertheless, the overall morbidity remains high; postoperative complications ranged from 43%[2] to 65%.[5] Rates of blood transfusions also remained high at around 90% for the majority of the studies. [1-5,8,10-12,17-19,21-22]

Alternative management

Several methods of conservative management have been reported in the literature to address EPH indications. Tamponade procedures and the administration of oxytocics (syntocinon, ergometrine, syntometrine) and prostaglandin analogues may have decreased the rates of EPH due to uterine atony. Haemostatic suturing, oversewing of the placental site, uterine and internal iliac artery ligation, and arterial embolisation techniques might reduce the incidence of EPH from placental site bleeding. The majority of studies advocated increased use of these 'uterine saving' procedures in order to reduce EPH rates. [1-2,4,5-6,9,11-14,17-18]

The time spent on alternative surgical manoeuvres may increase the risk of coagulation disturbance.[12,18] However, rates of disseminated intravascular coagulation reported are low.[12] The majority of studies did not record delivery-to-decision intervals or measures of blood loss prior to making a decision to proceed to EPH.

CONCLUSION

EPH remains a rare complication of delivery. Individual clinicians will consequently only see a handful in their practising years. However, it is a high risk procedure for which clinicians need to be prepared and avoid if possible. To do this it is preferable to have much information about the risk factors and indications for EPH.

The majority of studies reported no maternal mortality. Nevertheless, the overall morbidity remains high.

As the rates of caesarean section continue to rise, it is likely that EPH will follow suit. Recent advances allow for delivery in a controlled fashion with immediate uterine artery embolisation available. The key to this approach is identification of women at risk of EPH, which pooled data can provide. We are becoming increasingly aware that women with abnormal placentation need to be counselled carefully prior to delivery about the risk of EPH.

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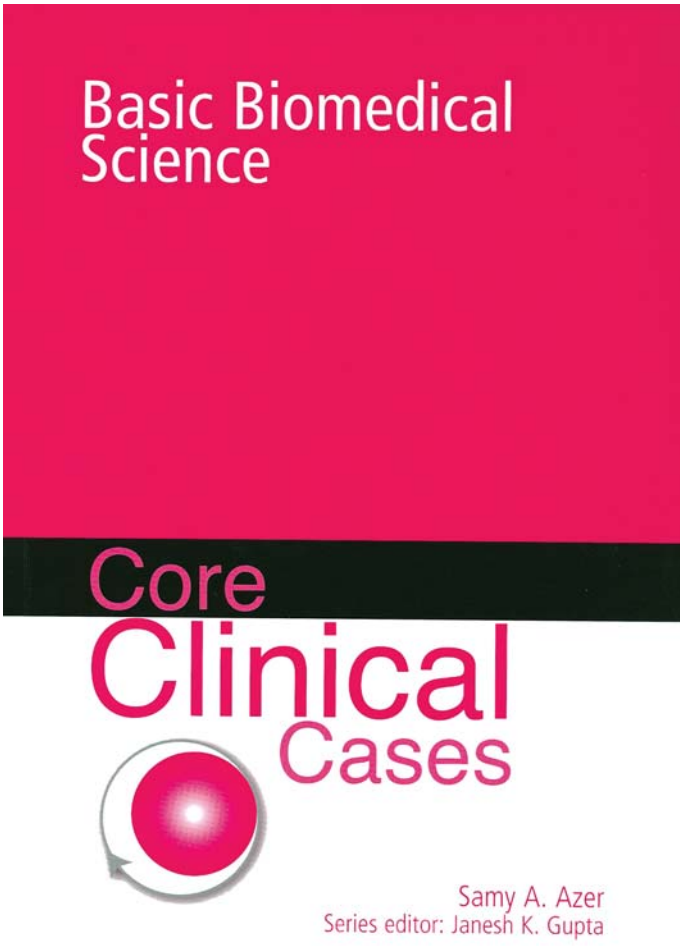
Core Clinical Cases
Series Editor: Janesh K. Gupta

As advancements are being made in the field of Medicine, so are the methods used to educate Medical Students. Throughout the UK, North America, Australia, New Zealand, South East Asia and the Middle East, medical curricula are increasingly incorporating the use of Problem-Based Learning in which students are required to apply knowledge gleaned from lectures and standard textbooks and apply them in a theoretical clinical scenario. With most textbooks being specifically for different areas of clinical medicine i.e. Pathology, Anatomy, Biochemistry, Pharmacology etc, it has become increasingly challenging for the medical student to locate and collate information pertaining to a specific disease. As such, with the publication of this series of books, the work of searching through endless pages of irrelevant data is eliminated and the required knowledge and information condensed in a concise and easy to use book.

In this issue, two books in the series are reviewed. Both have a similar layout and demonstrate consistency in the way information is presented to the reader. What is really useful to the reader is a small series of questions presented before each main chapter which gives the reader an opportunity to visualize the logical progression of the process of diagnosis and understand why one does not dive straight into applying for blood tests or MRIs and instead starts with the age-old approach of an accurate patient history being taken first. Each chapter covers a range of three to four cases which at first may seem similar in symptoms. The cases are explained in parallel to one another and the amount of information about the patient given to the reader in a gradual pattern starting with the history and progressing to the more challenging laboratory test or imaging. There is also a comprehensive explanation of the biomedical science behind the disease that enhances the reader's understanding of the system being discussed before further discussing the case. This enables the reader to compare and contrast the differences between the cases making for more interesting learning. However, this layout makes it difficult for the reader to just choose to follow one case, requiring the reader to constantly flip back and forth between sections in the chapter.

The information regarding each case is presented in an easy to read format with a large chunk of information being presented in point form. Besides diagnosis, the books also provide the clinical treatments and accompanying explanation for the chosen treatment. Each case in each chapter is given a short introduction and is then followed up by blood test results, patient history, and then a series of questions on the diagnostic procedure followed by several pages of key points on the biomedical science of the system being discussed.

Despite the series being targeted towards medical students and their new teaching curriculum, it is possible that the series be also used by more senior medical students in their clinical years as a revision tool and possibly as a study tool too. The series currently has four books, with two more being published soon.



Core Clinical Cases in Basic Biomedical Science

Core Clinical Cases in Obstetric and Gynaecology 2nd Edition

Core Clinical Cases in Paediatrics

Core Clinical Cases in Psychiatry

Coming soon:

Core Clinical Cases in the Medical and Surgical Specialties

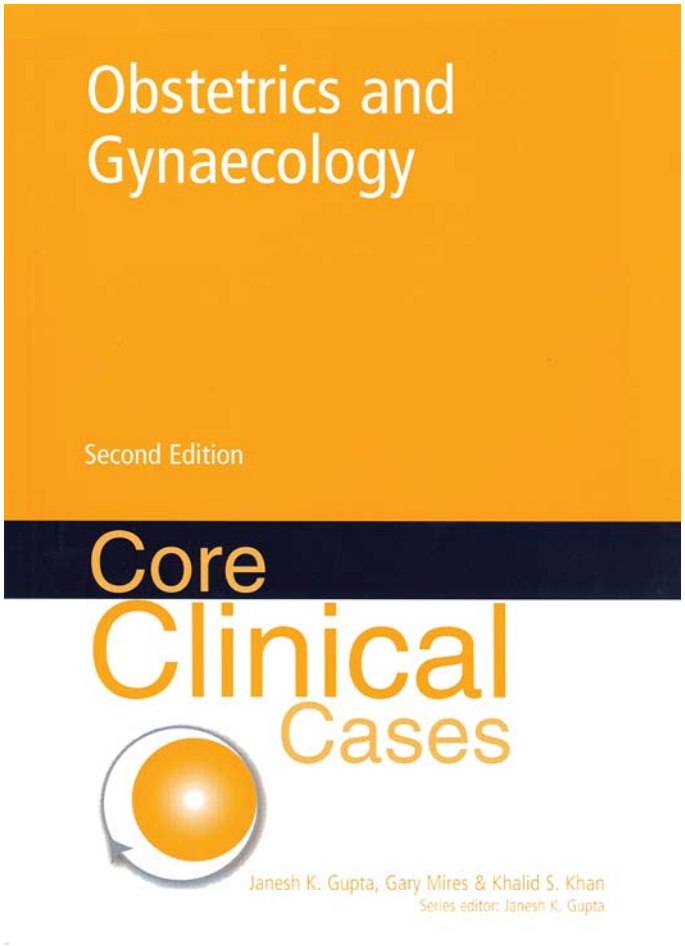
Core Clinical Cases in Medicine and Surgery

Core Clinical Cases in Basic Biomedical Science
Samy A. Azer, NZ$55.00

This book provides a highly structured case history text covering each of the important components of the undergraduate biomedical sciences, in the form of 45 clinical scenarios. Each scenario is followed by eight to ten questions and answers with detailed feedback. The book focuses on the following topics, Biliary system and pancreas, Liver, Gastrointestinal system, Nutrition and endocrine pancreas, Cardiovascular system, Respiratory system, Renal system, Endocrine system, Reproductive system, Locomotor system, Haematopoietic system, Autonomic nervous system, Central nervous system, Cranial nerves and Immune system. As consistent with the series, the book displays information in a succinct manner and encourages lateral thinking on behalf of the student by promoting the idea of differential diagnoses. At the end of each chapter is also a small gem of a page in which the author provides students with a list references of further reading material on the topic, if so desired.

Unfortunately, in an attempt to cover such a broad range of topics, the book falls short of being the definitive guide for medical students in their clinical years. However, it must be noted again that this series is targeted towards pre-clinical year students and therefore, is possibly sufficient. What is of value though to clinical year students is the thought process that the book tries to promote in investigating any disease, starting from taking a good patient history to the more complex laboratory tests.

This book can be considered a definite must-have for students yet to begin their clinical years.

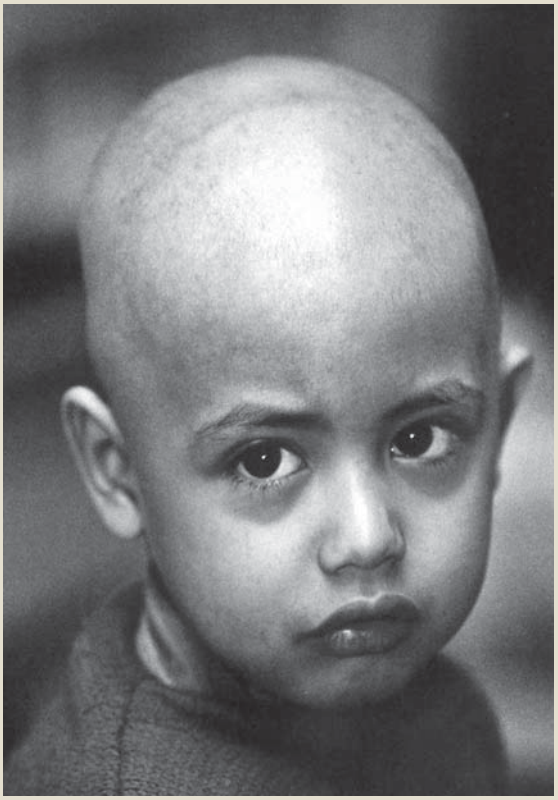


Core Clinical Cases in Obstetrics and Gynaecology 2nd Edition
Janesh K. Gupta, Gary Mires and Khalid S. Khan, NZ$45.00

This is the second book in the series and begins the tone of the remaining five books as it delves into the specific fields of Medicine. Key concepts and important information are highlighted and the reader-friendly layout reflects exactly the type of question you will encounter, making the perfect revision aid for all types of case-based examination. The book covers the following topics in the field of Obstetrics and Gynaecology, Early pregnancy problems, Pregnancy dating and foetal growth, Late pregnancy problems, Labour, Medical disorders of pregnancy, Puerperium, Abnormal uterine bleeding, Amenorrhoea and menopause, Incontinence and prolapse, Neoplasi, Discharge and pain, Infertility and Fertility control.

With the advent of a more rounded approach to Medicine in terms of attitudes to disease and illness, medical schools are moving away from the Biomedical approach to the Biopsychosocial approach. Keeping in line with this new approach to Medicine, the book provides additional information on cases that might require informed consent from the patient and how it should be presented to them. Readers may find it disappointing as to the depth at which this aspect is explored in the book, but to be fair to the authors and the series editor, this book is intended mainly to aid the medical student in learning about the diagnostic and investigative process. A full ethical discussion on patient rights would be excessive and not in line with the main intention of the series.

It is as it is intended to be, a tool for the medical student to learn better in the new problem-based curriculum.



A boy with leukemia (in the leukemia ward of Mansour Teaching Children's Hospital, Baghdad, Dec. 1999). This image is from an exhibition of black and white photographs that will be shown at New Zealand medical libraries that highlight the medical effects of using depleted uranium in warfare.

A Different Nuclear War: *Children of the Gulf War*

Photos and text by Takashi Morizumi.
Edited and published by the Global Association for Banning Depleted Uranium Weapons 2002.
For more information about the photographer:

www.savewarchildren.org/morizumi.html

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NZMA news

Dr Ross Boswell
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Funding for Medical Students

The New Zealand Medical Association is the largest medical organisation in New Zealand and the only one that represents all sectors of the medical profession – beginning at the student level and continuing throughout members' medical careers. This year will continue to be a busy one for our advocacy work with a diverse range of issues including medical student tuition fees, medical workforce shortages, GP viability and maternity services.

In terms of medical student tuition fees, the NZMA has welcomed a funding review for medical students, announced by the Minister for Tertiary Education Michael Cullen on 17 February. It's an important step towards reducing the debt burden on medical students and helping to address medical workforce shortages. The NZMA and the NZMSA have been expressing concerns about the fees situation for medical students for a number of years. Recent studies on student debt including one published in the NZ Medical Journal this month (www.nzma.org.nz), highlight that medical tuition fees strongly influence medical graduates' career decisions. Too many graduates choose to leave the country to work overseas. There are also far fewer graduates going into general practice, which in itself is already facing shortages. The article states that 9% of graduates surveyed would choose general practice. If you take into account that GPs make up 40% of the current medical workforce it is obvious that the shortage is only going to get worse.

While the NZMA fully supports a funding review, it is important for the Government to recognise that there are many factors affecting medical workforce shortages and we will continue to urge the Government to adopt a comprehensive strategy to resolve the need for medical workforce development.

NZMA Supporting Medical Students

We have a close relationship with the New Zealand Medical Students' Association and advocate alongside the NZMSA in its work, especially in the battle against the rising cost of medical education, particularly high student debt and fees. To highlight the negative effects of high student debt we published, in conjunction with NZMUSA and NZMSA, a casebook called 'Doctors & Debt: The Effect of Student Debt on New Zealand's Doctors.'

Too many graduates choose to leave the country to work overseas. There are also far fewer graduates going into general practice, which in itself is already facing shortages.

Having undertaken much work to raise awareness about debt and its effect on medical students – helping to promote the issue onto the Government's agenda – we were heartened at Labour's policy to abolish interest payments on student debts.

The NZMA also provides significant support for NZMSA including funding the attendance of the NZMSA President at NZMA forums and Council meetings, and we provide financial support for the NZMSA President to attend the Australia Medical Students Association Conference.

Advocacy for Doctors in Training

We have a Doctors-in-Training Council, of which the President of the NZMSA is a member. The Council advises the NZMA Board on issues relevant to doctors-in-training. At the DITC meeting in February a range of topics were discussed including UK registration, PGY1, medical workforce development, RDA MECA negotiations and the rural curriculum.

Other NZMA Advocacy 2006

The worsening shortage of medical professionals in New Zealand is a critical issue and needs to be addressed urgently. The NZMA has made a submission on a paper written by the Medical Reference Group, which looks at medical workforce shortages and covers issues such as student debt, retention and training.

The NZMA has continued to advocate for the right of private sector doctors to set their own fees. A six-weekly meeting has been established between GP leaders and the Ministry of Health to enable GP leaders to have more effective input into policy and implementation.

Find out more about the NZMA on the website:
www.nzma.org.nz

Prescribing of Antiepileptic Drugs (AEDs) during pregnancy

Continued from page 18

Epilepsy is a difficult condition to manage during pregnancy for a number of reasons. Firstly, inadequately controlled epilepsy is associated with dangers to mother and foetus. Secondly, most AEDs have known teratogenic effects.[11]

Anti-epileptic drugs (AEDs) can be divided into two groups:

Traditional (older) AEDs: Older drugs introduced before 1990 – Carbamazepine, Phenytoin, Sodium Valproate, Primidone, Phenobarbital

Newer AEDs: Newer drugs introduced after 1990 – Topiramate, Lamotrigine, Gabapentin, Vigabatrin

Teratogenicity with AEDs

The incidence of giving birth to a child with serious malformation in the general population is 2-3%. This rises to 4% if the mother is epileptic. If AEDs were taken by the mother, the incidence rises further to 5%. Abnormalities are more likely if mother takes more than one AED. However, these women are more likely to have severe epilepsy which may account partially for the increased risk.[3] Recent data from the Australian Pregnancy Register for Women on AEDs showed that out of 403 pregnancy outcomes for women taking AEDs, 87.8% resulted in a healthy birth, 6.5% had foetal malformations and the remaining 5.7% had spontaneous abortions or premature death in utero.[6]

Foetal malformations associated with AEDs

AEDs cause a characteristic pattern of abnormalities of varying severity commonly known as 'foetal anticonvulsant syndrome.' The problems seen most frequently are the minor dysmorphic abnormalities affecting the face and digits. Major abnormalities are attributed to all traditional AEDs but occur less frequently compared to minor abnormalities[3] (see Table 4).

Table 4: Foetal malformations associated with AEDs[3]

Minor abnormalities	Major abnormalities
V-shaped eyebrows Low-set ears Broad nasal bridge Irregular teeth or wide mouth Hypertelorism (wider than normal space between the eyes) Hypoplasia of nails & distal phalanges	Orofacial clefts Congenital heart disease (septal defects) Neural tube defects

Mechanism of teratogenesis due to AEDs

Several mechanisms have been proposed for teratogenic effects of AEDs. One theory, which focuses on the genetic predisposition principle of teratogenicity, is that unstable epoxides could interfere with the normal developmental process. Detoxification of these epoxides requires the enzyme epoxide hydrolase and a genetic defect in the activity of this enzyme in the foetus can increase teratogenic risk. Free radicals produced during the metabolism of AEDs can be cytotoxic. A genetic defect of free-radical scavenging enzymes can cause an excessive foetal exposure to these cytotoxins.

Another postulated mechanism for teratogenicity of AEDs is the induction of folic acid deficiency. Folic acid antagonists such as phenytoin, barbiturates, sodium valproate, and carbamazepine can cause folate malabsorption thus reducing serum folic acid levels which are thought to influence neural tube defects. The Medical Research Council study in 1991 reported a 70% reduction of neural tube defects recurrence among pregnant women who were supplemented with folic acid 4mg before conception and during gestation. All pregnant women are now advised to take 400mcg during the first 3 months of their pregnancy. All pregnant women with a family history of malformation or who are in a high risk category e.g. epileptics are advised to take 5mg of folic acid daily prior to conception and during the first 3 months of their pregnancies.

Vitamin K is needed so that the liver can produce clotting factors (eg prothrombin). The hepatic enzyme inducing AEDs (phenytoin, henobarbital, carbamazepine and topiramate) can cause vitamin K deficiency in the foetus. This results in early haemorrhagic disease of the newborn which manifests as intracranial haemorrhage in the newborn at birth. The exact mechanism of this defect is unknown but may involve induction of foetal liver microsomal enzymes that deplete the already low reserves of foetal vitamin K. This results in suppression of vitamin K dependent coagulation factors II, VII, IX and X. (Briggs & PJ article part 2) Vitamin K supplementation during pregnancy and for the neonate immediately after birth is recommended to prevent this from occurring. There are several regimens for vitamin K supplementation in pregnant women taking AEDs. The consensus guidelines recommend an oral daily dose of 20mg vitamin K to the mother from the 36th week of pregnancy and to give 1mg of vitamin K intramuscularly to the newborn at birth. The foetal dose is repeated after 12 hours. [3, 11, 12, 13, 14]

Clinical implications of pregnancy induced pharmacokinetic changes

Approximately one third of women with epilepsy will have an increase in seizure frequency when they become pregnant. Major seizures during pregnancy can lead to foetal hypoxia and lactic acidosis. Falls resulting from seizures can lead to trauma, early labour or miscarriage. This may occur due to hormonal changes or sleep deprivation but the main reason is thought to be pharmacokinetic changes which occur during pregnancy. These changes include an expansion in plasma volume, increased clearance rate and a change in protein binding.[12]

As most AEDs are acidic or neutral they are highly bound to serum albumin. During late pregnancy albumin levels fall with a corresponding decrease in the fraction of bound drug. This decrease in plasma protein binding leads to more free drug available for metabolism and clearance. The net effect is a decrease in the total (unbound and protein bound) plasma concentration of the AED during pregnancy.

It is helpful to have the baseline blood levels of AEDs taken at the beginning of pregnancy and also a baseline measurement of serum albumin. In women whose epilepsy is poorly controlled, an increase in seizures is more likely. Frequent or prolonged fits can cause miscarriage, intracranial haemorrhage in mother and premature labour. In extreme cases, seizures can cause alterations in placental blood flow and thus transfer of oxygen and nutrients to foetus, resulting in foetal hypoxia with bradycardia and brain damage. In these women who have poorly controlled epilepsy the dose of the AED may be increased to maintain a therapeutic level. The best practice is to adjust the dose of AED according to the woman's clinical condition corresponding to seizure frequency rather than blood AED levels. In some cases, clinicians measure levels every one to two months. This allows rapid dose adjustment to restore levels if seizures occur. If a dose of AED is increased during pregnancy then it should be titrated down to the original dose in the first few weeks post delivery. [3]

COMMONLY USED AEDS AND TERATOGENIC RISK DURING PREGNANCY

Traditional (older) AEDs introduced before 1990

The rates of major morphological abnormalities after foetal exposure to the older AEDs have been established at 4-6% for carbamazepine and pheytoin and 8% for sodium valproate.

Phenytoin

Risk factor: D [8]

Phenytoin is a hydantoin anticonvulsant whose teratogenic effects were first recognised in 1964. Foetal hydantoin syndrome (FHS) is a characteristic pattern of malformations which was first described in 1968. Clinical features of FHS are shown in Table 5.

Table 5: Foetal Hydantoin Syndrome[8]

Craniofacial	Limbs
Broad nasal bridge Wide fontanelle Low-set hairline Broad alveolar ridge Metopic ridging Short neck Ocular hypertelorism Microcephaly Cleft lip &/ palate Abnormal or low-set ears Epicanthal folds Ptosis of eyelids Coloboma Coarse hair scalp	Small or absent nails Hypoplasia of distal phalanges Altered palmar creases Digital thumb Dislocated hip

Other foetal malformations associated with phenytoin include impaired physical and mental growth, congenital heart defects and cleft lip and/or palate.[15] Phenytoin can cause haemorrhagic disease of the newborn and prophylactic treatment with vitamin K to prevent this condition has been discussed earlier. Phenytoin may also induce folic acid deficiency in the epileptic patient which has been linked to an increased risk of neural tube defects in the neonate. Folic acid supplementation at a dose of 5mg daily is recommended for epileptic women who are contemplating pregnancy and they should continue taking it up to week 12 of their pregnancy.

Phenytoin has non-linear pharmacokinetics and a narrow therapeutic window. It is highly protein bound (90-93%) and is cleared mainly by saturable hepatic metabolism. A fall in the total serum concentration which results in a lack of seizure control requires an increase in dosage of phenytoin. This decrease in protein binding of phenytoin may be an important mechanism for the decrease in total drug concentration during pregnancy as it is the free drug that becomes available for enhanced metabolism.[3, 12]

Sodium valproate (Valproic acid)

Risk factor: D [8]

Sodium valproate is known to increase the risk of neural tube defects. Exposure during days 17 to 30 after conception carries a 1-2% absolute risk of neural tube defects in the neonate. A characteristic pattern of minor facial defects has been associated with sodium valproate which includes trigonocephaly, tall forehead with bifrontal narrowing, epicanthic folds, medial deficiency of eyebrows and flat nasal bridge. The most common major congenital defects observed were neural tube defects, congenital heart disease, cleft lip and palate, genital anomalies and limb defects.[3,8] Some studies refer to this characteristic pattern of malformations as 'foetal valproate syndrome'.

Data from the Australian Pregnancy Register showed that the foetal malformation rate was significantly greater in pregnancies exposed to valproate in the first trimester compared with those exposed to all other AEDs. The mean daily dose of valproate was found to be significantly higher in those women who had children with foetal malformations than in those who had children without foetal malformations (1975mg vs. 1128mg), showing that risk of foetal malformations may be correlated with the dose of valproate used.[6]

Sodium valproate is rapidly absorbed and highly protein bound to plasma albumin (88-92%). The interpretation of its pharmacokinetics is limited by large fluctuations in the concentration-time profile, wide therapeutic index and concentration dependent protein binding. Analysis of unbound sodium valproate concentrations is not routinely done and there is no established therapeutic range. Dose adjustments during pregnancy are best made by clinical observations in conjunction with therapeutic in serum concentrations of sodium valproate.[12]

Carbamazepine

Risk factor: D [8]

Carbamazepine is a tricyclic anticonvulsant which has been in use since 1962. In earlier reviews, carbamazepine was recommended as the drug of choice during pregnancy as it was thought to present a lower risk to the foetus. However, in 1991 an association between carbamazepine and spina bifida was confirmed. The risk of this defect is thought to be about 1%. [16]

Investigators conducted a prospective study evaluating pregnancy outcomes for 72 women treated with carbamazepine during early pregnancy and compared this group to a control group. The investigators concluded that carbamazepine exposure was associated with a pattern of congenital malformations whose principal features consisted of craniofacial defects, fingernail hypoplasia, developmental delay and neural tube defects. This characteristic pattern of abnormalities was termed 'foetal carbamazepine syndrome'. These defects were noted to be similar to those observed with the foetal hydantoin syndrome described earlier for phenytoin. As both carbamazepine and phenytoin are metabolised through the arene oxide pathway, a possible mechanism for the teratogenicity of these two drugs was proposed which attributed their teratogenicity to epoxide intermediates.[8]

A 2000 study, using data from the MADRE (Malformation and Drug Exposure) surveillance project assessed the human teratogenicity of antiepileptics. 299 infants were exposed in the first trimester of their conception to antiepileptics. Of these, 46 infants were exposed to carbamazepine alone. A statistically significant association $p \leq 0.05$ was found between carbamazepine monotherapy and spina bifida.[8]

Like phenytoin, carbamazepine can also cause folate and vitamin K deficiencies which can be corrected by supplementation.

Carbamazepine is protein bound (70-80%) and has a relatively slow absorption. Carbamazepine is eliminated by hepatic metabolism. Dose intervals and sample times are critical in interpreting serum concentrations. Large peak-trough fluctuations can be minimised by using controlled release formulations. The concentration of the pharmacologically active metabolite (carbamazepine-10-11-epoxide) was reported to increase during pregnancy possibly due to an increase in carbamazepine metabolism. [12]

Newer AEDs introduced after 1990

New AEDs should not be used in pregnant women unless absolutely necessary because there is not much information available about the risks associated with them. The majority of information is from animal reproductive toxicology studies which are not fully predictive of human teratology.

There is little information regarding the pharmacokinetics of the new AEDs in humans and their safety during pregnancy. There have been reports of decreased lamotrigine levels during pregnancy. Topiramate, felbamate and oxycarbazepine have low levels of protein binding. Vigabatrin and gabapentin do not bind to protein. New AEDs are eliminated through the body by renal clearance.[17]

Topiramate

Risk factor: not assigned

Teratology studies in animals reported that topiramate induced right-sided ectrodactyly (congenital absence of all or part of a digit) in rats, whereas rib and vertebral malformations were observed in rabbits. Although topiramate is used widely in the treatment of patients with epilepsy, few pregnant women have taken it. In one case report, multiple minor abnormalities such as a third fontanelle, blunt distal phalanges and fifth nail hypoplasia were seen in a child born to a mother treated with topiramate 700mg twice daily as monotherapy throughout gestation.[17, 18]

Lamotrigine

Risk factor: C [8]

Lamotrigine is chemically unrelated to existing antiepileptic drugs. It is commonly used as an adjunctive therapy for the treatment of partial seizures in patients with epilepsy.[8] Lamotrigine is a weak inhibitor of dihydrofolate reductase. The antifolate activity of other established AEDs is associated with teratogenicity but this has not been proven for lamotrigine. Data on the effects of lamotrigine in pregnant women is limited. Two studies conducted to date were unable to attribute the foetal malformations seen to lamotrigine because the women were exposed to other AEDs during their pregnancy.[3]

An interim report from the Lamotrigine Pregnancy Registry was issued in 2000. A total of 362 prospective pregnancies were enrolled in the registry in the period between 1st September 1992 through to 31st March 2000. Of these, outcomes are known for 244 pregnancies (248 outcomes – including some multiple births). Lamotrigine monotherapy was used in 98 outcomes with the earliest exposure in the 1st trimester. These exposures resulted in nine spontaneous pregnancy losses, 27 elective abortions (two with birth defects), one death of foetus, 14 live infants with foetal malformations and 186 infants without foetal malformation (includes 2 sets of twins). The foetal malformations seen with lamotrigine monotherapy in the 1st trimester were:

Oesophageal malformation
Cleft soft palate
Right club foot

The Lamotrigine Pregnancy Registry advisory committee concluded that the number of exposed pregnancies outcomes represents a sample of insufficient size to reach definite conclusions regarding the safety of lamotrigine in pregnancy.[8, 17, 19]

Gabapentin

Risk factor: C [8]

Gabapentin is an antiepileptic used as an adjunctive therapy for the treatment of partial seizures in patients with epilepsy. Animal studies have shown that gabapentin at high doses is fetotoxic in rodents. Fetotoxicity is manifested as delayed ossification of bones in the skulls, vertebrae, forelimbs and hind limbs. [3, 8]

In 1998, a non-interventional cohort study described the outcomes of pregnancies in women who had been prescribed newly marketed drugs by general practitioners in England. Data was obtained by questionnaires sent out to the prescribing physicians. Gabapentin was taken during the 1st trimester in 17 pregnancies. The outcomes of these pregnancies included two spontaneous abortions, four elective abortions and 11 normal newborns. Although no congenital malformations were observed the study lacked the sensitivity to identify minor anomalies. A review in 1996 reported 16 pregnancies exposed to gabapentin. The outcomes of these pregnancies included five elective abortions, one ongoing pregnancy, seven normal infants and three infants with foetal malformations. No specific information was provided about the foetal malformations.
At present there is limited human data which does not allow an accurate assessment of the safety of gabapentin in pregnancy. A pregnancy register has been established to get more extensive and detailed information about the safety of this new drug in pregnant women.[8, 17]

Vigabatrin

Risk factor: not assigned

Vigabatrin induced cleft anomalies in rabbits when administered during pregnancy. A case report describes a pregnancy exposed to vigabatrin, carbamazepine and dexamethasone. This pregnancy resulted in an infant with multiple congenital abnormalities including bilateral anophthalmia, situs viscerum inversus, levo-isomerism, single ventricle, enlargement of the third ventricle and clubfoot.[17, 20]

SUMMARY

Best Practice guidelines for the management of pregnant women with epilepsy [11, 12, 13, 14, 21, 22]

Before Conception (should begin at least three months before conception)

- Women should be given preconception counselling about the potential risk of increased seizure activity in pregnancy and that the seizures carry a risk to the foetus, to ensure that they do not avoid taking their AEDs.

- Adequate patient information regarding the increased incidence of major malformations and risk of teratogenicity due to AEDs should be provided.

- Women should be referred to a neurologist and obstetrician to reassess treatment. Any medication reduction or substitution should take place before conception.

- Gradual drug discontinuation (over at least three months) should be considered if the patient has been seizure free for 2 or more years.

- Traditional AEDs should be preferred in women of child bearing age planning pregnancy. This is because the patient can be provided with adequate information about the risks and benefits of the AED.

- Doses of AEDs may need adjusting due to pharmacokinetic changes caused by pregnancy.

• Peak serum drug levels should be reduced by increasing the dosing frequency or using low doses of controlled release preparations.

• Avoid multiple drugs therapy as it is associated with an increased risk of foetal malformation. Use the lowest dose possible of a single agent.

• Women should start taking folic acid 5mg daily 3 months before conception and should continue taking it up to week 12 (during the 1st trimester) of the pregnancy.

After Conception

• If epilepsy is well controlled current medication should be maintained.

• Therapeutic drug monitoring should be performed every three to four months or more frequently if seizure control is not achieved.

• Alpha-fetoprotein is a glycoprotein produced initially by the yolk sac and then by the foetal liver and gastrointestinal tract. α-fetoprotein can be measured in amniotic fluid and in maternal serum and is now used widely as a marker in prenatal maternal serum screening programs. A maternal α-fetoprotein test can be performed at 16 weeks gestation as it can detect spina bifida, neural tube defects and major cardiac malformations.

• Targeted foetal ultrasound scan at 18 weeks should be done to detect spina bifida, open neural tube defects and major cardiac malformations.

• Amniocentesis and other specialised tests should be performed as required. Amniocentesis can be offered to women as a somewhat more accurate measure of alpha-fetoprotein levels than maternal serum testing, although clearly there are increased risks associated with this invasive procedure. Generally, amniocentesis is used when satisfactory ultrasound examination is not possible, for example in extremely obese women.

• If a woman is taking phenytoin, phenobarbitone or carbamazepine, then oral vitamin K (phytomenadione) at a dose of 20mg daily should be taken by the pregnant woman late in third trimester (week 36 onwards) to prevent neonatal haemorrhage.

LABOUR, DELIVERY AND BIRTH

Delivery should be in hospital due to the increased risk of seizures (1 to 2%) during labour or after birth. Convulsive seizures at the time of labour and delivery are commonly treated with administration of intravenous benzodiazepines or phenytoin. Caesarean section is often necessary.

After Birth

• Infant will need vitamin K administered intramuscularly on delivery with another dose 12 hours later.

• Any increase in the dose of antiepileptic therapy during pregnancy should be reviewed at this time. In the postpartum period, free serum levels should be measured for the first eight weeks to avoid drug toxicity, which may result from the shift back to prepregnancy pharmacokinetics.

• All AEDs are excreted into breast milk. With the exception of phenobarbital, primidone (high concentrations excreted in breast milk) and vigabatrin (can cause visual field defects), mothers taking antiepileptic drugs should be encouraged to breast feed. The amount of drug the baby would receive is likely to be small.

CONCLUSION

Proper seizure control is the primary goal in treating women with epilepsy. Patients should understand the risks associated with uncontrolled seizures as well as the teratogenicity of the AEDs. When AEDs are used during pregnancy, the most appropriate first line drug for the seizure type should be used at the lowest effective dose. Proper management before, during and after pregnancy can lead to a favourable outcome for the majority (90%) of pregnancies in women with epilepsy.

Continuing Education

Readers are invited to submit their answer to the question in the case "What are the risks associated with taking phenytoin during pregnancy?" and to formulate recommendations for treatment of Mrs R's epilepsy during pregnancy.

Submit answers by emailing them to:
medstudent.journal@stonebow.otago.ac.nz

Answers will be published in the next issue of the journal. The best answer will win a medical textbook.

DISCLAIMER

Please note that the best practice guidelines and the information above regarding the management of epilepsy during pregnancy are based on the literature reviewed by the author. This review is intended only as a guide for the clinical management of pregnant women with epilepsy and may not cover all diagnostic or therapeutic options available. Consult the appropriate medical specialists and your local hospital medicines information service for advice on the management of individual patients.

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Clinicians *Medical Education Convention Aotearoa*

Aim: To bring together both clinical and pre clinical medical students from across New Zealand, in order to enhance their interest and motivation for the field of medicine, whilst at the same time developing collegiality and a wider knowledge base.

Method: Meet annually in the form of a convention where students will attend lectures on current research and practice, partake in workshops designed to enhance their clinical skills, discuss issues relevant to medicine now and in the future, and attend social functions that will highlight the importance of collegiality in medicine.

Results: A happier, more motivated and intellectual group of future doctors with an interest in advancing medical knowledge, who are aware of and not afraid to, confront big picture issues. This should in turn lead to higher quality health care provision for all New Zealanders across all specialities.

Conclusion: Set aside the weekend of September 15-17, 2006 and keep an eye out for more information on how you can join the pilgrimage towards a better tomorrow. Register your interest now and receive more information by e-mailing

kilja036@student.otago.ac.nz

Subject: Clinicians MECA'06.

medical leadership development seminar

The New Zealand Medical Students' Association is hosting the inaugural Medical Leadership Development Seminar (MLDS) in Wellington this year. This event will bring together 70 medical student leaders from around the nation and a selection of outstanding speakers from key social, political, humanitarian, management and clinical leadership roles. Speakers include

Hon. Pete Hodgson
Minister of Health

Mr Ron Paterson
Health and Disability Commissioner

Sir Thomas Davis
Former Cook Islands Prime Minister

Hon. Dame Silvia Cartwright
Governor-General of New Zealand

These key speakers will be presenting alongside practising physicians from diverse specialty groups. The MLDS represents a unique opportunity for New Zealand medical students to interact with these outstanding health leaders and gain an awareness of contemporary health issues.

We are very excited about this event and look forward to meeting the participants in July.

New Zealand Medical Students' Association

New Zealand Medical Students' Association
www.nzmsa.org.nz
te rōpū akonga rongoā o aotearoa

NZMSJ author guidelines for submissions

Format requirements

Use Microsoft Word
Include figures, legends and tables
Save as 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 supervisors are 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:
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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.

Submissions
received before July 10
will be considered
for issue 5

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 July 2006.**

NZMSJ

New Zealand Medical Student Journal

Te Hautaka o ngaa Akongaa Rongoaa

http://hedc.otago.ac.nz/nzmsj