- Military ‘live tissue trauma training’ using animals in the U.S
- From the Vietnam War to Retirement
- A Protocol For The Longitudinal Study Of Psychological Resilience

The Journal of the Australasian Military Medicine Association
INNOVATIONS
FROM THE BATTLEFIELD
AMMA ANNUAL CONFERENCE

ADELAIDE CONVENTION CENTRE
ADELAIDE, 1-3 NOVEMBER 2013

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Australasian Military Medicine Association

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STATEMENT OF OBJECTIVES
The Australasian Military Association is an independent, professional scientific organisation of health professionals with the objectives of:
• Promoting the study of military medicine
• Bringing together those with an interest in military medicine
• Disseminating knowledge of military medicine
• Publishing and distributing a journal in military medicine
• Promoting research in military medicine

Membership of the Association is open to doctors, dentists, nurses, pharmacists, paramedics and anyone with a professional interest in any of the disciplines of military medicine. The Association is totally independent of the Australian Defence Force.

ISSN No. 1835-1271
On the 21 July 1919, the RMO of 30th Battalion AIF, Captain Gordon Robertson demobilised after returning to Australia on the Leicestershire on 21 June 1919. Post demobilisation, he took up a station near Tumblong, New South Wales, where he built his new home. He set up a medical practice in nearby Gundagai, becoming a well-respected General Practitioner in the local community. In 1933, he moved back to Melbourne, where he took up a role as a doctor in the Victorian Division of the Department of Repatriation, where he worked until he retired.

As Dr Gordon Robertson focussed on the ongoing health issues of returned veterans of World War I later in his career, this issue looks particularly at issues affecting the veterans of the many wars and conflicts since. In particular, we look at the Vietnam Veterans and their ongoing health issues as they enter their retirement years. We are also fortunate to have a range of abstracts on veterans’ health from the recently held Repatriation Foundation Research Paper Day in South Australia.

In this issue, we also look at psychological resilience in the Australian Defence Force, the use of animals in military training and research, the benefits of exercise on trunk strength and lower limb stability, and the history of syphilis and its origins. All the articles are intended to challenge, educate and broaden the operational and strategic viewpoint of our members. We would particularly welcome continuing discussion on the issues of current military operations, current military and veterans health issues, military health history and military-civil interactions.

In October 2012, we had an excellent annual AMMA Conference in Brisbane. We would strongly encourage all the presenters to consider turning their presentations into articles for the Journal, which will ensure the wider consideration and coverage that they deserve. As we head towards 2013, we have further themed issues, including an issue on Chemical, Biological and Radiological Defence, and ask prospective authors to consider whether they may have suitable articles for those themed issues. Other military and veterans’ health articles are always very welcome and we would encourage all our readers to consider writing on their areas of military or veterans’ health interest.

Dr Andy Robertson
Editor-in-Chief

Welcome to the latest edition of JMVH, in October the association conducted its annual conference in Brisbane with over 340 delegates and 34 trade exhibitors. It was magnificent occasion and a great opportunity to catch up with old and new friends and hear the latest advances in military medicine. There were some very impressive presentations with our keynote speakers, Professor Dame Carol Black and Colonel Bob Hale adding to the occasion. This year also saw the inaugural Rear Admiral Graeme Shirtley Oration with was delivered by Air Vice Marshall Hugh Bartholomeusz who set a high standard for those to follow. I like to thank all those who contributed to ensuring the conferences success; our 86 presenters, the organising committee and, the Association’s secretariat.

Congratulations, too, to the award winners;

• Weary Dunlop Award – Kylie Douglas
• JMVH New Author’s Award – Rolf Sellentin & Penny Sanchez
• JMVH Editor’s Award – Stephen Pullent, Eva Pietrzak, Cristina Cotea and Peter Nasveld
• Patron’s Award – Anthony Holley

• Foundation Park Award (Best Veteran Paper) – Kathryn Pushkar

Next year the conference will be our 22nd and will be held at the Adelaide Convention Centre from 1-3 November.

During the conference the Association’s annual general meeting was held with Jenny Lumsden being elected to council following the non-renomination of Stewart Robertson. But the big news is that the association is now called the Australasian Military Medicine Association as this better reflects the association’s membership and future directions. We hope, too, in the coming months to be able to report on developments with the Journal and sponsorship which will assist in ensuring the Journal’s sustainability.

Wishing all members and readers a Merry Christmas for 2012 and Happy New Year in 2013.

Greg Mahoney
President

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Military ‘live tissue trauma training’ using animals in the U.S. – its purpose, importance and commentary on military medical research and the debate on use of animals in military training

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Introduction

There has been a significant change in the types of injuries sustained on the modern battlefield due to the use of improvised explosive devices (IEDs) which are designed to cause severe penetrating injuries to limbs and torso, often resulting in massive haemorrhage in injured soldiers. Massive haemorrhage is the most common preventable cause of death for soldiers wounded in combat. Hence lifesaving training techniques and practices are being used by US military medical personnel in an effort to reduce this incidence. 'Live tissue trauma training' (LTTT), or 'combat medic training', as it is referred to in the US, involves the use of animals (mostly goats and pigs) for the purposes of direct surgical intervention in which physicians and paramedical personnel (military and civilian) obtain surgical skills by treating severe traumatic injuries. Once animals are deeply anaesthetized, wounds of the type army paramedics and doctors are likely to see in combat situations are inflicted. Such wounds are then appropriately treated in order to gain valuable 'trauma care' experience not likely to be offered in any other form. Upon completion of LTTT, animals are humanely euthanased without ever regaining consciousness. Despite the understandable highly emotive and sensitive nature of LTTT, by providing new combat medics with methods in how to manage critically-injured soldiers within the first few hours post-event, and where there is no local access to doctors or medical facilities, military personnel assert that such realistic training programs are necessary and have facilitated the saving of countless lives of soldiers who have sustained life-threatening injuries on the battlefield. In this ‘opinion’ article the author explains how and why animals are used for LTTT and in some areas of military medical research (MMR), as well as why he feels that the continued use of animals for LTTT is justified at this time.

Why LTTT needs to continue

Jim Hanson, a former member of a US Special Forces unit, writes in the Washington Times ('Save people, not pets'), that in his view animal use should continue for LTTT because 'banning medic training using live animals could kill US troops'. Interestingly, this publication was intentionally timely and was in direct response to a bill before the US Senate at the time. This bill, known as the ‘Battlefield Excellence Through Superior Training Practices Act’, sought to amend the US Defense Appropriations Act which aimed to phase in human-based training methods.
and replace the current use of live animals for LTTT. If passed, this bill will require the US Department of Defense, no later than 1st October 2014, ‘to use only human-based methods for training members of the Armed Forces in the treatment of severe combat and chemical and biological injuries’. It will also prohibit the use of animals in such training. One of the main groups that are seeking this change is the U.S. Physicians Committee for Responsible Medicine (PCRM), who strongly oppose the use of animals for research and training in any arena. Many believe that this bill (known as the ‘BEST Practices Act’) will likely end up costing the lives of US troops in order to save the lives of some animals simply because US military medics will no longer have access to vital and realistic LTTT.

The PCRM, and other groups that oppose vivisection (surgery used for experimental purposes on living organisms) such as People for the Ethical Treatment of Animals (PETA) seek an expanded use of simulators and other training aids so as to completely replace LTTT, despite the fact that such simulators and training aids cannot adequately mimic bodily functions or recreate the reality of a wounded living being. In contrast, it is widely accepted in US defense circles that, were it not for training programs such as LTTT, most medics would be sent into combat situations never having had the experience of treating a real traumatic injury. The viewpoint of most medics is that the visceral reaction that a living animal can invoke, being similar to that which each medic must face when a (human) life is in danger, is something that no simulator or training aid can provide. According to the PCRM, the US Department of Defense currently uses approximately 9,000 pigs and goats, and 20 vervet monkeys annually to teach Army medics, Navy corpsmen and Air Force personnel to respond to conditions for hours on end’. Faces are often destroyed due to blast and burns injuries caused by IEDs used by insurgents, and there is a need to rapidly apply surgical airways. Hence, ‘the spectrum of care they are expected to provide at any given moment exceeds what an entire civilian trauma centre might encounter in a week or month’.7

While most LTTT tuition involves the infliction of wounds using surgical instruments, some select US special operations units8,9,10 have conducted LTTT using various ‘projectile’ methods such as gunshot wounds, (bayonet) stab wounds, (napalm) burns, and amputations. Such courses, known as ‘Combat Trauma Management’, are ‘designed to test and reinforce the application of knowledge with regard to patient stabilization and treatment on an injured animal-patient. The use of ballistic wounding in these courses is used to create a variation of wounds and environments to complicate patient management and increase training realism’. It should be stressed that during such procedures, animals are always deeply anaesthetised (at a surgical plane of anaesthesia) for the entire period, given appropriate analgesia, and humanely euthanased post-training.

The production of extensive injuries in animals used for LTTT is important so that medics, when faced with a real combat situation are unlikely to ‘freeze’ due to emotional shock and they are able to quickly identify what they need to do, and apply it immediately and confidently. Such is the reality of LTTT that even hardened military personnel, when observing a gunshot wound for the first time, cannot remain unaffected by the experience. LTTT training also provides clinical and psychological ‘conditioning for the horrors and chaos of war.’ Indeed there are many medics belonging to Special Forces (elite) units who would gladly provide testimonials in support of the fact that such training, albeit graphic, has saved the lives of their colleagues who had sustained severe wounds in actual combat.2,8,9,10 Despite numerous advances in modern military technology, such as personal body armour and armour-plating of vehicles, it cannot be disputed that a confident and well-trained combat medic is probably the most likely ‘instrument’ to save a wounded soldier on the battlefield. Furthermore, a military spokesman for the US Army in Europe recently announced that effective combat trauma training, such as LTTT, had contributed to the lowest ‘killed-in-action rate in military history’.11 Thus, as LTTT actually saves lives, military personnel believe that this vindicates their position, and that LTTT should continue. The author, who also believes that priority should be given to human life over that of animals, concurs with this view. Indeed, it would seem that others are also of this view. David Hull, in his review of ‘Animal Liberation’,12 wrote that ‘if a choice has to be made between saving a human being and saving a pig,
we would be morally obligated to save the human being because human beings are capable of greater sentience (possession of feelings such as pain and emotional states such as fear) than pigs. One must be careful when drawing such conclusions however as the degree of pain experienced by an organism cannot be assumed to be proportionate to its level of sentience.\textsuperscript{13}

Military Medical Research

In the area of MMR numerous devices (for example, tourniquets), procedures (damage control surgery) and clinical practice guidelines (use of balanced plasma to packed cell ratios) have been promulgated in the military through initial animal studies and subsequent clinical studies. Subsequently, training procedures employing the use of animals have been modified to reduce the use of animals, refined to maximize their use and where possible, replaced by the introduction of wide and varied techniques including simulators.

Another major factor within the battlefield scenario, is the issue dealing with blood loss. Uncontrolled haemorrhage is by far the major cause of death for wounded soldiers.\textsuperscript{2,7,8,9,10} Blood loss accounts for 40\% of all combat deaths in Iraq and Afghanistan, according to the Army Institute of Surgical Research Joint Trauma System, but 79\% of ‘potentially survivable’ deaths.\textsuperscript{14} Medics in the field are restricted in their ability to maintain blood pressure and to ensure that there is enough circulating blood as possible within the body. Mostly the only tools a medic has in order to achieve these aims include the use of compression bandages, various bandaging techniques, the use of thrombotic drugs to assist in slowing the loss of blood and the knowledge and experience gained from LTTT in dealing with complex traumatic injuries. Through their experience on the battlefield, medics have found that soldiers can often recover relatively well if haemorrhage and potential massive blood loss has been arrested.\textsuperscript{7,14}

The Pentagon has recently invested approximately $10 million dollars in MMR to investigate strategies to increase the survival rate of soldiers through induction of a hibernation-like state.\textsuperscript{14} The medical research arm of the US military has commissioned Texas A & M University to undertake studies which initially have shown that hydrogen sulphide can put rodents into a state of ‘induced hibernation’. An extension of this work will seek to find scientific solutions that could potentially allow human cells to survive with less oxygen carried in the bloodstream and able to keep soldiers alive for up to six hours despite massive blood loss.\textsuperscript{14} Essentially, such research is aimed at reducing the body’s requirements at the cellular level regardless of the state of consciousness. If successful, this area of MMR is likely to have applications within the civilian world as well, for example in assisting victims of motor transport accidents.

Another significant part of MMR is the issue of chemical weapons defense research (CWDR; as opposed to chemical weapons offence research - banned in US for decades). This is another area where animals are used for military purposes.\textsuperscript{1,2,4,5} In order to find cures for soldiers exposed to deadly chemical attacks on the battlefield, vervet monkeys are used as a model for CWDR. In this work, the monkeys are anaesthetized and administered a non-lethal dose of a drug that mimics the symptoms of a chemical weapon, and then given an appropriate treatment. The efficacy and safety of chemical warfare antidotes and vaccines must be screened on animals prior to their use in humans. This methodology has to date become standard practise in this area of MMR.

Combat-experienced soldiers, having first-hand experience with regard to the types of injuries often sustained in modern military conflicts as well as seeing the benefits of LTTT, haemostatic training and CWDR, are strong advocates of LTTT and MMR for the purposes of saving human lives (lives of soldiers sent to war) over animals. They feel that LTTT should not be considered as a ‘callous disregard of animals. It is the careful and thoughtful regard for the survivability of the men and women that are sent to war’ by giving them (medics) all the tools and training that can help them save lives.\textsuperscript{2}

The LTTT situation in Australia

LTTT has been similarly practised in Australia to aid in the training of both civilian doctors and Australian Defence Force (ADF) personnel in the initial assessment and management of the trauma victim. This training essentially concentrates on the first hour of emergency care post-event, and does not include the infliction of firearm/projectile injuries (ie. gunshot, grenade wounds) as is practised by select US military groups conducting LTTT. In Australia, LTTT is known as Early Management of Severe Trauma (EMST)\textsuperscript{15} and since 1988, training programs have been regularly provided for civilian and ADF medical and paramedical personnel across the country. It is important to note that EMST training, when it is conducted, is carried out in full compliance with National Health & Medical Research Council Guidelines, NHMRC (2009). Guidelines on the use of animals for training interventional medical practitioners and demonstrating medical equipment and techniques.\textsuperscript{15} The EMST focus is purely on the ‘trauma’ patient, regardless of whether that is within a
civilian casualty or a military casualty context. EMST training was essentially ‘imported’ into Australia in the early 1980s when the Royal Australian College of Surgeons (RACS) liaised with its equivalent body in the United States, the American College of Surgeons, to seek support and permission in setting up the Advanced Trauma Life Support (ATLS) training programme for the Australasian region. As a result, the first EMST course, made available by the RACS, was offered to potential trainees in 1988, and has to date been providing this type of training as well as refresher training (normally undertaken if not done within four years of the initial EMST training) ever since.

The LTTT situation in the United Kingdom

In an article supporting the use of LTTT, Reeds (2010) states that ‘it would be prudent to clarify that the Royal College of Surgeons of England (RCSE) neither supports nor objects to the use of live animals for trauma training’. In a document published by the RCSE in 1999, titled ‘Surgical Competence Challenges of Assessment in Training and Practice’, the RCSE remained ‘neutral’ by providing information as to the benefits of LTTT, but also emphasizing the disadvantages relating to animal welfare considerations. Rather than outlining the formal policy of the RCSE on LTTT, this document was simply a discussion of issues relating to surgical training and LTTT, which was collated as a summary of various conference presentations. As such, the document ‘has confirmed that it does not hold any formal opinion or policy (on LTTT) nor has it ever considered the same.’

Anti-animal testing protesters marching through the streets of London (sourced from an anonymous internet source) 3518089112_6a7198e73f.jpg/flickr.com

Anti-vivisectionist groups also oppose civil medical research

Anti-vivisection groups such as PCRM, PETA and the more militant group Animal Liberation Front (ALF) of the UK have traditionally been strongly opposed to the use of animals for research purposes of any kind. Effectively they believe it is ‘inhumane’ and claim that those biomedical research organisations who conduct animal research, do so in a totally unregulated environment which is fraught with animal cruelty. Recently, these groups have been very active on a world-wide scale by protesting (PETA and ALF, violently) against any form of animal-based research or training. PETA, ALF and recently PCRM, seem to have realised that if they can’t force a change to their views on various industry and government bodies, they can certainly be more effective by using official processes to file complaints against major US research institutions. This results in the delay or cessation of research progress, the waste of much-needed resources and results in frustrating delays while complaints are investigated, many of which usually result in ‘non-event’ outcomes. It seems that their collective influence is spreading, for example, one just has to take note of the ever-increasing, official filed complaints to animal welfare regulatory bodies such as the US Department of Agriculture (USDA) and Animal and Plant Health Inspection Service (APHIS). These obstructive tactics have had, at least in some cases, their desired effect, with a few major internationally-respected research institutions very recently having ceased using live animals.

This has occurred not due to the institutions in question having breached any federal animal welfare laws but rather because it simply was easier for the institutions to avoid the time-consuming nature of such USDA investigations and the associated disruption to research, teaching and training. The two Canadian hospitals in question, namely Hamilton Health Sciences in Ontario and Saint John Regional in New Brunswick Canada, have indeed halted their Advanced Trauma Treatment Courses (ATTC) using live pigs, and have commenced using patient simulators. Despite being accused of ‘caving in’ to external pressure exerted by the PCRM by some commentators, there was resistance by the Hamilton institution staff to the loss of the ATTC. Surgical residents at Hamilton openly expressed their opposition to the changes, as they considered the new simulators as poor replacements in their training when compared to their previous experience using live pigs. The medical students repeatedly demanded the return of the pigs for this type of training, because they felt that the ‘tissue’ on the mannequins simply was neither lifelike nor realistic.

Citing stark factual differences, a university veterinarian at Hamilton made it clear that some (anti-vivisectionist) groups often deliberately used misinformation to get their point across. For
example, in this very situation, the pigs used in ATTC were cared for by well-trained, dedicated staff who would ensure that they were housed in a comfortable environment, were well-fed and treated with the utmost care and respect. Pre-delivery to the institution, the pigs would be transported in an air-conditioned van and given a period in which to acclimatize to their new surroundings. The pigs would be carefully anaesthetized before undergoing the ATTC procedure, and prior to the conclusion of the training, they would be humanely euthanased with an overdose of anaesthetic while still unconscious. This entire protocol certainly does not reflect a portrait of inhumane treatment of animals, as claimed by some anti-vivisectionist groups.

PETA filed a complaint in 2010 to the USDA against the University of Michigan (UM), which conducts Survival Flight Training using animals. It claimed that the UM had violated the US Animal Welfare Act because it used cats and pigs in an emergency training course for its Survival Flight nurses (personnel providing emergency air transportation service for patients in critical care). PETA stated that the UM should use human simulators instead of live animals to practise common emergency procedures such as endotracheal intubation, which involves inserting a breathing tube into the trachea to ventilate the lungs.

Responding to the PETA complaint, the UM veterinarian and director for laboratory animal medicine stated that ‘the work of the Survival Flight nurses required that such procedures were performed on living tissue’, and that there was no substitute for this type of training, claiming that both simulators and associated teaching aids simply weren’t adequate. This training was designed for practising various essential life-saving techniques, which ultimately would be used for helping young children. The clinicians felt that because of the anatomical similarities between some animals and humans, they were simply the best training models available for this training, and importantly, the animals were under anaesthesia when such training was being conducted.

In another separate animal welfare complaint, filed by the PCRM to the USDA’s APHIS against the University of Washington (UW) School of Paediatrics, the PCRM claimed that this institution was breaking federal animal welfare laws because it used live (anaesthetized) ferrets as a model to train paediatric medical residents to insert breathing tubes, as would be used for emergency procedures in premature babies. Responding to the complaint, a UW Medical Director and Professor of paediatrics stated that up to ten ferrets (maximum) were used for paediatric training sessions per year. He reported the species was a good model for such training as they were a hardy animal which, when anaesthetized, could easily tolerate between six to eight intubation attempts with minimal airway irritation. Recovery is rapid and they could be used again within a few weeks. The Professor said that this training was important as it helped train medical students to insert breathing tubes in very low birth weight babies, where medical simulators (mostly plastic models which contain semi-realistic anatomical features, and unable to adequately duplicate the airway passage in extremely small infants) simply weren’t at the level of sophistication required for these tiny infants.

Anatomical and physiological differences

Anti-vivisection groups often cite the anatomical and physiological differences between animals and humans as one of their main arguments in opposing LTTT. In a brief prepared by the PCRM for consideration by the US Senate in relation to the BEST Practices Act, the PCRM states that ‘the use of pigs and goats for combat casualty care training (another name for LTTT) is suboptimal due to, among other issues, the animals’ anatomical and physiological differences from humans. Compared with humans, pigs and goats have smaller torsos and limbs, thicker skin, different responses to anaesthesia and analgesia, and important differences in anatomy of the head and neck, internal organs, limbs, blood vessels and airway’.

The same report also seems to recognise however that the most important elements of LTTT for practitioners is realism, human-specific injuries and treatments, volume of trauma exposure and ‘team-building’. In essence, they recommend combined use of simulators, human cadaver use and access to civilian trauma centres. While in theory this combination of training elements does sound ideal for LTTT, and in fact they are used by the military wherever and whenever possible, all of these separate elements do have their own inherent problems.

In addressing the first argument above, it needs to be stated that it is the reaction or response of living tissue to injury or irritation, rather than the anatomical or physiological species differences which is the main issue in question. Live tissue appears to be the most suitable element in training combat medics. ‘Most patient simulators do not bleed, and those that can, do not respond in the same biological way that bleeding patients do in clinical practice’. Using the example of physician training, real vascular injuries allow trainees opportunities to perform various techniques that respond authentically to injuries.
that they realistically encounter during clinical practice; this is a distinct advantage of the Advanced Trauma Operative Management course (or LTTT) that uses the live tissue porcine model and which has been shown to be of great benefit to trainees. An additional benefit is the pathophysiological response to traumatic injuries that live tissue provides and the appropriate physiologic response of the patient that is observed to the trainees interventions/clinical management. Simulators and human cadavers cannot produce this same effect. Endoscopy and other associated training techniques have also been used as part of LTTT. Some operators, Barthe et al (2007), also have ‘demonstrated significantly increased competence using live liver tissue in performing diagnostic procedures with regard to visualizing anatomic structures, performance of fine needle aspiration, and, to a lesser extent, endoscopic ultrasound-guided celiac neurolysis (endoluminal ultrasound)’. With respect to the use of human cadavers and simulators as an alternative to LTTT, another distinct advantage of live tissue is that organ texture and tissue handling characteristics are optimal, both of which are limited in cadavers and simulators. Although cadavers and simulators have their uses in certain applications, neither respond authentically to surgical procedures and other medical interventions in the same way that living patients do in everyday trauma practice. There are various (human) simulators on the market, most of which have been developed to meet certain requirements for training. One of them, ‘Trauma Man’ (Simulab Corporation) was constructed specifically for advanced trauma surgical skills training. According to the Surgeon General of the US Army, Major General Gale S. Pollock, ‘use of this simulator is not applicable for haemorrhage control, the largest, preventable killer of our Service members on the battlefield’. Furthermore, in a study done at the US Army Base at Fort Lewis, a haemorrhage simulator was used to training military medics. However the control group had received no exposure to the simulator. There was no comparison with live animal haemorrhage training. It should be remembered that simulation is a training step; it is not the end of the training process.

The use of civilian trauma centres, as an alternative to LTTT and on the scale that the military requires it, is also unrealistic and naïve. Hospital emergency rooms simply do not have the capacity or the resources to accommodate the needs of the military. As a rough guide, their programmes can only provide training for approximately 24 men (only) every 6-8 weeks. To put the US military’s requirements into some perspective, Major General Pollock made the following statement in 2007, “On any given day more than 12,000 Army medics - physicians, dentists, veterinarians, nurses, allied health professionals, administrators, and combat medics - are deployed around the world supporting the (US) Army in combat, participating in humanitarian assistance missions and training throughout the world”. Furthermore, he added that “to date, more than 17,800 Combat Medics have received training in Medical Simulation Training Centers which use computerized mannequins that stimulate human response to trauma. (Only) use of live tissue best simulates the challenges and stress inherent in stopping actual bleeding”. From the above statements, it should be obvious to the reader that LTTT is the optimal method of training delivery and that the ‘through-put’ of hospital trauma centres cannot provide pre-deployment training requirements for combat medics, especially in adequate emergency case management experience. Other problems with the use of civilian trauma centres for combat medics is that the types of injury encountered in hospital trauma centres are quite different to the spectrum of injuries that service members often encounter on the battlefield. Lastly, putting combat medics in civilian trauma centres for the purposes of training also removes them from their daily duties and thus reduces their capacity to provide healthcare for other military personnel.

In terms of military medical preparation for the treatment of combat casualties, advocates strongly believe that LTTT is the current solution because it is effective (it saves lives) and is the most advanced kind of training available. It trains its participants to observe, assess, triage and treat based on the severity of the penetrating trauma presented, and all set within a ‘battlefield scenario’ where the need for rapid decision-making in a ‘high-stress’ environment is a constant challenge for the course participants. Participants in LTTT build an individual proficiency and a level of confidence in their ability to treat real combat casualties.

The US military already uses a range of simulators including Trauma Man, the Combat Trauma Patient Simulation System, and other training modalities as described by Cherry and Ali. While these simulators are used where appropriate, and although they can enhance the experience of learning trauma training, they are only at best a progression towards, rather than a replacement for, LTTT, as they cannot replace all of the procedures used in training combat medics. So, effectively, the use of live animals cannot be eliminated altogether and this remains the reason that the US military uses the LTTT model for its troops pre-deployment. However, ‘hybrid’ courses
have been developed by military training providers which offer a combination of LTTT, use of simulators, human cadavers and civilian trauma centres to aid in the training of military medical personnel. Though the success of some of these programmes has been variable, the use of live tissue has remained an essential component of such training.

One of the better developed hybrid courses is the US Army’s ‘Tactical Combat Casualty Course’ which consists of didactic sessions, interactive human surgical simulators, triage scenarios, use of animal tissues and LTTT. It would be interesting to see how changing the relative proportions of such hybrid training may affect overall tuition, hence further research in this area is needed. Currently, until a simulation technique is developed that is documented to equal the benefit of live tissue training in preparing medics to manage combat trauma, appropriately conducted LTTT should be supported as an essential component of combat medic training.

There are a number of simulators available for generic training which, although improved in their ability to provide useful training, they do not yet have the full capability of encompassing all aspects of live tissue training. It is for this reason that the American College of Surgeons (ACS) “supports the use and humane care and treatment of laboratory animals used in research, education, teaching and product safety testing in accordance with applicable local, state, and federal animal welfare laws”. The ACS also states that “wherever feasible, alternatives to the use of live animals should be developed and employed” but “believes that now and in the foreseeable future it is not possible to completely replace the use of animals and that the study of whole living organisms, tissues and cells is an indispensable element of biomedical research, education and teaching”.

The benefits and controls of animal-based research and training

Military medical personnel and researchers across most institutions acknowledge the use and usefulness of alternative approaches as being very important. They do not use animals unnecessarily or uncaringly. All personnel consider it a privilege to use animals in research or training, and demonstrate this by treating them with the utmost level of care and respect.

Military research groups often support their argument by reminding us as to the many lives of soldiers saved directly, both in the past and currently, as a consequence of LTTT, CWDR and MMR. This has similarly been the case in the civilian arena of medical research as well, where the life-saving benefits to human health have been enormous, as has the reduction of human suffering caused by widespread, global infectious diseases. This has only been possible, because of the far-reaching implications of animal-based research and training. Interestingly, recent figures from the US National Academy of Science confirm that world rankings on average life expectancy have shown that they have increased over the last 25 years, due mostly to the advances in medical research and training. There have also been immense direct benefits to veterinary medicine as a result of animal-based biomedical research. Unfortunately, many anti-vivisection groups continually dismiss these enormous advances in human and animal medicine and continue to incorrectly propagate the view that these advances have been achieved at the expense of ‘humane’ care of animals.

Surely the ‘common denominator’ on both sides of this debate must primarily be the increased protection and safety of service personnel, together with enhanced humane welfare and protection of animals used for LTTT, CWDR and MMR purposes. It should be noted that the US Animal Welfare Act does permit the use of live animals for research and training purposes in both the civil and military arenas. However, it is the role of this Act to regulate whether animals are treated humanely. Violations of the Act are promptly investigated. Routine monitoring of conduct often involves unannounced visits to research and training establishments, aiming to ensure that animals are being treated humanely and with the utmost care. Actions taken for non-compliance can be severe and range from official warnings to fines being imposed on the institution, with the possibility of suspension of work or the revocation of research licenses.

The majority, if not all, research and training institutions both military and civil, operate within a rigid environment of internal and external controls governing their use of animals. This environment is highly regulated by the federal government, overseen by federal agencies which mandate several layers of review and involve a dedicated staff of caretakers and research animal veterinarians. Additionally, each institution has effective animal care and use committees set up to provide internal controls. A requirement of these committees mandates that a lay-person (an ordinary member of the community) serve as a member of its quorum. Indeed, the system on which this model is based is in place in many western countries today. Taking all of these factors into account, it should be evident that claims such as ‘inhumane treatment’, ‘fraught with animal cruelty’ and the like, appear to be without foundation. Nonetheless, there is no room for complacency as it
is important that regulatory authorities continue to monitor the welfare of animals used for military and civil research and training activities, and continue to maintain the high standards expected of such institutions. Those ‘high standards’ have long been a tradition in the military services as ‘military medicine has always been at the forefront of research. It spans everything from disease prevention to rehabilitation’.

Summary

This article highlights the importance of military training in life saving techniques and treatments developed through clinical research and now used by physicians and combat medics operating in the emergency arena of warfare. To this end, it should be remembered that such protocols have been refined to minimise pain and distress to animals, that the number of animals used is always reduced to the absolute minimum possible and that where effective non-animal alternatives exist, every effort is made to promptly implement or adapt them for current use. And although military and civil researchers will make use of new alternate technology and training methodologies wherever possible, at this point in time, animals (along with other types of tuition) remain vital in advancing medicine and for use in life-saving training techniques.

Acknowledgments

This work is based on an article previously published in ‘Lab Animal’.

The author would like to thank Dr. Julianne Djordjevic and Dr. Julie Ferguson for their critical review of the manuscript.

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References


From the Vietnam War to Retirement: Are Veterans Healthy Enough to Enjoy Their “Golden Years”?

David N. Vander Goes and Stephen E. Snyder

Introduction
Our aim in this paper is to demonstrate the impact of Vietnam era active duty service on the later-life health of American veterans. Using the statistical technique of instrumental variables, we show that estimates of this impact from a simple evaluation do not accurately capture the causal impact. Simple estimates are biased down by the selection effects of recruitment into military service; no veterans were disabled at the time of their induction or they would not have qualified for service. We show that accounting for selection by recruits (who volunteer) and by the military (who enforce standards for enlistment) substantially increases estimates of the negative health effects of military service. We also find that service has different effects for Caucasian-American and African-American veterans.

This paper contributes to a debate among economists over changes in the U.S. veterans disability system1-3. Some have argued that an over-generous system may have led to spurious claims of service-related disability. Our findings, particularly the different impact on different racial groups, do not provide support for this view, but are consistent with the notion that the earlier disability system was under-generous, and the changes may represent a move towards greater equity.

While economists worry about the efficient level of support for veterans, health sciences researchers have found evidence for simultaneous over-use and under-use of support programs for veterans5-10. That is, there may be some evidence for spurious claims of disability, but there are also populations that do not use benefits to which they have legitimate claims.

Behind the conflicting empirical claims lie some issues of philosophy. If a person, veteran or otherwise, has no financial alternative, that person may continue to work despite substantial physical impairment. If this person is offered public support, that person may well take it. This imposes a cost on society but may radically improve the quality of life for the beneficiary of the new policy. Was the old policy appropriate or cruel? Is the new policy appropriate or wasteful? A recent review by government researchers concluded that decisions had to be made without perfect scientific knowledge, and appropriately had to blend scientific and policy considerations6.

This policy debate has arisen because large numbers of recent disability claims stem from Post-Traumatic Stress or chemical exposure. Also, levels of claims are higher from recent cohorts than from earlier cohorts, World War Two veterans for example. Economists typically work with secondary data. Clinicians see patients suffering from a variety of symptoms, and develop procedures to detect malingering5,7,8,11-14. The economist sees a response to financial incentives; the clinician sees symptoms of premature wearing out.

Our approach has been to avoid the legal claim of disability, but to focus on self-reported disability in confidential surveys conducted by the U.S. Census. In particular, we examine how Caucasian and African-American U.S. males estimated level of disability changes as we correct for selection bias, which we define in the next section. During the period in which these men served, the military, while far from perfect, offered opportunities for African-Americans to progress which they could not obtain in the civilian labor market15,16. We hypothesised, therefore, that correcting for selection should have a larger effect in the African American population because their likely health in the absence of service would have been relatively good.

Previous economic studies of veterans have looked at earnings, education levels, and mortality as outcomes of service, but until recently have not focused on disability. Contributions to this literature include Angrist (1990)17, Angrist (1993)18, Angrist and Chen (2007)19, Dobkin and Shabani (2006)20, Dohrenwend et al. (2006)21, Hearst, Newman, and Hulley (1986)21. The Bedard and Deschênes (2006) paper on the mortality rates of World War II and Korean War veterans provides a basic framework for eliminating selection bias associated with military service.22 They were unable to fully implement their approach due to...
Vietnam War. To capture this large a share of the cohort we necessarily include some who served prior to the Vietnam War and some who served after the war ended. Overall the data encompass people aged 43 (the youngest cohort in 2000) to people aged 66 (the oldest cohort in 2006) at the time they were surveyed.\footnote{1}

For this entire period the U.S. military was staffed by a combination of those who were drafted and those who volunteered for service. Regulations determining eligibility for service, the likelihood of being drafted, and eligibility for deferment from the draft changed substantially over this period.\footnote{24} The share of each annual cohort reporting veteran status is summarised by race in Figures 1 and 2. Both populations show a peak population share of veterans for those born in the late 1940’s. In our estimation those with a high likelihood of service are compared to both older and younger cohorts; this means our estimates are not confounded by the secular improvement in cohort health over the study period.

We wish to estimate the impact of military service on veterans’ self-reported disability to gain insight into the long-term impact of military service on health, but cannot simply compare disability rates between veterans and non-veterans because of the selection issues outlined above. Simple comparisons are biased by the unobserved selection process. Even when we control for observable differences in the two groups, we may be omitting important, systematic differences. Fortunately a regression procedure exists which can correct for selection issues—instrumental variables. It requires a researcher to find a variable which is correlated with the explanatory variable of interest, but is not correlated with the selection process. Even when we control for observable differences in the two groups, we may be omitting important, systematic differences. Fortunately a regression procedure exists which can correct for selection issues—instrumental variables. It requires a researcher to find a variable which is correlated with the explanatory variable of interest, but is not correlated with the selection process. Figures 1 and 2 show that the share of each annual cohort which served in the military varied data limitations. However, more recent U.S. Census Bureau surveys contain richer data sets for labour market participation and health. We use this more recent data to estimate the effect of military service on a variety of self-reported disabilities.

Methods

This paper uses data from the 2000 decennial census and the more recent American Community Surveys for 2001 to 2006 conducted by the United States Census Bureau which we extract from the Integrated Public Use Micro Samples (IPUMS), publicly available data fully representative of the non-institutionalised U.S. population.\footnote{23} We include all males reporting a year of birth between 1940 and 1957 and race of either White or Black. We restrict analysis to men because recruitment, military experience and labour market experience for women are all so different from men in the era under study. Also, our method for removing bias from our estimates depends on draft eligibility and U.S. women were not subject to the draft. The effect of military service on women deserves attention, but requires a completely different approach and a separate paper. Because we observe the same cohort in multiple years, we are able to include both age and year-of-survey effects. The data are then divided into two samples – one white and one black – because we expect systematic differences by race given the different labour market opportunities in the United States; previous research on veteran earnings has found this to be the case.\footnote{17,24} We exclude other racial groups only because sample sizes for the non-white, non-black populations are too small to make separate analysis useful.

We determined in a preliminary analysis of the IPUMS data that males born between 1940 and 1957 represent 90% of those men who served in the Vietnam War. To capture this large a share of the cohort we necessarily include some who served prior to the Vietnam War and some who served after the war ended. Overall the data encompass people aged 43 (the youngest cohort in 2000) to people aged 66 (the oldest cohort in 2006) at the time they were surveyed.\footnote{1}

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We wish to estimate the impact of military service on veterans’ self-reported disability to gain insight into the long-term impact of military service on health, but cannot simply compare disability rates between veterans and non-veterans because of the selection issues outlined above. Simple comparisons are biased by the unobserved selection process. Even when we control for observable differences in the two groups, we may be omitting important, systematic differences. Fortunately a regression procedure exists which can correct for selection issues—instrumental variables. It requires a researcher to find a variable which is correlated with the explanatory variable of interest, but is not correlated with the selection process. Figures 1 and 2 show that the share of each annual cohort which served in the military varied data limitations. However, more recent U.S. Census Bureau surveys contain richer data sets for labour market participation and health. We use this more recent data to estimate the effect of military service on a variety of self-reported disabilities.
substantially over the cohorts in our analysis. We use this variation in “draft pressure” as an instrument to eliminate the bias from selection. Even those who volunteer for the military may do so because the alternative is the draft; how likely they are to be drafted affects the likelihood that marginal recruits choose to enlist. We implement our instrumental variables approach in a linear probability model, a modified version of least squares regression.²

We demonstrate the concept of an instrumental variable using an example: suppose there were 2 possible levels of service for an annual cohort, either a low level, 20%, or a high level, 50%. Then there is a 30% share of the population that serves in high years but not in low years. We assume these 30% shares would have the same expected health in the absence of military service, and we have some ability to test the validity of this assumption by looking at the 20% of the population that consistently served and the 50% which consistently did not. Conceptually, the 30% shares in the low years are the control group, the 30% shares in the high years are the treatment group; the difference between them is the corrected estimate for the average impact of service in the U.S. military during the Vietnam era.² We assess our instrument quality using standard tests, but the ultimate validity of this procedure rests on the assumption that in the absence of service the health of the different cohorts would be similar except for random variation, which we account for by taking a large number of cohorts, and trend, which we eliminate through controls on age. The non-monotone shape of Figures 1 and 2 allows us to implement this strategy and yet have sufficient variation for our estimates.

Instrumental variables procedures control for bias, but the price researchers pay is loss of efficiency.²⁶⁻²⁸ Large samples are essential for successful implementation.

For dependent variables the study uses 6 disability variables that come directly from the IPUMS data, and 1 composite variable. Four of the 6 variables are available for all 7 years of data: DISABWRK, DISABMOB, FERSHCARE, and DIFFPHYS. DISABWRK indicates a long-term physical or mental health condition that limits or prevents work; long-term is not defined. DISABMOB specifies whether a respondent has a disability lasting 6 months or more that restricts or eliminates leaving the home. FERSHCARE indicates a condition lasting longer than 6 months which limits the ability to bathe, dress, or move around inside the home. DIFFPHYS indicates a long-term health problem that limits walking, lifting, or carrying. Two variables, DIFFEYE and DIFFREM, are not available for 2003 and 2004, reducing sample sizes in their analysis. DIFFEYE is for long-lasting severe vision or hearing impairment including deafness and blindness. DIFFREM is defined as a difficulty in learning, remembering, or concentrating lasting 6 months or longer, and represents our only measure of cognitive function. The final dependent variable is a composite, Any Disability. A respondent who reports positively to any of the six specific conditions is included in this category.

We present data on mean levels of disability in the cohorts under analysis (Table 1), the results corrected for selection bias (Table 2) and some alternative specifications (Table 3). All statistical analysis was conducted using STATA version 11.2. All estimates use person-level weights and regression standard errors are clustered on birth year.

Results

Table 1 compares mean levels of disability by veteran status in the U.S. population born between 1940 and 1957 and surveyed between 2000 and 2006. For the composite measure of disability, black veterans and non-veterans are indistinguishable statistically while white veterans have a disability rate which is higher and statistically distinct from non-veterans at the 1% level. For whites 21.1% of veterans report some disability while 17.3% of non-veterans do. Blacks report higher levels of disability than whites in almost all categories. White veterans generally report statistically higher levels of disability than non-veterans, but in Table 1 this pattern is reversed for blacks.

Table 2 reports the results of regression analysis corrected for selection bias. All rows report results controlling for age when surveyed and year of census data. Compared to Table 1 we see fewer statistically significant results largely because the instrumental variable procedure entails a loss of efficiency. Nevertheless, for both blacks and whites the effect on “disability that causes difficulty working” (DISABWRK) is statistically significant and positive. That is, military service raises this disability rate for both study groups. Additionally, the estimated effects are statistically significant for blacks in the composite disability measure and the physical disability measure. The results for whites marginally fail to achieve statistical significance for these measures, but are suggestive. Whites show a statistically significant effect for difficulties with hearing or vision and difficulties with memory. For blacks, difficulties with memory just fail a test of statistical significance. All significant or near-significant results are positive, that is, all evidence points to an increased risk of disability for U.S. veterans from the Vietnam era.
### Table 1: Means and Sample Size

<table>
<thead>
<tr>
<th></th>
<th>Black Men</th>
<th>White Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Veterans</td>
<td>Non-vets</td>
</tr>
<tr>
<td>1. Any Disability</td>
<td>0.294</td>
<td>0.296</td>
</tr>
<tr>
<td>Specific Disabilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Disability that causes difficulty working</td>
<td>0.197</td>
<td>0.201**</td>
</tr>
<tr>
<td>DISABWRK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Long-term difficulty with mobility</td>
<td>0.085</td>
<td>0.091***</td>
</tr>
<tr>
<td>DISABMOB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Long-term difficulty with personal care</td>
<td>0.049</td>
<td>0.053***</td>
</tr>
<tr>
<td>PERSCARE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Physical Disability</td>
<td>0.182</td>
<td>0.181</td>
</tr>
<tr>
<td>DIFFPHYS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Long-term difficulty with vision or hearing</td>
<td>0.057</td>
<td>0.061***</td>
</tr>
<tr>
<td>DIFFEYE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Difficulty with memory</td>
<td>0.074</td>
<td>0.084***</td>
</tr>
<tr>
<td>DIFFREM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Average number of disabilities reported (max=6)</td>
<td>0.622</td>
<td>0.646***</td>
</tr>
</tbody>
</table>

Observations (N) = 36,154 for Black Men and N=78,353 for White Men.

Notes:
1. This variable equals 1 if an observation reports having one or more of the 6 specific disabilities listed in the table.
2. See chapter or usa.ipums.org for a detailed description of each disability. In italics on the line below each disability is the IPUMS variable name for each.
3. This variable is the total number of disabilities reported for each observation.
4. N refers to data from 2000 to 2006. N is smaller for disabilities 6 and 7, as they are not reported in the 2003 and 2004 ACS. N=94,882 for Black Men and N=1,020,339 for White Men.
   • *, **, *** indicate 10, 5 and 1 percent statistically significant difference in means between veterans and non-veterans (listed in non-veteran column), respectively.
   • Standard deviations are reported in parentheses.
   • Numbers in italics are the percentage of all disabilities attributable to each disability type. Disabilities 6 and 7 are not available in years 2003 and 2004 and percentages are weighted accordingly.

### Table 2: Results from Instrumental Variable Regressions, Coefficients on Veteran

<table>
<thead>
<tr>
<th></th>
<th>Black Results</th>
<th>White Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Any Disability</td>
<td>0.167***</td>
<td>0.077*</td>
</tr>
<tr>
<td></td>
<td>[0.047]</td>
<td>[0.046]</td>
</tr>
<tr>
<td>Specific Disabilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Disability that causes difficulty working</td>
<td>0.181***</td>
<td>0.042**</td>
</tr>
<tr>
<td>DISABWRK</td>
<td>[0.048]</td>
<td>[0.021]</td>
</tr>
<tr>
<td>3. Long-term difficulty with mobility</td>
<td>-0.022</td>
<td>0.008</td>
</tr>
<tr>
<td>DISABMOB</td>
<td>[0.026]</td>
<td>[0.009]</td>
</tr>
<tr>
<td>4. Long-term difficulty with personal care</td>
<td>0.027</td>
<td>0.010*</td>
</tr>
<tr>
<td>PERSCARE</td>
<td>[0.021]</td>
<td>[0.006]</td>
</tr>
<tr>
<td>5. Physical Disability</td>
<td>0.115***</td>
<td>0.062*</td>
</tr>
<tr>
<td>DIFFPHYS</td>
<td>[0.037]</td>
<td>[0.035]</td>
</tr>
<tr>
<td>6. Long-term difficulty with vision or hearing</td>
<td>0.036</td>
<td>0.054***</td>
</tr>
<tr>
<td>DIFFEYE</td>
<td>[0.028]</td>
<td>[0.018]</td>
</tr>
<tr>
<td>7. Difficulty with memory</td>
<td>0.061*</td>
<td>0.025***</td>
</tr>
<tr>
<td>DIFFREM</td>
<td>[0.032]</td>
<td>[0.005]</td>
</tr>
</tbody>
</table>

Observations (N) = 114,507 for Black Men and N=1,252,378 for White Men.

• N refers to data from 2000 to 2006. N is smaller for disabilities 6 and 7, as they are not reported in the 2003 and 2004 ACS. N=94,882 for Black Men and N=1,020,339 for White Men.
• *, **, *** indicate 10, 5 and 1 percent statistical significance, respectively.
• Standard errors are reported in brackets.
The reported coefficients for veterans are uniformly larger in Table 2 than the differences reported in Table 1. For DISABWRK, the coefficient for whites in Table 2 is 0.042, while the difference in Table 1 is only 0.021 (0.129 – 0.108). That is, correcting for the generally better health of those eligible to serve roughly doubles the estimated impact of military service on disability. These estimates are percentage point differences, and we discuss their interpretation in the next section. We further note that while in Table 1 black veterans have a slightly lower rate of disability as measured by DISABWRK than non-veterans, after correction for the selection process the impact of military service is very large and positive. Military service increases the risk of work-limiting disability for both races.

Discussion

In this section we discuss how to interpret our percentage point differences as increases in the relative risk of disability, offer some working hypothesis as to why military service raises disability rates, and discuss the limitations of the present study. Table 1 shows blacks suffer higher rates of disability. Instrumental variables do not alter this basic finding; it changes estimates of the cause-and-effect impact of military service on health. We conclude that in the absence of service, their disability rates would be substantially below that of non-veterans. The magnitude of this selection effect is quite large, but should not be surprising. Every veteran was able to pass a physical exam in early adulthood, not every civilian could. Later-life health status is correlated with health status in youth, so we should expect veterans to report fewer disabilities in their fifties in the absence of a negative impact from military service. We attempt to bound the magnitude of the projected increase in disability below, but ask readers to remember: we are not comparing veterans to the actual civilian population, but to their own later-life health status in the absence of service. The military population was healthier in their youth; this is no longer true.

The predicted level of work-limiting disability in Table 2 is (Xw+0.042) for white veterans and (Xb + 0.181) for black veterans, while the level these populations would have experienced without service is Xw and Xb. Neither of these variables is equal to the non-veteran values from Table 1, since we expect veterans to be healthier at the time they enter service; they passed a physical to enter the military. Also note the larger Xw and Xb are, the lower the increase in relative risk from military service. Therefore, an upper bound for Xw and Xb would be 0.129 and 0.201 respectively, the highest level observed for DISABWRK in each racial group in Table 1. Thus a lower bound for the relative risk for whites is 60% ((0.129+0.077)/0.129) and 83% for blacks ((0.167+0.201)/0.201). The corrected values are substantially higher for both racial groups than what is seen in the simple analysis of Table 1. We further note that although simple means do not show elevated disability rates for black veterans, the corrected effects are larger for blacks than whites. The relative impact of military service goes from being smaller for blacks to being larger. What this implies is that blacks who entered military were a relatively healthy group. The similar levels of reported disability by black veterans and non-veterans in Table 1 represent the deteriorating health of an initially healthy group.

Table 3 offers 2 alternate specifications for each racial group. Columns 1 and 3 show the results for a standard OLS regression, using controls for age and year of Census data but not correcting for selection bias. These results are more like results for Table 1 than Table 2, demonstrating the importance of our instrumental variables approach. Columns 2 and 4 of Table 3 show the corrected results change very little when we add controls for place of birth (state dummies). These controls are plausibly related to unobserved social and economic variables, and the similarity to Table 2 offers reassurance that our baseline results are not caused by omitted variables. Other researchers report a similar impact when including birthplace.4,14 People who died before our data were collected could potentially bias our findings. However, researchers with access to Social Security data find the mortality for the relevant cohorts to be inconsequential.4 Also, mortality by veterans who would otherwise report a disability would reduce our estimated effects rather than increase them.

We test the validity of our chosen instrument using four standard statistical tests. Three supported the validity of the instrument for each measure of disability. The fourth tested whether simple least squares regressions show evidence of bias and confirmed the need to use instruments in 5 of the 14 regressions but generated inconclusive results in the other nine. While the instruments may be valid, the instrumental variable strategy is only feasible for conditions that affect a relatively large share of our study population. Our estimation strategy is of limited value when the disability is relatively rare. Despite these limitations, the overall message of Table 2 is clear. Veterans suffer increased rates of disability as a result of their service. Black veterans have higher rates of disability than white veterans.
and issues of selection appear larger for blacks than for whites in that the differences between Table 1 and Table 2 are greater.

It is a limitation of our methods that we can offer little insight into the pathways by which military service produces disability. We do note that a substantial share of the impact is clearly associated with hearing, vision and memory problems for whites (DIFFEYE, DIFFREM) and, while not statistically significant, was suggestively associated with the same problems for blacks. In neither group do mobility issues approach significance. This is consistent with the emerging literature on the long term effects of repetitive brain trauma, but not consistent with gross battlefield injuries as a source of disability. Clearly, better identification of the specific causes of disabilities is a direction for future research. Our results are consistent with a human capital view in which military service leads to higher depreciation of some veterans’ capacity for work and full functioning, an effect which may not manifest itself for many years. It is not clear to us why disability claiming would be related to self-reported health in a census survey, and we find it especially unlikely that black veterans would be more likely to claim disability than non-veterans in general (Table 1, Table 3 column 1), but would show a large effect when we use “draft pressure” to correct for selection effects (Table 2). Our findings do not support those who feel that recent claims of disability are spurious.

Another significant limitation of this research is our use of self-reported rather than clinical health outcomes. Although we find higher rates of disability for veterans, it is possible that it only captures high rates of reported disabilities. Veterans may differ from non-veterans in how they perceive health or states of disability, a possible source of bias which we are unable to exclude.

We included a relatively sparse set of covariates in our regressions. There are other variables we could potentially have included, but all are tangled in the same selection issues we have sought to eliminate. For example, marital status is likely correlated with both veteran status and disability status. It is not likely to be a cause of disability, and so its omission does not produce bias, but because it is correlated with both the explanatory and outcome variables its inclusion would be likely to bias our findings.

Despite these limitations, we present substantial evidence that U.S. veterans from the Vietnam era bear substantial long- run negative effects from their service. This paper documents this situation using data from the years in which veterans are nearing retirement age and may well show the long-run effects of deficits they have borne. Better estimation of the magnitude of these deficits should assist those concerned with the well-being of veterans.

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References


The Effect of Core and Lower Limb Exercises on Trunk Strength and Lower Limb Stability on Australian Soldiers

Rolf Sellentin and Dr Rhondda Jones

Abstract

**Study Design:** A before and after design in the collection of data and using analyses of variance to examine the changes in each test score.

**Objectives:** The objectives and hypotheses of this study are: (1) Do specific core exercises, incorporating the lower limbs improve lower limb stability and trunk core muscle strength?; (2) Can the Star Excursion Balance Test be used as a measure of ankle and lower limb stability without a history of ankle instability?; (3) Can static core tests be used as a measure of core stability?; and (4) Is the Cumberland Ankle Instability Tool (CAIT) questionnaire sufficiently sensitive to show any changes to ankle instability following the outcomes of this study?

**Background:** An earlier study undertaken by Sellentin and Sanchez (2011) identified specific injuries sustained by Australian garrison soldiers of the 16 Air Defence Regiment. These injuries involved the neck, low back, knee and ankle. This current study was designed to address these injuries by providing exercises to specifically strengthen the core and lower limb muscles and to improve proprioception and muscle movement patterns, with the aim of reducing the number of injuries in Australian soldiers.

**Methods and Measures:** Eight young adult males volunteered for this study (mean age of 22 years). Female Australian soldiers did not participate in this study, as there were none available at the time and there were very few women in the Regiment. The eight male subjects undertook a twelve week supervised exercise programme loosely based on the validated FIFA 11+ programme. Subjects performed specific exercises over twelve weeks which were gradually increased in intensity, difficulty and resistance week by week. Each subject also completed a CAIT questionnaire before and after the 12 week exercise programme. In order to measure any effect from our exercise programme, each subject was asked to perform a series of sustained flexion, extension, side holds and prone hold tests and the Star Excursion Balance Test (SEBT), which were recorded before and after the exercise programme as assessment tools. The SEBT was also used to assess if there were any sensorimotor deficits related to chronic ankle instability in any of the subjects. We chose to use the SEBT as it has strong intratester and intertester reliability, is sensitive in the detection of functional deficits associated with chronic ankle instability, and with the possibility that this instability might be related to performance deficits in the entire affected extremity (Hertel et al 2006). This is particularly relevant when one of the purposes of our study was to examine if our exercise programme could reduce the risk to the knee and ankle by improving lower limb stability.

**Results:** Even though the sample size was small, there were significant effects in the before and after tests following the 12 week exercise programme:

- The Sustained Flexion test showed significant improvement.
- The Prone Hold showed an increase but not a significant change.
- The Left and Right Side Bridge showed a levelling out.
- The SEBT showed significant effects on average reach scores in all of the posterior reach directions, improvements in the lateral and medial reach (left and right limb stance), and in anterior reach directions, subjects with low starting values tended to show larger improvements, while subjects with high starting values tended to increase less or to decrease.
- Averaging over all the scores of all the tests of the SEBT showed a significant improvement.
Introduction
This study sets out to determine if core exercises, that encompass lower limb movements and balance, improve core trunk strength and stability and lower limb balance. It also sets out to determine if the SEBT can be used as a measure of lower limb stability, and if static core tests can be an effective assessment tool.

Kibler et al. (2006) defines core stability as "the ability to control the position and motion of the trunk over the pelvis and to allow optimum production, transfer, and control of force and motion to the terminal segment in integrated athletic activities."

A previous study (Sellentin and Sanchez. 2011) identified that injuries to Australian garrison soldiers occurred in the neck, low back, knee, and ankle. The object of this current study was to find exercises that could improve a soldier’s core strength with the aim of reducing neck and low back injuries, and to improve lower extremity strength, coordination and proprioception to reduce knee and ankle injuries. Our exercises have been identified as being effective in improving core strength and lower extremity balance. A future study could be undertaken to compare two regimens, one using our exercise programme and the other participating in standard PT exercises as the control, to determine if the incidence of injury is reduced using our programme.

Methods
Subjects
Australian soldiers from the 16th Air Defence Regiment volunteered for this study. The operational tempo of the regiment only allowed for twelve (male) soldiers identified by the Chain of Command who could be available for the duration of this study. From this, eight males volunteered for our 12 week exercise programme, with their age ranging from 19 to 26 with a mean age of 22 years and a body weight mean average of 83 kg. All subjects were right hand dominant. No female soldiers were available for this study.

Exclusion criteria included those potential subjects with an acute musculoskeletal injury, ankle sprain less than three months old, inner ear dysfunction/tinnitus, flu, or habitual users of balance equipment such as wobble boards. Inclusion criteria of potential subjects required full pain-free joint range of movement for all extremities and trunk, physical fitness in order to cope with the exercise programme and a commitment to complete all phases of the 12 week programme. All eight volunteers met these criteria.

All subjects signed an informed consent form approved by the Australian Human Ethics Committee (ADHREC) to participate in this study. This study was approved by the ADHREC with the designated research protocol number 607-10. The soldier’s rights and anonymity were protected throughout this study.

Age, weight, previous injury history, hand dominance and leg length were also recorded. Of the eight male subjects, three had a past history of ankle instability, one a knee ligament strain and two with shoulder strains. All subjects self-reported to be free of lower extremity injury, including an inversion ankle injury, within 3 months of this study. Each subject was asked if they were free of cerebral concussions, vestibular disorders, ear infections, upper respiratory infection, head cold, and if they had had prior balance training.

The first author, who is a physiotherapist, instructed the subjects in detail on performing the core assessment tests and SEBT, how to engage their core muscles, and supervised their 12 week exercise programme to ensure the exercises were performed correctly. Although data collection would be consistent using one person, this might also be a limitation, as it could be subject to possible bias.
Original Articles

Analysis
We used a repeated measures analyses of variance to examine the changes in each test score (and in composite measures recommended by Plisky et al (2006)) from the beginning to the end of the 12-week programme. We also examined correlations between starting values and changes in score to determine whether the changes were related to the physical capabilities of the subject at the start of the exercise programme. We used box plots rather than confidence intervals (which would have been imprecise) around each mean to show the whole distribution of values because the sample size was small.

Results

Core strength tests
There was evidence of improved core strength in three of the five tests (Table 1): flexion (a 68% increase), prone hold (30%), and right bridge (25%). Trunk extension scores were very similar before and after the programme, and left bridge scores tended to decline, though the average change does not achieve statistical significance.

Table 1: Effects of the exercise programme on core strength measures.

<table>
<thead>
<tr>
<th>TEST</th>
<th>Mean before program</th>
<th>Mean after program</th>
<th>Mean change</th>
<th>ANOVA result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexion</td>
<td>112.8</td>
<td>189.7</td>
<td>76.9 (68%)</td>
<td>F1,7 = 5.82, p = 0.047</td>
</tr>
<tr>
<td>Extension</td>
<td>91.6</td>
<td>90.0</td>
<td>-1.6 (-1.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Prone hold</td>
<td>173.4</td>
<td>226.6</td>
<td>53.2 (30%)</td>
<td>F1,7 = 2.02, P = 0.086</td>
</tr>
<tr>
<td>Right bridge</td>
<td>79.4</td>
<td>106.1</td>
<td>26.75 (25.2%)</td>
<td>F1,7 = 11.82, p = 0.0014</td>
</tr>
<tr>
<td>Left bridge</td>
<td>122.9</td>
<td>103.0</td>
<td>-19.9 (-16%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

At the start of the trial, left bridge scores were, in most subjects, substantially higher than right bridge scores, with a highly variable left bridge: right bridge ratio averaging about 1.7. At the end of the trial, the left and right bridge scores were almost equal, with a left bridge: right bridge ratio close to 1 in all subjects (Figure 1a). The change in variance is significant (Levene’s test, F1,14 = 16.8, p = 0.0011). The balancing-out between left and right occurs as a result of both increases in score (when starting scores were low), and decreases in score when starting scores were high (Figure 1b).

Figure 1a Variability of left bridge:right bridge ratios between subjects decreased during the exercise program. Boxplots show median, interquartile range, and total range.

Figure 1b: Change in a bridge score during the exercise program is strongly correlated with its starting value.

Star Tests: individual test scores.
The effects of the exercise programme on individual test scores are shown in Table 2. Except for the anterior lateral reach direction, where right and left stances are shown separately in the table, there were no significant differences between right and left leg stances and average values for both stances combined are presented.
The results in Table 2 indicate significant effects on average reach scores in all the posterior directions as well as the medial and lateral directions, but not in any of the anterior directions.

However, in every case, there is a moderate to strong negative correlation between the starting value and the change over the course of the programme. That is, even for anterior reach directions, subjects with low starting values tended to show larger improvements, while subjects with high starting values tended to a smaller increase or to a decrease. Four examples are shown in Figure 2.

Figure 2: Relationship between starting value and change during the exercise programme for four of the SEBT reach measures.

<table>
<thead>
<tr>
<th>Reach direction</th>
<th>Mean before program</th>
<th>Mean after program</th>
<th>Mean change</th>
<th>ANOVA result</th>
<th>Change/start correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior medial</td>
<td>89.7</td>
<td>90.0</td>
<td>0.3</td>
<td>NS</td>
<td>-0.71, p=0.002</td>
</tr>
<tr>
<td>Anterior lateral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>71.6</td>
<td>72.5</td>
<td>0.9</td>
<td>NS</td>
<td>-0.69, p=0.003</td>
</tr>
<tr>
<td>Right</td>
<td>67.6</td>
<td>68.1</td>
<td>0.5</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>83.6</td>
<td>85.2</td>
<td>1.6</td>
<td>NS</td>
<td>-0.71, p=0.002</td>
</tr>
<tr>
<td>Medial</td>
<td>95.3</td>
<td>98.6</td>
<td>3.3</td>
<td>F1,23= 8.97, p = 0.0065</td>
<td>-0.52, p = 0.04</td>
</tr>
<tr>
<td>Posterior medial</td>
<td>99.2</td>
<td>107.3</td>
<td>8.1</td>
<td>F1,23= 22.82, p = 0.0001</td>
<td>-0.84, p=0.0001</td>
</tr>
<tr>
<td>Posterior</td>
<td>104.7</td>
<td>110.3</td>
<td>5.7</td>
<td>F1,23= 17.24, p = 0.0004</td>
<td>-0.70, p=0.003</td>
</tr>
<tr>
<td>Posterior lateral</td>
<td>95.9</td>
<td>101.0</td>
<td>5.1</td>
<td>F1,23= 10.19, p = 0.0041</td>
<td>-0.41, p=0.11</td>
</tr>
<tr>
<td>Lateral</td>
<td>70.0</td>
<td>83.4</td>
<td>13.3</td>
<td>F1,23= 15.28, p = 0.0007</td>
<td>-0.81, p=0.0001</td>
</tr>
</tbody>
</table>
Star Tests: composite scores

In a large study of basketballers, Plisky et al (2006) derived a composite score averaging anterior, posterior medial, and lateral reach. They demonstrated in that study that values below 94% in that composite score were a predictor of lower extremity injury in their study population. The average composite score for our sample improved significantly and similarly for both left and right stance over the period of the exercise programme, from 92.9 to 97.8 (F1,23=33.68, p < 0.0001), with most of the group moving out of the “at risk” category over the course of the study (Figure 2).

The subjects also completed a CAIT questionnaire before and after the 12 week exercise programme. The CAIT is a measure of instability in subjects, and is a valid and reliable method for diagnosing and measuring the severity of FI using a graded scale between 0 and 30 (Coughlan and Caulfield, 2007). Scores greater than 27.5 represent highly stable ankles, and scores less than 24 represent ankles with increasingly severe instability. Tables 4 and 5 show a mixed result for the CAIT questionnaire. Before the exercise programme subject “d” indicated an FI of the left ankle and subject “g” indicated an FI to both ankles. Post exercise programme subject “g” indicated an improvement in functional stability and subject “d” indicated a small improvement to the left ankle but a reduction in the right ankle. There was also a reduction in the before and after scores for subject “h”, indicating FI.

### Table 3: Mean absolute differences in left and right reach.

<table>
<thead>
<tr>
<th>Reach direction</th>
<th>Mean difference before program</th>
<th>Mean difference after program</th>
<th>Mean change</th>
<th>ANOVA result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior medial</td>
<td>51.0</td>
<td>28.5</td>
<td>22.5</td>
<td>NS</td>
</tr>
<tr>
<td>Posterior lateral</td>
<td>54.0</td>
<td>42.6</td>
<td>11.4</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior</td>
<td>36.9</td>
<td>37.2</td>
<td>-0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 4: CAIT BEFORE Exercise

<table>
<thead>
<tr>
<th>Subject</th>
<th>Left ankle</th>
<th>Right ankle</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td>b</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>c</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>d</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>e</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>f</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>g</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>h</td>
<td>27</td>
<td>27</td>
</tr>
</tbody>
</table>

### Table 5: CAIT AFTER Exercise

<table>
<thead>
<tr>
<th>Subject</th>
<th>Left ankle</th>
<th>Right ankle</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>b</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>c</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>d</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>e</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>f</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>g</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>h</td>
<td>22</td>
<td>22</td>
</tr>
</tbody>
</table>

Left-right imbalances

An additional predictor of lower extremity injury identified by Plisky et al (2006) was an imbalance between left and right reach, with a difference of 40mm or more between left and right in posterior medial, posterior lateral or anterior reach identified as a risk factor. We earlier noted that the exercise programme corrected left-right imbalances in core strength measures: while there is some indication that there may also be reductions in posterior reach imbalance (Table 3), the gains are variable and do not achieve statistical significance in any of the reach measures in this small sample.
Procedures

The eight subjects under took a 10 minute warm up consisting of a light jog, arm movements and leg and arm stretches prior to the commencement of the assessment tests and for each day of the programmed exercises.

The eight subjects performed the following sustained core tests as suggested by Brukner and Khan (2006); a prone hold, a side hold (left and right), sustained flexor hold and sustained extension, all of which were recorded in seconds before and then repeated again after the 12 week exercise programme. These tests assessed the subject’s muscle strength and endurance and synergistic activation of the trunk muscles, and demonstrate how well the muscles functioned together. The prone hold test assesses primarily the anterior and posterior core muscles with the subject required to keep the pelvis and lumbar spine in a neutral position. Failure occurs if the subject loses this posture due to a loss in muscular strength and the lumbar spine falls into a lordotic position with an anterior rotation of the pelvis. The side hold assesses lateral core muscles, with the subject needing to maintain the body in a straight line. Failure occurs if the hips fall towards the floor. The static flexor hold assesses the torso flexors, with the subject asked to maintain a seated 60 degree trunk flexion (a metal frame set at 60 degrees was fabricated to ensure repeatability) with hips and knees flexed at 90 degrees. Failure occurred when the torso fell below 60 degrees.

The sustained extension test assesses the torso extensors as the subject overhangs over the end of a treatment table maintaining a horizontal posture. Failure occurs if the subject dipped below the horizontal.

These tests were used as a measurement of core strength before and after the exercise programme, and indirectly to determine if these tests were sensitive enough to detect any change.

Weir et al. (2010) state that “there are no widely accepted reliable tests for testing core stability in the clinic”. However, core tests as described by Brukner and Khan (2006) were selected for our study as Weir et al. (2010) state that a “static test results in a better reliability when compared with dynamic tests”. Bliss and Teeple (2005) advocate these same static core tests as they “yield significant information”. Weir et al. (2010) further state that other so called Core Tests, such as Transverse, Frontal and Sagittal plane testing and the unilateral squat and lateral step down tests, as a means of measuring core stability, are questionable and have poor reliability. They conclude that there are “no other studies available on clinical core stability tests (and) no reliable clinical tests with which core stability can be assessed”. Our study is significant since it demonstrates that static core tests are a sensitive measuring tool to detect changes to core strength following specific exercises.

The SEBT used in our study was the same as that described by Hertel et al. (2006). Four intersecting 3cm wide lines at 45 degree increments were painted onto a concrete floor, with the centre marked by “cross hairs” (Figure 3).

Each subject had the soles of their feet measured lengthways and widthways, the centre marked with intersecting “cross hair” lines. On testing, the subject’s stance foot with its “cross hair” was meticulously placed upon the floor cross hair so that the test could be replicated after the 12 week exercise programme with minimal variation. Subjects were required to maintain a single leg stance whilst reaching with the contralateral leg, touching as lightly as possible and as far as possible with the most distal part of their foot along each line. The reach was disqualified and redone if the subject propped on the out-stretched foot, or if they lost their balance, or lifted their stance foot from the grid, or did not maintain the...
start and return position for a full second, or they failed to touch the black line. Each subject practised six trials in each of the eight directions on each leg followed by 5 minutes of rest before the recording began. Subjects then performed three trials in each direction on each limb, with the length of reach being marked by a pencil at the point where the most distal part of the foot touched the black line, with 10 seconds of rest between individual reach trials. The marks were measured and recorded in millimetres from the centre of the star to the point of contact and then were erased before the subject swapped legs. The average of the three reaches for each leg in each of the eight directions was calculated for analysis. It was atypical for the subjects to have their scores discarded, and none of the subjects reported fatigue during or after the SEBT.

The eight lines were labelled: anterolateral (AL), anterior (ANT), anteromedial (AM), medial (MD), posteromedial (PM), posterior (PO), posterolateral (PL), and lateral (LAT). The eight lines were named according to the direction of reach in relation to the stance leg. Half the subjects began by performing the right-leg stance tests first, and the other half began using the left-leg stance. The order of reach directions was assigned using a Latin square to avoid order effects from contaminating the data. The reach leg (right, left) order of excursions performed (clockwise, counterclockwise), and direction of the first excursion (A, M, L, P) were counterbalanced to control for any learning or order effect (Olmsted et al. 2002), and all trials were then performed in sequential order in either the clockwise or counterclockwise directions.

Our 12 week exercise programme consisted of exercises loosely based on the validated FIFA “The 11+” programme and from other research studies on neuromuscular training, such as Pasanen et al. (2008) study. The FIFA 11+ programme of strengthening and balance exercises had shown a 30–50 percent reduction in injured soccer players from a study with almost 2,000 female players. Our study was designed around the FIFA 11+ as it is a validated programme that has shown to reduce the incidence of lower limb injuries in soccer players. It was our need to design a similar but augmented programme with the view to reduce injury rates to Australian soldiers by improving their core strength and stability and lower limb stability for the manual tasks and sustained physical activity that is often required in their day-to-day duties. A strong core is necessary for a stable base from which the lower and upper extremities can work. Our design incorporated a high proportion of balance exercises with the view to improve lower limb proprioception, muscle co-ordination and reaction times in order to minimise the risk of injury to knees and ankles during physical activities.

Most rehabilitation studies for acute and chronic ankle instability involve a 6 week to 8 week training period, but changing a functional activity requires more intensive training (Coughlan and Caulfield, 2007) and a longer period of time. Thus our study was conducted over 12 weeks, as this allowed sufficient neuromuscular adaptation. Scutter et al. (1995) also state that before 5 weeks any change may be attributable to neural factors and it is not until after 5 weeks that muscle hypertrophy becomes the dominant factor and strength increases.

The eight subjects in our study undertook specifically designed exercises three times a week over 12 weeks (Figure 4). The exercises were divided into three blocks (weeks 1 – 4, 5 – 8, and 9 – 12), and the exercise hour was further divided into two 25 minute circuits, giving a 5 minute water break and equipment change-over between the circuits. Each piece of equipment was doubled to accommodate the number of subjects and each subject positioned themselves at a station to commence the circuit. The number of repetitions at each station before rotating to the next station was dictated by the pace setter which was the person doing the prone hold (in Blocks...
proprioception, lower limb strengthening, dynamic and multilayered exercises, balance and plyometric running and jumping drills, as advocated by Bliss and Teeple (2005). O'Sullivan et al. (1997) point out in their study that Choleswicke and McGill (1996) reported lumbar stability is maintained in vivo by increasing the activity (stiffness) of the lumbar segmental muscles, and they highlighted the importance of motor control to coordinate muscle recruitment between large trunk muscles and small intrinsic muscles during functional activity to ensure stability is maintained. Our exercises were designed to provide a soldier with an all-encompassing comprehensive programme which engaged the neuromuscular system and targeted the main areas of the body that the previous study (Sellentin and Sanchez, 2011) had identified. Our exercises commenced with a neuro-developmental stage of bracing the core muscles until it became second nature, and ending at 12 weeks with engran motor programming becoming automatically

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Action</th>
<th>Time/Week</th>
<th>Return</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single lunges</td>
<td>with medicine ball</td>
<td>Hip press</td>
<td>3-5 reps</td>
</tr>
<tr>
<td>Back wood chop</td>
<td>participants required to throw the band anchored to a high point, standing on the band (foot under shoulder) with band further away from band and lower hand to hip, raising to opposite shoulder</td>
<td>hand blue</td>
<td>reps per side</td>
</tr>
<tr>
<td>Bounding</td>
<td>participants required to continuously load each leg while moving forward</td>
<td>moving forward, balance is key to progression</td>
<td></td>
</tr>
<tr>
<td>Alternate large with chest press</td>
<td>two large with a chest press (bilateral) each hand (preferred to the right hand)</td>
<td>standing band</td>
<td>green/blue</td>
</tr>
<tr>
<td>Large with bilateral</td>
<td>with arms clasped</td>
<td>front holding a barbell, 12 alternating lunges, maintain core activation</td>
<td>reps</td>
</tr>
</tbody>
</table>

Our exercises were designed to incorporate both static and dynamic core strengthening. They also encompass neuromuscular facilitation,
The idea for a specific and concise exercise programme was developed by the need to reduce the number of injuries to soldiers. Australian garrison soldiers undertake daily physical training (PT), usually for cardiovascular fitness and general over-all body conditioning rather than regular core strengthening and lower limb balance exercises.

Since lower limb and low back were the predominant injuries found to occur in Australian garrison soldiers (Sellentin and Sanchez, 2011), a specific 12 week exercise programme was designed to encompass both core strength and lower limb stability (Figure 4). The reader may note that many of the exercises combine dynamic core related strengthening with lower extremity proprioception exercises, while others specifically target only the core muscles.

Discussion

The Australian Defence Force (ADF) has adopted a strategic focus in preventing occupational injury, illness and disease. Prevention is the primary objective of the ADF’s approach to occupational health and safety. Injury can result in significant and long term personal disability and financial cost, and both a significant cost to the Australian Government in terms of compensation and a cost to the ADF in the reduction in operational capabilities.

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Hodges and Richardson (1996) and Sharp et al. (2004) advocate that dynamic lumbopelvic stabilisation is achieved through training of both local and global systems. The local system consists of transverse abdominus and multifidi muscles that have direct attachment to the spine and control segmental motion and stability. While the global system consists of rectus abdominus, the internal & external obliques and the thoracic iliocostalis muscles which do not have direct attachment to the spine but through a larger torque, are the prime movers of the trunk. The theoretical basis of core training is to increase the recruitment efficiency and strength of the smaller, deeper ‘stabilising’ muscles of the spine and pelvis (transverse abdominus, multifidi and gluteus medius) and to improved movement patterns and body awareness.

Our 12 week programme consisted of exercises that both strengthened and stabilised the spine through a graduated progression of resistance, effort and difficulty. There is an important distinction between strength and stability. To assess stability on its own is very difficult, so the assessment of strength was used in our study. Core strength refers to the ability of the muscle to generate force and power, whereas stability is the inherent result of strength acting on the spine. The greater the strength, together with neuromuscular facilitation, the greater the stability. Core strength was assessed using prone hold, a side hold (left and right), sustained flexor hold and sustained extension.

Bliss and Teeple (2005) explain that dynamic stabilisation refers to the ability to utilise strength and endurance in a functional manner through all planes of motion and action despite changes in the centre of gravity. The SEBT is a test that assesses both lower limb stability and indirectly the functional dynamic stability of the core muscles through the different directions and planes of movement. This will be discussed further.

Hodges and Richardson (1996) and Sharp et al. (2004) advocate that dynamic lumbopelvic stabilisation is achieved through training of both local and global systems. The local system consists of transverse abdominus and multifidi muscles that have direct attachment to the spine and control segmental motion and stability. While the global system consists of rectus abdominus, the internal & external obliques and the thoracic iliocostalis muscles which do not have direct attachment to the spine but through a larger torque, are the prime movers of the trunk. The theoretical basis of core training is to increase the recruitment efficiency and strength of the smaller, deeper ‘stabilising’ muscles of the spine and pelvis (transverse abdominus, multifidi and gluteus medius) and to improved movement patterns and body awareness.

Our 12 week exercise programme was designed to target both the local system using prone hold, side hold and wood chops, and the global system using weight loaded lunges (lunges are an excellent functional dynamic stability exercise, requiring a great deal of co-ordination of trunk and pelvic stabilising muscles). The findings in the Peate et
al. (2007) study on core exercises performed on fire-fighters suggested that functional movement enhancement programmes, such as those found in our programme, prevent injuries in high risk workers.

Peripheral neural facilitation (PNF) was incorporated (such as the wood chops) to enhance neuromuscular function and learning, and balance exercises of varying levels of difficulty (such as on a BOSU ball, sponge mats, and single leg stance) were also incorporated to facilitate proprioception. Balance was a large part of our study since proprioceptive training is effective at developing better overall balance and reducing the chance of injury by increasing muscle reaction time and the contraction patterns that favour the correction of excessive inversion (Ross 2006). Furthermore, Zazulak et al. (2007) state “there is strong evidence that neuromuscular control of the trunk and lower extremity can improve with neuromuscular training”. Our study set about to strengthen the core muscles which also assisted lower limb stability, since the inability to transfer forces generated at the core to the extremities can result in decreased efficiency or even injury (Bliss and Teeple, 2005).

Even although the sample size was small, the results from our study show that there were significant effects on re-testing following the conclusion of our exercise programme. The sustained flexor hold test showed significant improvement and the left and right side hold showed a substantial levelling out (Table 1). This strongly supports the premise that the exercises had a direct strengthening effect on the local system. The greater the core strength, the greater the stability to the spine. Akuthota and Nadler (2004) cite Nadler et al. (2002) who found in their study a 47% reduction in the incidence of low back pain in male athletes (although it was not statistically significant) after a core strengthening programme using sit-ups, pelvic tilts, squats, lunges, leg press, dead lifts, hang cleans and roman chair exercises. The importance of a strong core is highlighted by Peate et al. (2007) who state that “current research suggests that decreased core strength may contribute to injuries of the back and extremities [and] that training may decrease muscular damage”. We therefore propose that with the greater trunk strength and stability developed by our subjects following the exercise programme, would produce a concurrent reduction in the risk to low back injury and would have a beneficial effect on lower extremity stability. Further research using a larger population and comparing injury rate between two groups - one group using our exercises and the other who undertake normal PT - would be informative.

Sustained extension showed no change, (mean of 102 seconds) in our study. This may possibly be due to the subjects having the maximum extensor strength already (although Brukner and Khan (2006) state that men can hold extension for a mean of 161 seconds) or the sample size was too small to detect a difference in this particular measurement. A study using our exercises on a much larger population might detect greater changes in sustained extension.

Not only does our study demonstrate significant improvements in core strength, but it also shows that static core tests can be a measure of core strength. This is an important finding, since a valid test for core stability is difficult, as indicated in the literature.

Our study also looked at the effect of the 12 week exercise programme on lower limb stability using the SEBT. There were indications that Australian garrison soldiers sustain knee and ankle injuries (Sellentin and Sanchez, 2011) through PT and sports. Enhancing lower limb stability through proprioception and lower limb strength may reduce this occurrence. A study by Pasanen et al. (2008) show that from the types of exercises not too dissimilar to the ones used in our study, showed “significantly fewer non-contact leg injuries (that) occurred in the intervention group than in the control group”. They go on to say that “a neuromuscular training programme was effective in preventing acute non-contact leg injuries in female floorball players...by 66%”. Similar exercise programmes in the literature have established that they can be effective in reducing the risk of lower limb injury “through improving the players’ motor skills and body control as well as preparing the neuromuscular system for sports specific manoeuvres” (Pasanen et al. 2008). Our exercises were similarly designed with the intention of reducing lower extremity injury to Australian soldiers. What has not been shown in the literature is: WHY the incidence of injury is reduced. Our study answers this by showing definitive improvement in areas of balance and lower limb control in our subjects performing the SEBT following our specific exercise programme.

Our study shows that there were improvements in the SEBT Lateral (left and right stance), Anterior (right stance), Medial (right and left stance) reach directions, and significant improvement in all of the Posterior reach directions (left and right stance). This suggests that our 12 week exercise programme had a direct influence on improving lower limb balance through proprioceptive facilitation at the ankle or entire lower limb and/or the improvement in core strength and stability. Zazulak et al. (2007) state that a “decreased core proprioception could alter...
dynamic knee stability and may explain the risk of knee injury during sports activity”. They further state that there is an “association between decreased neuromuscular control of the body’s core and increased knee injury risk”. Performing our exercises could therefore have a significant reduction in lower extremity injury rates to Australian soldiers, since the SEBT showed significant improvement. The Anterior reach scores, however, made no change and may be attributed to the subject already achieving their maximum reach.

The SEBT was used in our study to reliably detect and measure any changes to the base line objective measures to lower limb stability by comparing before and after data following the 12 week exercise programme. Hertel et al. (2006) identify in their study that the SEBT was “sensitive in detecting functional performance differences related to chronic ankle instability (CAI) both within limbs of individuals with unilateral CAI and between subjects with and without CAI”. Hertel et al. (2006) were “able to identify statistically significant differences between limbs with and without CAI”. Olmsted et al. (2002) also state that SEBT is “the first non-instrumented, functional tests that have been shown to be both highly reliable and sensitive to deficits between subjects with and without CAI”. Although Hertel et al (2006) recommend the use of AM, MD, and PM based on their data, all 8 directions of the SEBT were chosen in our study since we were assessing the whole lower limb, as they suggest, to “identify which reach directions are most appropriate for detecting functional deficits related to other lower extremity pathologies such as anterior knee pain”. Furthermore, we were also interested in the effect, if any, of dynamic core strength on balance in all directions.

The use of the SEBT in our study was to identify any lower limb deficits in our subjects, to determine if our subjects fell into the “at risk of lower extremity injury” category, and it was an excellent test to assess the overall global muscle function of each subject. Plisky et al. (2006) state that the SEBT requires other neuromuscular characteristics such as lower extremity coordination, flexibility, and strength and each reach direction activates muscles to a different extent. They also suggest that injury risk is multifactorial and the SEBT requires multiple neuromuscular characteristics that may identify those who are at greater risk for lower extremity injury. The Plisky et al. (2006) study on basketball player injuries showed that the SEBT can predict lower extremity injury. Their results indicated that on the SEBT, a decreased normalised right composite reach distance of equal to or below 94%, and a greater anterior right/left reach difference of 4cm for boys predicted lower extremity injury. Our study shows that before our exercise programme, all eight subjects had an SEBT score below 94%, which may indicate that they were at risk of lower limb injury. After the exercise programme, most of the subjects were above 94% which indicates that the programme provided greater stability to the lower limb and therefore a reduction in the potential risk to lower limb injury. Plisky et al. (2006) suggest that the use of a neuromuscular training programme may improve deficits detected by a SEBT and decrease risk of lower extremity injuries, especially those using disc balance training. Zazulak et al. (2007) also state that “there is strong evidence that neuromuscular control of the trunk and lower extremity can be improved with neuromuscular training”. Our current study answers the question expressed in Plisky et al. (2006) on whether the SEBT reach distance improves after completing a neuromuscular training programme.

Olmsted et al. (2002) state that a “dynamic postural stability has been defined as the extent to which a person can lean or reach without moving the feet and still maintain balance”. They go on to say that they “believe that performance of the SEBT challenges the subjects limits of stability as he or she maximally reaches and is, thus, at least somewhat indicative of dynamic postural stability”. The SEBT may then also measure functional core stability, and its use as a measure is further justified in this study. Olmsted et al. (2002) conclude in their study that SEBT is a “cost-effective tool for assessing functional deficits in a variety of lower extremity conditions...with future research to examine different injured populations” (e.g. anterior cruciate ligament strains and patellofemoral pain syndrome). They also suggested a SEBT study to determine if lower extremity reach improves with rehabilitation would be beneficial. The results from our study have shown this to be the case.

The use of the SEBT in predicting lower extremity injury was advocated by Plisky et al. (2006) in their study on basketball players. Equally, the SEBT could be used as a lower extremity injury predictor for Australian soldiers and recruits. This would save considerable money in injury compensation, rehabilitation, disability and suffering from lower limb injuries in Australian defence personnel by addressing those identified as having lower extremity issues and by providing our exercises to improve their lower limb stability.

A CAIT was used to determine if any of the subjects had functional instability (FI) and if their score improved following the 12 week exercise programme. Three of the eight subjects had a previous history of ankle sprain (“a”, “d”, and “g”). Subjects “d” and “g”
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in Table 4 show FI. After the exercise programme, subject “g” indicated greater stability, while “d” had a mixed result with the FI ankle marginally improving and his other ankle score deteriorating (Table 5). Perhaps this could be attributed to a general perception by the subject that both ankles were of equal stability post exercise compared with a much larger difference pre-exercise. Although subject “a” did not indicate FI, his scores also improved as indicated in Table 5. On the other hand, subject “h” decreased score (Table 5) implies that his ankles became more unstable! Looking back over his questionnaire suggests that he might have misinterpreted two of the questions in the follow up questionnaire to give this lower score.

What is significant is that when comparing Table 5 to Table 4 there is a levelling of the scores between the left and right ankles. This could be because of the subject’s perception that both ankles had become equally stable instead of one being unstable or the other possibly having to over-compensate. This result has not been previously found in the literature. Interestingly, there was also a levelling a of left and right core imbalances (Table 1), a correlation which possibly adds further to the association between core strength and lower limb stability. Ross (2006) suggests that if there is a deficiency in any area of the synergistic function of muscle and nerve control of the ankle, then a perceived sense of instability may be noted and an altered sense of balance will heighten functional ankle instability because of increased movement at the body’s periphery, away from the centre of gravity. This then might help to explain the evening of the CAIT scores in Table 5. He also states that studies have shown balance and coordination training has reduced the chance of recurrent ankle sprains by reducing muscle onset latency of the Anterior Tibialis, Peroneus Longus, Flexor Digitorum Longus, and Posterior Tibialis, but other studies indicate that proprioceptive exercise may not be effective in reducing the chance of ankle sprain. He suggested that more studies were needed to show the overall benefits of proprioceptive exercise for both the stable and unstable ankle. Zazulak et al. (2007) state that interventions that incorporate core neuromuscular training, including proprioceptive exercises, may significantly reduce knee injury risk, although this was supported in their study using female athletes who have a superior ability to control body sway on a single limb compared to men. In our study there appears to be on the whole a greater sense of equalised stability to both ankles, and this might further help to reduce lower limb injuries if the central nervous system has this perception of ‘equal balance’ where the control and effort is evenly divided to both lower extremities. An additional question added to the follow up CAIT questionnaire asked ‘what benefit, if any, have you noticed from doing these exercises?’ with all eight subjects answering that they felt that their core muscle strength and lower limb stability had greatly improved.

Should time be a factor regarding training, our exercise programme could possibly be reduced to once a week instead of three times a week and may still be effective. Scutter et al (1995) state that isometric training once per week had the same effect as dynamic training once per week or more often, and stated that Graves et al. (1989) showed that a frequency of training of once per week was as effective as two or three times per week. However, the FIFA 11+ programme upon which our programme is based supports a frequency of at least twice a week.

Possible limitations of our study might be: biases from a single person collecting the data, although an individual might possibly be consistent in the before and after collection of that data; the small sample size may not represent a given population or accurate results; however, even though our sample size was small, significant results were found which might suggest some credence; limited resources for equipment, although standard gym equipment was used consistently throughout our 12 week programme; and the lack of validated and standardised core assessment tests in the literature that we could utilise.

Conclusion

Our 12 week exercise programme using a combination of static core and ‘dynamic stability’ exercises has supported our hypothesis that it improves core strength and stability. The programme focused on the deep stabilising core muscles which are not recruited in isolation but in an efficient and co-ordinated manner to maintain correct alignment of the spine and pelvis when moving the extremities. Our study has also supported the hypothesis that static core tests are adequately sensitive to detect changes of strength in the core muscles.

Our exercise programme has also shown via the SEBT to enhance lower limb stability by improving core strength and lower limb muscle control (proprioception). Our study supports our hypothesis that the SEBT can be a measure for ankle and lower limb stability without a history of ankle instability. It can be used as a predictor of lower extremity injury, and as an assessment tool for measuring proprioception based exercises.
The CAIT questionnaire showed a levelling of scores that may indicate a more balanced perception between left and right lower limb stability.

From our results, and on the balance of evidence from other studies regarding the reduction of injury rates using similar programmes, our exercises may be very beneficial in preventing or reducing the rate of low back and lower extremity injury to Australian soldiers.

Future directions for research could be the following: the same study performed on a much larger population of Australian soldiers to assess if similar results are obtained; to study the rate of injury between core exercises and non-core exercises in Australian soldiers; to assess the effect of detraining (i.e. a 12 week intervention followed by a 6-8 week rest from the programme, which will occur when a unit deploys to a field environment, when the subjects will be retested to see if there has been any degradation of their results); the effect of this exercise programme on a more physically task-orientated population group such as infantry; to assess if performing core exercises just once a week would have the same outcomes since there are competing time interests for all soldiers; to conduct further research in static core tests to validate their use in future research; further investigation into the CAIT and how balance exercises act on perception of stability and how that might relate to injury prevention; and a longitudinal follow-up of the soldiers involved in our study to see if they had maintained their gains or to see if they regain them in a shorter time frame – the gold standard for the effectiveness of the programme.

Acknowledgements

The authors wish to give special thanks to LTCOL McLean, Commanding Officer of 16th Air Defence Regiment, for his support in this study; to the eight subjects who participated in the study; to the 16th Air Defence Regiment PTI, SGT Greg Probyn, for his expert guidance in exercise prescription and valuable assistance in this study; and to the reviewers for their constructive feedback and suggestions.

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Introduction

In the last two decades there has been increasing attention directed at the analysis of psychological resilience. The number of modern-day veterans returning from Iraq and Afghanistan has sparked great interest in identifying mechanisms that can either erode or facilitate psychological resilience. In November 2009, the Australian Defence Force (ADF) in collaboration with the Australian Centre for Posttraumatic Mental Health (ACPMH) launched a longitudinal study of psychological resilience dubbed LASER (Longitudinal ADF Study Examining Resilience). The study is anticipated to inform psychological resilience training and mental health policy within the ADF.

The purpose of the present paper is four-fold. First, this paper will outline the operational definition of psychological resilience used by the ADF. Second, we describe previous findings on psychological resilience while examining how these findings are limited by cross-sectional design. Third, this paper will review previous resilience methodology and discuss the merits of a longitudinal methodology. Fourth, this paper will describe the LASER study protocol, key challenges and implemented solutions.

Operational definition of psychological resilience in the ADF

The definition of psychological resilience adopted by the ADF was developed by the Technical Cooperation Panel (TTCP) Technical Panel 13 (TP-13) and is “the sum total of psychological processes that permit individuals to maintain or return to previous levels of well-being and functioning in response to adversity.”

TTCP is an organisation that provides a structure for contributing nations (Australia, New Zealand, Canada, United Stated and United Kingdom) to share information. TP-13 focuses on psychological health in the military context. While definitions of psychological resilience are often controversial, this definition has been chosen to reflect the goals of the five nations contributing to the panel: to identify the processes of psychological resilience so that those processes may be influenced during military training and service. The LASER study is one of the TP-13 inspired mental health initiatives.

While the TP-13 definition has been adopted because of its particular relevance to the research question with this population, there are strengths and limitations when compared to other definitions in the literature. It has the strength of expressing resilience as a response to adaptation to life stressors and other adverse events, not only to potentially traumatic events as some definitions imply. The definition adopted for this study clearly defines resilience as a psychological process that takes place in the context of adversity rather than regarding it as a psychological trait. In this way it adopts a view of resilience as a trajectory. It is also worth noting that this definition focuses on the recovery of prior levels of well-being, rather than the achievement of greater levels of well-being after adversity. While the latter would not be unwelcome, the scope of this study is of psycho-social factors that protect and maintain functioning and well-being.

Previous findings relating to psychological resilience

Outside the military context, the past 40 years have seen many and varied correlates of psychological resilience identified. For example, positive emotion, coping flexibility, dispositional hardiness, and gratitude have all been considered. In recent years, there has been considerable focus on factors that contribute to resilience in military populations. Studies in military populations have identified factors associated with adjustment to military life and psychological resilience. Adler and Dolan (2006) found that higher ‘military hardness’ (context-specific form of hardiness) was related to lower post-deployment depression when deployment stressor levels were high. According to Kobasa (1979) and Maddi and Kobasa (1984) a hardy person views potentially stressful situations as: (1) an opportunity for growth (challenging), (2) changeable (control),
and (3) interesting and meaningful (commitment). Adler and Dolan (2006)\textsuperscript{13} suggested that the adaptive event appraisal associated with high military hardiness may underpin the association between military hardiness and psychological resilience. In another study, Florian, Mikulincer and Taubman (1995)\textsuperscript{10} found that a self-reported commitment (a sub-component of hardiness) to training improved mental health in Israeli soldiers largely by reducing perceptions of threat.

The limitations of cross-sectional study design

The aforementioned studies identify factors associated with psychological resilience and well-being. However, these studies are limited in several ways by their cross-sectional design. Importantly, cross-sectional analyses cannot reveal important changes in mental health status. It is unclear whether psychological resilience is a trait (remaining relatively stable over time) or whether psychological resilience may be increased or decreased due to intra-individual or contextual changes, including targeted intervention (e.g., resilience training). A longitudinal methodology enables the analysis of dynamic individual-level and group-level change. It may be that individuals are not always psychologically resilient, but rather there is considerable movement in and out of resilient psychological states. Longitudinal analysis allows the identification of such movement and the discovery of factors that influence the changes.

Cross-sectional studies often require participants to retrospectively report on behaviours or emotional states considered to be related to psychological resilience. The validity of retrospective scales is problematic when participants are required to remember their behaviour or psychological state prior to discrete points in time (e.g., “prior to enlistment...”). Bernard et al. (1984)\textsuperscript{16} describe the over and under-reporting of behaviour inherent in retrospective information in several areas of enquiry (e.g., child care, health care, communication and social studies). Retrospective reports that aim to measure psychological resilience are likely to be especially inaccurate. Such measures require participants to compare their level of functioning prior to, and after, a stressful or traumatic event. There is much evidence of mood-related bias in retrospective reports of prior exposure to traumatic events\textsuperscript{17} and prior levels of symptoms.\textsuperscript{18}

Moreover, retrospective reporting means that respondents are likely to confuse recovery and resilience trajectories. Bonnano, (2004, 2005)\textsuperscript{19} proposed that the recovery trajectory, characterised by major and long-term disruptions in emotional and physical well-being, is distinct from the resilience trajectory. In the resilient trajectory, individuals are able to acknowledge the presence of stress and experience short and mild disruptions in emotional and physical functioning (e.g., sleeplessness, difficulty concentrating and difficulty achieving positive states). Retrospective self-report measures of psychological resilience are unlikely to be sensitive enough to detect divergent trajectories in participant responses. Thus important differences in variables associated with trajectories are likely to be missed. Longitudinal methodologies overcome these problems because individuals make repeated judgements about their well-being over shorter time frames. These multiple time-sequenced reports allow an individual’s functional trajectory to be tracked and categorised.

Finally, cross-sectional designs are unable to inform on the aetiology of psychological resilience. Little is known about whether these factors represent protective, risk or vulnerability factors, or simply co-occur. Only a longitudinal methodology allows causal pathways to be examined.\textsuperscript{20}

Previous longitudinal investigations of psychological resilience in the military

The work of Maguen et al., (2008)\textsuperscript{21} is a notable attempt at the examination of psychological resilience. Maguen et al., (2008)\textsuperscript{21} studied Air Force medical personnel prior to deployment to Iraq and followed-up these personnel during and after deployment. Resilience as measured by the Connor and Davidson Resilience Scale was not found to predict PTSD when life stressors, previous traumatic events, and positive military experiences were included in the model. Psychological resilience was found to negatively predict a negative effect. A limitation of this study, acknowledged by the authors, is that Air Force medical personnel may not be representative of all military personnel. Furthermore, the authors did not investigate the predictors of psychological resilience as part of their analysis.

Importantly, no studies currently examine the interaction between pre-military factors and military service in the emergence of psychological resilience. As Schnurr, Rosenberg and Friedman (1993)\textsuperscript{22} point out, a problem with attempting to address the issue of military service on psychological outcomes is that appointment to the military is not random nor are the jobs personally assigned. Consequently, events are not experienced randomly. In order to control for this, most military studies conducted collect baseline information from currently serving members and measure pre-military variables retrospectively (e.g., “Prior to joining the military...”) for use as covariates in their analysis of post-military
outcomes (e.g., the Millennium Cohort Study). In these studies, pre-enlistment information is attained solely through retrospective self-report measures that cannot exclude intervening military experiences relevant to the study hypotheses.

There are a range of challenges identified in the literature that have been associated with conducting longitudinal research generally and in the military context specifically. These include: participant tracking in a mobile population, survey fatigue, motivational biases, and concern about asking about traumatic events. It is critical that in the development of a protocol for longitudinal research in the military context such challenges are carefully considered.

The current longitudinal study of resilience in military personnel

To date, there are no comprehensive longitudinal studies focusing on a multi-dimensional investigation of psychological resilience in the military; rather, studies often attend to psychological dysfunction as a consequence of military service. The LASER study makes two important contributions. First, it is a comprehensive longitudinal study of military psychological resilience, rather than dysfunction. Second, the study will examine the interaction between pre-military factors and military service in the development of psychological resilience. This paper will outline the development of the study protocol, highlighting the challenges associated with such research and the manner in which these issues have been addressed.

Method:

a. Participants
Participants enter the study via a phased enrolment strategy. The primary sampling frame is full-time general enlistees with surnames between L – Z and all appointed officers entering the Australian Navy, Army, and Air Force between November 2009 and December 2012. There are no additional exclusion criteria. The number of expected new study participants each year is estimated to be 1,200. The study has been approved by the Australian Defence Human Research Ethics Committee.

b. Study design
The LASER study has a longitudinal panel design. The same cases in multiple cohorts will be followed over five waves of data collection. Cohorts are defined by the month and year of enlistment. Wave one occurs at enlistment to measure pre-enlistment factors. Most examinations of mental health in military members have been concerned with the impact of military service over the course of service, rather than also measuring pre-enlistment factors and exploring their interaction with service. Many questions remain regarding pre-potentially traumatic event factors that contribute to psychological resilience and the unique consequence of military service more generally on the well-being of personnel, both beneficial and detrimental.

Wave two data is collected at the end of initial training for general enlistees and officers for which training does not exceed 12 months. For officers where initial training exceeds 12-months (e.g., Australian Defence Force Academy) Wave two data is collected at 12 months. The intention is to capture variability in coping styles and mental health outcomes after an arduous and demanding training period and adjustment to military life. Waves Three to Five occur annually after the completion of Wave Two and aim to examine coping styles after exposure to potentially traumatic events. Figure 1 illustrates the data collection timing for all the different personnel groups.

c. Analytic procedure
To make the most of the longitudinal methodology it is important that the most suitable analysis is applied. In order to achieve this, the analysis aims to discriminate between trajectories identified by Bonanno (2004). Bonanno (2004) identified the presence of four distinct trajectories emerging after trauma or significantly adverse events: (1) the resilience trajectory is characterised by a mild loss of functioning (e.g., disturbed sleep) followed by a quick return to prior levels of well-being, (2) delayed trajectories are characterised by no initial change in functioning followed by an increase in dysfunction over time, (3) chronic trajectories are typified by a consistent loss of functioning over time, and (4) recovery trajectories reflect a loss of initial functioning resulting in dysfunction followed by a gradual improvement in functioning. Latent growth curve modelling this complex analysis allows the identification and analysis of changes that are both linear and non-linear in fashion. Moreover, this style of analysis will allow the identification of variables that predict the type of trajectory (e.g. resilience trajectory) that a person may experience following adversity.

d. Data collection and the challenges of data collection in a military population
Wave One data for general enlistees is collected differently from appointed officers. General enlistee questionnaires are posted to residences...
Figure 1: Illustration of the data collection time points for the different ADF personnel groups.
Challenge 1: Participant tracking in a mobile population

False attrition, where non-response is attributable to the failure to receive a survey, is problematic in longitudinal surveys, and particularly so with a very mobile military population. Military members continually move through posting cycles and deployments causing major contact problems for longitudinal studies. To combat these issues, annual e-mail and post-cards sent immediately prior to the posting cycle will request that participants update the contact details on their personnel records. Similar longitudinal military studies have ensured up-to-date contact information and maintained interest in the study. Deployed personnel with limited internet access have the option to complete a paper survey with a reply paid envelope to facilitate return. Telephone contact with participants will be used to verify contact details and ensure receipt of the survey.

Challenge 2: Dealing with survey fatigue in the military

Survey fatigue is an issue of significance in the present study. Longitudinal research of this nature requires respondents to complete surveys several times. Porter, Whitcomb and Weizter (2004) report that non-response is still likely even when participants have agreed to take part in the series of surveys. Atrostic et al., (2001) found that refusal rates increased with subsequent interviews, although the pattern tapered off after the first few interviews. Drop-out and recruitment rates, particularly in military studies addressing potentially sensitive issues vary, but are generally below 50%. A drop-out rate of 34% (primarily due to drop out from training) was reported by Martin et al. (2006). Johnsen, Eid and Laberg (1998) reported a 47% drop-out rate over a series of four follow-up surveys. The drop-out rate was in part attributed to practical implementation issues related to duty rotations.

Initial recruitment rates in military studies of mental health issues reported in the literature also vary and rarely recruit a majority of the initial target population. Ryan et al. (2007) report an initial participation rate of 36%. In Army basic training personnel, Martin et al., (2006) had a participation rate of 45%. Riolli, Savicki and Spain (2010) obtained an initial participation rate of 43.7% in a population of United States Army personnel deployed to Baghdad. In the LASER study Wave one initial recruitment rates range between 60-75% for general enlistees and 85-90% for officer appointees. Wave two response rates for general enlistees improved to approximately 90-95%, but declined for officer appointees to 80-85%. Wave three response rates are quite low and initial figures indicate response rates of between 19-23%. The decline in response rates at Wave three is likely to be due to the lack of face-to-face administration of the LASER survey at this time point.
While there has not yet been an exploration of the presence of systematic bias in the early lower response rate, in order to improve Wave three response rates, a small study was conducted by the LASER team. Twenty-nine ADF members were given the LASER survey to complete and then asked to indicate which, of five options, would be most likely to encourage him/her to complete future surveys similar to the one just completed. The options included: ‘I have the time’, ‘there is an incentive’, ‘I receive a copy of the results’, ‘I have no concerns about my privacy’, ‘I know how my data will be used’ and ‘other, please specify’. Eleven participants (22.4%) reported that an incentive would be most likely to encourage their completion of the survey, closely followed by eight participants (16.3%) reporting that having the time was most important (supporting the use of face-to-face classroom administration), and six participants indicated that knowing how the data would be used would most encourage them. Interestingly, only a single member (3.4%) indicated that addressing privacy concerns would encourage their completion of the survey; this may have been because respondents were satisfied with the privacy information already delivered.

Based on the above pilot study, strategies to improve recruitment have targeted incentives and the time required to complete the study. Our findings suggest that the time needed to complete the survey was likely to be a barrier to survey completion and this is consistent with the work of Sosdian and Sharp (1980) and Sharp and Frankel (1983) who concluded that survey length is the largest contributor to survey fatigue. In response, the timing of all LASER survey is limited to 30 minutes and this is promoted on survey materials and by administrators. Respondents are also informed that they are “on-duty” while completing the survey. Moreover, to manage repeated survey demand, the optimal data collection time points were identified so that unnecessary participant contact is avoided. The optimal time points are as follows: (1) at recruitment; (2) at completion, or the 12-months mark, of initial training; (3) annually, after completion of training. Participants are also provided with wallet size membership cards to remind them of their involvement in the study.

The provision of incentives to study participants is an area of debate within the ADF and is highlighted as potentially valuable for the retention of study participants. The attrition rate is monitored, and the sample at each wave is profiled against the total population of new ADF members. It is important to note, however, that the target sample for the study is effectively 50% of the total new ADF recruit population. With this in mind, the key factor in assessing the ongoing rigour of the study will revolve around confirming that the study sample remains relatively representative of the Wave two sample.

A further issue for survey fatigues is that multiple surveys may operate in the military space at any one time. ADF personnel are required to undergo health screens, complete organisational surveys and evaluation of training and services. Different agencies will often administer overlapping surveys without coordination. Asiu, Antons and Fultz, (1998) used focus groups to determine U.S. Air Force Academy students’ attitudes toward surveys. Students reported their frustration with the number of surveys being conducted. A content analysis of student definitions of the term over-surveyed revealed that students felt over-surveyed because of the frequency and perceived irrelevance of the surveys. Thus, the relevance as well as frequency of surveys appears to be of critical importance.

To reduce survey fatigue attributable to over-surveying, a review of ADF surveys currently being administered was undertaken. Another longitudinal study was found to be sampling from the same population as the intended psychological resilience longitudinal survey. In response, the two studies negotiated to divide the ADF population. The current study targets those with a surname beginning with a letter from L-Z. Preliminary data analysis of the other survey indicated no significant differences due to alphabetical categorisation. Second, to ensure the perceived relevance of the study, the importance of the study is communicated to study participants via survey administrators, telephone follow-ups and letters from the Chiefs of Service.

A further organisational-level strategy to assist with minimising potential survey fatigue among ADF members is the requirement that all proposed surveys are presented to the Australian Defence Human Ethic Committee for approval. This committee reviews the scientific merit of any proposed study and is intended to provide central oversight of research activity; however, the extent to which it achieves this goal depends on compliance. Other organisational strategies implemented to manage and coordinate research in the ADF will further support the LASER study.

e. Measures used and the challenges of self-report measurement

The substantial investment of Government resources in this longitudinal study requires stringent decisions on the measures used. Scale inclusion was based on: (1) quality of measures: empirical
Six domains are assessed. The first domain includes scales that address psychological well-being and personal psychological resilience. This domain includes measures of psychological resilience, the experience of traumatic symptoms (both prior to enlistment and during enlistment) and general psychological distress. The second domain addresses physical health status through self-reported measures of global health and self-reports of specific symptom experiences. The third domain addresses exposure to potentially traumatic events (e.g., sexual assault, physical violence) and stressful life events (e.g., financial difficulties, relationship problems). The potentially traumatic events checklist was included for the first time in the second wave with the time reference “ever in your lifetime”. The time reference for the stressful life events checklist was “prior to enlistment” at Wave 2. These data provide baseline information about potentially important variables in future vulnerability. In Waves Three, Four and Five the time reference for these questions was from the present time to the exact date of the last survey (pre-populated into the survey as a specific date). The fourth domain aims to measure coping and adjustment styles. This domain includes the comprehensive measurement of problem-focused, avoidant, and emotion-focused coping. Moreover, coping through substance use (i.e., alcohol and tobacco use) is also targeted. The fifth domain is an assessment of psychosocial functioning. Because social support is considered central to coping, attention to this area has been addressed through the inclusion of scales examining interpersonal relationship quality, social capital, quality of life and social identification. The final domain measures access to mental health service providers and barriers to service providers including stigma.

Outcome measures assess self-reported psychological well-being and personal psychological resilience. In the Kessler-10 Psychological Distress scale (K10), respondents indicate the frequency of the 10 most common psychological distress symptoms in the previous four weeks and receive a total score ranging from 10 to 50. Cut-offs from the 2001 Victorian Population Health Survey are used to determine risk of anxiety or depressive disorders. Scores groupings are: below 19 (no current risk); between 20 and 24 (mild risk); between 25 and 29 (moderate risk); and above 30 (significant risk). The internal consistency and validity of the K10 has been demonstrated in Australian populations. Four additional items assess the impact of symptoms on everyday functioning. These items have been used in Australian population health surveys such as the New South Wales Population Health Survey 2008 (HOIST).

To screen for symptoms of Posttraumatic Stress Disorder (PTSD), a four-item form of the Posttraumatic Check List–Civilian Version (PCL-C) was used. These items were the most informative for assessing PTSD symptoms in the re-experiencing, avoidance and hyper-arousal dimensions. Psychological resilience was measured with the brief Connor Davidson Resiliency Scale (CD-RISC2). Vaishnavi, Connor and Davidson, (2007) demonstrated that the CD-RISC2 has good test-retest reliability for people who showed no clinical change in symptoms of General Anxiety Disorder and PTSD (intra-class correlation =86.5%).

Indirect measures of psychological functioning gauge somatic symptoms (from the Patient Health Inventory (PHQ)) and sleep impairment (Sleep Impairment Index (SII)). Smith and Trinder (2001) found that the SII correlated well with other measures presumed to measure insomnia and demonstrated high accuracy in discriminating between control and insomnia populations. Table 1 lists the measurement schedule and includes information about the scale source, number of scale items and time of scale presentation.

Challenge 3: Motivational biases
Motivational biases, such as social desirability and impression management, are central issues for consideration in all sensitive self-report research, as these biases contribute to measurement error. Studies comparing different assessment conditions and tools find that enhanced perceptions of anonymity, privacy and credibility cause an increase in accuracy of assessment.

Occurrences of motivational biases are particularly of concern when behaviours are stigmatised or undesirable, rather than normative or desirable and when sensitive information is required.

The stigmatised nature of mental illness is well recognised in military contexts and thus motivational biases should be expected in mental health research. Durant, Carey and Schroeder (2002) demonstrated that the social desirability and impression of the management of questions could be determined by assessing ‘question threat’. Question threat refers to the degree a question
Table 1: Measurement construct, scale source and brief development information, number of items per scale and the survey wave (W) of inclusion.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Source and scale development information</th>
<th>No. of items</th>
<th>W1</th>
<th>W2</th>
<th>W3</th>
<th>W4</th>
<th>W5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic symptoms from Patient Health Questionnaire</td>
<td>Adapted from: Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J Psychosom Res 2006; 60:631-637.</td>
<td>11 items</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Self-efficacy</td>
<td>No reference: developed for use in the military setting.</td>
<td>7 items</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Mild traumatic brain injury prior to enlistment</td>
<td>Scale based on the Diagnostic Criteria for Mild Traumatic Brain Injury by the American Congress of Rehabilitation Medicine (ACRM). Ontario Neurotrauma Foundation, Guidelines for mTBI and Persistent Symptoms.</td>
<td>2 items</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived stigma and barriers to care</td>
<td>Adapted from the ADF Mental Health Prevalence and Wellbeing Study: <a href="http://www.defence.gov.au/health/DHM1-i-MHRF.htm">http://www.defence.gov.au/health/DHM1-i-MHRF.htm</a></td>
<td>5 items</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Life satisfaction</td>
<td>Adapted from the Household Income and Labour Dynamics in Australia Study: <a href="http://www.melbourneinstitute.com/hilda/">http://www.melbourneinstitute.com/hilda/</a></td>
<td>1 item</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supportive and negative interactions scale: partner, family, friends</td>
<td>Adapted from Schustler TL, Kessler RC, Aseltine RH Jr. Supportive interactions, negative interactions, and depressed mood. Am J Community Psychol. 1990; 18: 423-438.</td>
<td>12 items</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>
**Review Article**

<table>
<thead>
<tr>
<th>Scale Description</th>
<th>Source/Adaptation</th>
<th>Items</th>
<th>Validated?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive and negative interactions scale: instructor, superior staff, peers</td>
<td>As above.</td>
<td>16</td>
<td>✔</td>
</tr>
<tr>
<td>Social identification with ADF membership</td>
<td>Adapted from Cameron JE. A three factor model of social identity. Self and Identity. 2004; 3:239-262.</td>
<td>6</td>
<td>✔</td>
</tr>
<tr>
<td>Community participation</td>
<td>Adapted from Berry H, Shipley, M. Longing to Belong: Social Capital and Mental Health in an Australian Coastal Community. 2007. The Australian National University: Canberra. Scale shortened on the basis of collaboration with scale author.</td>
<td>9</td>
<td>✔</td>
</tr>
<tr>
<td>Use of social networking sites</td>
<td>No reference: developed for use in the military setting.</td>
<td>7</td>
<td>✔</td>
</tr>
<tr>
<td>Sense of morale in the smallest work/training group membership</td>
<td>From the Australian Defence Attitudes Survey, 2008.</td>
<td>1</td>
<td>✔</td>
</tr>
<tr>
<td>Mate support scale</td>
<td>Developed in collaboration with United States Army research advisors</td>
<td>4</td>
<td>✔</td>
</tr>
<tr>
<td>Coping strategies</td>
<td>Adapted from Carver, CS. You want to measure coping but your protocol’s too long: Consider the Brief COPE. Int J Behav Med. 1997; 4: 92-100.</td>
<td>24</td>
<td>✔</td>
</tr>
<tr>
<td>Location and length of deployment</td>
<td>Adapted from the ADF Mental Health Prevalence and Wellbeing Study: <a href="http://www.defence.gov.au/health/DMH/i-MHRP.htm">http://www.defence.gov.au/health/DMH/i-MHRP.htm</a></td>
<td>1</td>
<td>✔</td>
</tr>
<tr>
<td>Access to professional support services</td>
<td>Adapted from the ADF Mental Health Prevalence and Wellbeing Study: <a href="http://www.defence.gov.au/health/DMH/i-MHRP.htm">http://www.defence.gov.au/health/DMH/i-MHRP.htm</a></td>
<td>2</td>
<td>✔</td>
</tr>
<tr>
<td>Mental health literacy items</td>
<td>Developed in collaboration with United States Army research advisors.</td>
<td>12</td>
<td>✔</td>
</tr>
<tr>
<td>Flexible coping scale</td>
<td>Developed in collaboration with United States Army research advisors</td>
<td>6</td>
<td>✔</td>
</tr>
<tr>
<td>Stressful events checklist</td>
<td>Developed on the basis of piloting within Australian military populations.</td>
<td>8</td>
<td>✔</td>
</tr>
<tr>
<td>Potentially traumatic events checklist</td>
<td>As above</td>
<td>18</td>
<td>✔</td>
</tr>
<tr>
<td>Participants response to survey completion</td>
<td>Scotti et al. How much is enough? Reducing response to research participation questionnaires to their essential elements. Presented at Conference on Innovations in Trauma Research Methods; Chicago, November 2008.</td>
<td>3</td>
<td>✔</td>
</tr>
</tbody>
</table>
makes the participant uneasy while responding to the question. Thus, LASER items were piloted to assess perceived threat. Interviews were conducted with 38 LASER survey respondents (Navy n=18, Army n=9, Air Force n=11) recruited from the Defence Force Recruitment Centre in Brisbane, Australia. Survey respondents felt that responses that reflected inadequate mental health or potentially negative behaviours would reflect poorly on them as military enlistees or would impact their career progression if the information were to be made available beyond the research. Thus, concerns clearly go beyond impression management in response to researchers and include the impact of research on their career and livelihood.

The pilot data and interviews assisted in the resolution of motivational bias issues in three ways. First, the pilot data and interview determine sensitive items that are particularly vulnerable to bias responding. This information will assist during data analysis when it may be necessary to apply statistical adjustment. For example, as a result of the pilot study items regarding coping with stress, psychological distress, pro-social behaviour and alcohol consumption were flagged for potential data quality concerns. Second, the questionnaire items were modified in response to participant concerns. Items flagged as particularly sensitive to motivational biases and less critical to the study objectives were removed. For example, the focus of this research on psychological resilience meant that the suicidal ideation items could be justifiably removed. Suicidal ideation is an outcome of poor coping processes and these poor coping processes could be detected using scales less sensitive to motivational biases. Third, to create a greater degree of anonymity, longitudinal data are linked via a unique identification code, rather than the participants' personal identifying details. Participants generate their unique code in accordance with a systematic pattern that is reproduced on every survey and consent form. This procedure allows the decoupling of the survey data from identifying information. Participants are informed of this to increase confidence about privacy and confidentiality. In addition, less stigmatised measures of psychological distress (e.g., somatic symptomatology, sleep impairment) were adopted to supplement more threatening measures.

Challenge 4: Concern about the risk of asking about prior trauma

Concerns about asking sensitive questions also emerged from key military research stakeholders. Debate regarding the risk of distress and re-traumatisation of participants occurred regarding a checklist of the traumatic events used in the study. While sensitive questions may spark concern, they often provide a fuller picture of the factors contributing to the variables of interest, as is the case in the present study. The measurement of potentially traumatic exposure is central to the study of psychological resilience.

Military stakeholders identified two areas of concern about the sensitive items: (1) the re-traumatisation of participants and (2) the effect of the items on respondent dropout. The first issue was addressed by reviewing the literature on participant reactions to traumatic events checklists. The review found no evidence of re-traumatisation or severe distress in survey respondents. Cromer et al., (2006) demonstrated that while sensitive questions may be uncomfortable for a minority of participants, these participants still view them as useful. Moreover, the LASER survey items were again piloted with 12 military personnel. Of the twelve participants interviewed by psychologists after completing the survey, none reported distress. Participant distress continues to be monitored by a 3-item version of the 14-item Response to Research Participation Questionnaire (RRPQ) developed by Scotti et al. (2008) to routinely evaluate the impact of research participation. These questions assess the level of distress experienced as a consequence of completing the questions, whether completing the survey was worthwhile and whether the respondents clearly understood the voluntary nature of the survey.

To address the second concern, a further pilot study asked 22 survey participants whether they would be discouraged from participating in a similar study in the future after completing the current survey including traumatic life events scales. All interviewees indicated that they would consider participating in similar studies in the future. Military stakeholders were given a briefing detailing the results of the pilot study and a review of the literature as well as an outline of the mitigation measures in place for the care of participants.

Practical implications of the LASER study for the ADF

The LASER study is now within its third wave of data collection and analyses are beginning to reveal some important practical implications for the ADF. First, a key contribution of the LASER study is to identify personnel entering the service that may be at higher risk of developing psychological distress. For example, personnel entering the service with a certain number of recent traumatic events which may be flagged as a potentially at-risk sub-population. This may be useful for selection purposes, but perhaps be more useful as a targeted psychological resilience.
training for those recruits highlighted early. Second, the study will assist in the development of resilience training content. At present, resilience training within the ADF is largely based on empirically supported techniques used within the civilian population. It is possible that military personnel require a different diversity of techniques targeted to address the unique challenges of the military environment. Third, LASER will determine the unique impact of military service on personnel when pre-military factors (e.g. pre-military trauma exposure) are controlled. This will allow a unique and more precise insight into how military training and service impacts personnel resilience.

Concluding remarks
The Longitudinal ADF Study Examining Resilience (LASER) has been designed to investigate how personnel cope with the range of challenging circumstances and potentially traumatic events common to military service. This issue has great relevance to military agencies around the world and clarifying the optimal methodology to index trajectories, predictors, and moderators is essential. Inadequate recruitment, excessive attrition, and unrepresentative sampling are just a few of the major issues confronting attempts to accurately index the impact of deployment on personnel. It is important to obtain indices of personnel at the commencement of enlistment lest any inferences concerning risk are confounded by service-related factors, even if they occur prior to actual deployment. Developing a broader dialogue on longitudinal methodologies between military agencies is essential if advances are to be made in (a) comparing data between agencies, and (b) facilitating more effective approaches to addressing the key question of resilience.

References
Syphilis - Its Early History and Treatment Until Penicillin, and the Debate on its Origins

**Introduction**

“If I were asked which is the most destructive of all diseases I should unhesitatingly reply, it is that which for some years has been raging with impunity ... What contagion does thus invade the whole body, so much resist medical art, becomes inoculated so readily, and so cruelly tortures the patient?” Desiderius Erasmus, 1520.

In 1495 an epidemic of a new and terrible disease broke out among the soldiers of Charles VIII of France when he invaded Naples in the first of the Italian Wars, and its subsequent impact on the peoples of Europe was devastating – this was syphilis, or grande verole, the “great pox”. Although it didn’t have the horrendous mortality of the bubonic plague, its symptoms were painful and repulsive – the appearance of genital sores, followed by foul abscesses and ulcers over the rest of the body and severe pains. The remedies were few and hardly efficacious, the mercury inunctions and suffumigations that people endured were painful and many patients died of mercury poisoning.

Sexually transmitted diseases (STD’s) have posed a threat to military service members throughout history. In the US Army during World War I they were the second most common reason for disability and absence from duty, being responsible for nearly 7 million lost person-days and the discharge of more than 10,000 men. Only the Spanish influenza epidemic of 1918-1919 accounted for more loss of duty during that war. During World War II between 1941 and 1945 the annual incidence of STD’s in the US Army was 43 per 1,000 strength. In the Vietnam War during the period 1963 to 1970 the overall average annual incidence of STD’s was 262 per 1,000 strength, compared with, at the time, 30 per 1,000 in continental US-based army personnel. In Vietnam 90% of STD cases were due to gonorrhoea and slightly over 1% were due to syphilis. The impact of gonorrhoea and syphilis on military personnel in terms of morbidity and mortality was greatly mitigated after 1943 due to the introduction of penicillin, as well as other factors such as education, prophylaxis, training of health personnel and adequate and rapid access to treatment.

Up until the early 20th century it was believed that syphilis had been brought from America and the New World to the Old World by Christopher Columbus in 1493. In 1934 a new hypothesis was put forward, that syphilis had previously existed in the Old World before Columbus. In the 1980’s palaeopathological studies found possible evidence that supported this hypothesis and that syphilis was an old treponeal disease which in the late 15th century had suddenly evolved to become different and more virulent. Some recent studies however have indicated that this is not the case and it still may be a new epidemic venereal disease introduced by Columbus from America.

The first epidemic of the ‘Disease of Naples’ or the ‘French disease’ in Naples 1495

In August 1494, King Charles VIII of France led his army of 50,000 soldiers and a large artillery train into northern Italy. The soldiers were mostly mercenaries – Flemish, Gascon, Swiss, Italian, and Spanish – and were accompanied by 800 camp followers including cooks, medical attendants and prostitutes. Charles’ objective was to take over the Kingdom of Naples from Alphonso II so that he could use Naples as a base from which to launch a campaign to the Crusades. The soldiers of Alphonso II were mostly Spanish mercenaries. Charles’ army led by General Louis II de la Tremoille crushed all resistance from intervening Italian cities and in February 1495 took Naples. While occupying Naples the French soldiers indulged in a long bout of celebration and debauchery, and within a short space of time it came apparent that they were afflicted by a terrible disease.

The disease started with genital ulcers, then progressed to a fever, general rash and joint and muscle pains, then weeks or months later were followed by large, painful and foul-smelling abscesses and sores, or pocks, all over the body. Muscles and bones became painful, especially at night. The sores became ulcers that could eat into bones and destroy...
the nose, lips and eyes. They often extended into the mouth and throat, and sometimes early death occurred. It appears from descriptions by scholars and from woodcut drawings at the time that the disease was much more severe than the syphils of today, with a higher and more rapid mortality and was more easily spread, possibly because it was a new disease and the population had no immunity against it.\textsuperscript{5,6,7}

During the Battle of Forova at Emilia in Italy on Charles' retreat back to France, many soldiers were so ill they were unable to fight. On Charles' return to France the army disbanded and the soldiers and their camp followers took the disease with them back to their respective homelands. Voltaire wrote:

‘On their flippant way through Italy, the French carelessly picked up Genoa, Naples and syphilis. Then they were thrown out and deprived of Naples and Genoa. But they did not lose everything - syphilis went with them.’

By the end of 1495 the epidemic had spread throughout France, Switzerland and Germany, and reached England in 1497. In August 1495 the Holy Roman Emperor Maximilian I proclaimed that nothing like this disease had been seen before and that it was punishment from God for blasphemy. By 1500 syphilis had reached the Scandinavian countries, Britain, Hungary, Greece, Poland and Russia. It was a time of world exploration and Europeans took the disease to Calcutta in 1498, and by 1520 it had reached Africa, the near East, China, Japan and Oceania.\textsuperscript{5}

Syphilis had a variety of names, usually people naming it after an enemy or a country they thought responsible for it. The French called it the 'Neapolitan disease', the 'disease of Naples' or the 'Spanish disease', and later grande verole or grosse verole, the 'great pox', the English and Italians called it the 'French disease', the 'Gallic disease', the 'morbus Gallicus', or the 'French pox', the Germans called it the 'French evil', the Scottish called it the 'grandgore', the Russians called it the 'Polish disease', the Polish and the Persians called it the 'Turkish disease', the Turkish called it the 'Christian disease', the Tahitians called it the 'British disease', in India it was called the 'Portuguese disease', in Japan it was called the 'Chinese pox', and there are some references to it being called the 'Persian fire'.\textsuperscript{5,8,9}

Early descriptions of the disease

In 1496 Sebastian Brandt, best known for his work Der Narrenschiff, 'The Ship of Fools', wrote a poem entitled De pestilentiali Scorra sive mala de Franzos relating how the disease had spread all over Europe and how the doctors had no remedy for it.\textsuperscript{1}

Johannis (Giovanni) de Vigo, an Italian surgeon who was appointed as surgeon to Pope Julius II, wrote about the contagiousness of the disease, its origin from sexual intercourse with an infected person and its rapid dissemination throughout the body in De Morbo Gallicus, 1514, the fifth book of his work Practica in arte chirurgica copiosa. He accurately described the primary chancre, the secondary eruption of rash, ulcers and pustules, the terrible night bone pains and the late "tumours of scirrhus hardness". De Vigo expressed the view that this was a new disease.\textsuperscript{10}

“The contagion which gives rise to it comes particularly from coitus: that is, sexual commerce of a healthy man with a sick woman or to the contrary. ... The first symptoms of this malady appear almost invariably upon the genital organs, that is, upon the penis or the vulva. They consist of small ulcerated pimples of a colour especially brownish and livid, sometimes black, sometimes slightly pale. These pimples are circumscribed by a ridge of callous like hardness... Then there appear a series of new ulcerations on the genitalia... Then the skin becomes covered with scabby pimples or with elevated papules resembling warts... A month and a half, about, after the appearance of the first symptoms, the patients are afflicted with pains sufficiently to draw from them cries of anguish... Still very much later (a year or even longer after the above complication) there appear certain tumours of scirrhus hardness, which provoke terrible suffering.”\textsuperscript{10}

Ulrich von Hutton, a German scholar who suffered from the 'great pox,' described its effects and its treatment with guaiacum, or holy wood, in his work De Morbo Gallico of 1519, dying from the disease himself four years later on the island of Ufenau on Lake Zurich. Von Hutten wrote of the terrible abscesses and sores, the nocturnal bone pains, dolores osteocopi nocturne, and the diseases of the internal organs, ulcers in the bladder and muscle disease.\textsuperscript{7}

In 1527, Jacques de Bethencourt in his work New Litany of Penitence, introduced the term Morbus venerus, or 'venereal disease'. Bethencourt rejected the term morbus gallicus, and suggested that "since the disease arises from illicit love it should be called the malady of Venus or venereal disease". He also considered it was a new disease not known to the ancients and not appearing in Europe until the end of the 15th century.\textsuperscript{10}

In 1530, Girolamo Fracastoro in his poem Syphilis sive morbus gallicus described in detail the symptoms
of syphilis and its treatment with guaiacum, the holy wood, a herb made from the bark of trees from the guaiacum family which was brought back from the Caribbean and South America in the New World, and the treatment with mercury. Fracastoro coined the term ‘gumma’ (L. ‘gumma’ meaning gum or resin), referring to the pus that escapes from the body and hardens into scabs like resin that were the late scirrhous skin lesions.7

The origin of the term ‘syphilis’
The name for the disease, ‘syphilis’, originates from an epic Latin poem Syphilis, sive morbus gallicus, ‘Syphilis, or the French disease’, published in 1530 by Girolamo Fracastoro (L. Hieronymus Fracastorius). Fracastoro was a poet, mathematician and physician from Verona in the Republic of Venice, who in his work De contagione et contagiosis morbis first described typhus and wrote on contagion, contagious particles that could multiply in the human body and be passed from person to person or through the mediation of fomes, and which were the cause of many epidemic diseases.4,11,12

Fracastoro blended the writings of the historian Gonzalo Hernandez de Oviedo y Valdez with a fable Metamorphoses from the ancient Roman poet Ovid. In his poem Syphilis, sive morbus gallicus, Fracastoro tells of a mythical shepherd named Syphilus who kept the flocks of King Alcithous. When a drought affected Syphilus’ people, he insulted the Sun-God by blaspheming against him and blaming the god for the drought, and as punishment the Sun-God struck Syphilus and his people down with a disgusting and odorous new disease.5,6,14,15

Verses from the poem where Fracastoro refers to naming the disease after Syphilus are:

"A shepherd once (distrust not ancient fame)
Possest these downs, and Syphilus his name."

“He first wore Buboes dreadful to the sight.
First felt strange pains, and sleepless passed the night.
From him the malady received its name.
The neighbouring shepherds catch’d the spreading Flame”14,15

When Desiderius Erasmus (1466-1536) used the term ‘syphilis’ in his essays, many other scholars followed suit.6, see p. 193. Daniel Turner (1667-1741) was the first English medical author to use the term syphilis, as well as writing on the use of the ‘condum’ to prevent its transmission.16 However the name syphilis was not in general use to describe the disease until the early nineteenth century. Up until that time the disease was usually known as the French disease or French pox, the Spanish pox, or just simply, “the pox”.6,7

Syphilis in the 16th century and its social ramifications
Fifty to a hundred years after its appearance in Naples the disease became less virulent and less lethal. The disease had several distinct phases. The first began with genital sores, or “pocks”, later called chancres. After these had healed and several weeks following, there appeared a generalised rash, often accompanied by fevers, aches and the night bone pains, dolores osteocopi nocturne, described by Von Hutton and De Vigo.7,8,10 As well, a rash of verrucous papules often broke out in the genital area. When these healed, a long latent period occurred, lasting months initially and as history passed, several years, in which there were few symptoms. The last phase consisted of the appearance of abscesses and ulcers, and the gumma referred to by Girolamo Fracastoro, often ending with severe debility, madness or death.7

It was this phase of the disease for which syphilis was greatly feared, because of the disfigurement it caused and the social ostracism that ensued. It was viewed by ordinary people as a sign of sin, for which they were shunned and punished.9

During the 1520’s it became clear to historians and physicians of the time that the disease was contracted and spread by sexual intercourse. In Europe the authorities had become so concerned with the rise
Syphilis as the cause of this condition. Called “general paralysis of the insane”, establishing brains of people who had died from a condition discovered in 1905 by Fritz Schaudinn, from the Spirochaeta pallida, which had previously been and Hideyo Noguchi isolated the syphilis spirochaete as tabes dorsalis.

Syphilis with a wasting and paralysis disorder known no cure. He described the association of late stage treatment of the disease but cautioned there was an understudy to Ricord, published a work on the anatomist and military surgeon, firmly established that syphilis and gonorrhoea were separate diseases. In 1838 Philippe Ricord, a physician and surgeon who worked under Guillaume Dupuytren, a French anatomist and military surgeon, firmly established that syphilis and gonorrhoea were separate diseases and differentiated the three stages of syphilis, and the primary lesion of syphilis was given the name of Ricord’s chancre. In 1861 Jonathan Hutchinson, surgeon to the London Hospital, described the features of congenital syphilis. In 1893 Jean-Alfred Fournier, a French dermatologist who worked as an understudy to Ricord, published a work on the treatment of the disease but cautioned there was no cure. He described the association of late stage syphilis with a wasting and paralysis disorder known as tabes dorsalis. In 1913 Joseph Waldron Moore and Hideyo Noguchi isolated the syphilis spirochaete Spirochaeta pallida, which had previously been discovered in 1905 by Fritz Schaudinn, from the brains of people who had died from a condition called “general paralysis of the insane”, establishing syphilis as the cause of this condition.

16th and 17th century writers and physicians were divided on the moral aspects of syphilis. Some thought it was a divine punishment for sin, and as such only harsh treatments would cure it, or that people with syphilis shouldn’t be treated at all. In 1673, Thomas Sydenham, a British physician, wrote an opposing view that the moral aspect of syphilis was not the province of the physician, who should treat all people without judgement.

Syphilis and medicine in the 18th and 19th centuries
During the 18th century medical thinking on the disease began to advance. In 1736 Jean Astruc, a French royal physician and professor of medicine at Montpellier and Paris, wrote one of the first great medical works on syphilis and venereal disease, De Morbus Veneris. In 1761 the Italian pathologist Giovanni Battista Morgagni published De Sedibus et Causis Morborum per Anatomen Indagatis in which he wrote that the symptoms of syphilis and gonorrhoea arose from separate conditions.

Up until the 19th century, there was still much confusion as to whether syphilis and gonorrhoea were manifestations of the same disease. In 1838 Philippe Ricord, a physician and surgeon who worked under Guillaume Dupuytren, a French anatomist and military surgeon, firmly established that syphilis and gonorrhoea were separate diseases and differentiated the three stages of syphilis, and the primary lesion of syphilis was given the name of Ricord’s chancre. In 1861 Jonathan Hutchinson, surgeon to the London Hospital, described the features of congenital syphilis. In 1893 Jean-Alfred Fournier, a French dermatologist who worked as an understudy to Ricord, published a work on the treatment of the disease but cautioned there was no cure. He described the association of late stage syphilis with a wasting and paralysis disorder known as tabes dorsalis. In 1913 Joseph Waldron Moore and Hideyo Noguchi isolated the syphilis spirochaete Spirochaeta pallida, which had previously been discovered in 1905 by Fritz Schaudinn, from the brains of people who had died from a condition called “general paralysis of the insane”, establishing syphilis as the cause of this condition.

Sir William Osler (1849-1919), a founder of the John Hopkins School of Medicine and pioneer of modern medical and clinical education and later Regius Professor of Medicine at Oxford, described the history of the sudden appearance of this new and terrible disease in 16th century Europe:

“A mysterious epidemic, hitherto unknown, which struck terror into all hearts by the rapidity of its spread, the ravages it made, and the apparent helplessness of the physicians to cure it.”

By the early 18th century syphilis had ceased to be a virulent epidemic disease and became more of the episodic disease it is today. From about the middle of the 19th century to the middle of the 20th century the incidence of syphilis in developed countries declined, except in times of war. During each of the World Wars, the Korean war and the Vietnam War, the incidence of syphilis, and STD’s in general, rose sharply but only briefly. After 1943 and with the advent of penicillin and institution of public health measures, its incidence declined again, although in past decades it has slowly increased.

The early treatments of syphilis
In the early 16th century, the main treatments for syphilis were guaiacum, or holy wood, and mercury skin inunctions or ointments, and treatment was by and large the province of barber and wound surgeons. Sweat baths were also used as it was thought induced salivation and sweating eliminated the syphilitic poisons.

In his 1530 poem Syphilis, sive morbus gallicus, Fracastoro described the use of guaiacum:

“.. in external use for dressing ulcers, abscesses and pustules. For internal use drink the first potion by the beaker twice a day: in the morning at sunrise and by the light of the evening star. The treatment lasts until the moon completes its orbit and after the space of a month conjoins again with the sun. The patient must remain in a room protected from wind and cold, so that frost and smoke do not diminish the effect of the remedy.”

Guaiacum was not effective as a cure and the alternative was mercury. Mercury had been used as a treatment for epidemic diseases since Guy de Chauliac, (personal physician to the Pope in Avignon), advocated its use in his work La Grande Chirurgie in 1363, and this became the accepted treatment for syphilis.
Paracelsus (1493-1541) derided the use of guaiacum as useless and expensive and instead promoted mercury, metals being one of Paracelsus’ favoured medicinal treatments for disease. After a time however he did recognise its toxicity when administered as an elixir and resorted to using it either as an inunction, an ointment made from metallic mercury and rubbed into the skin, or as a suffumigation, the inhalation of and bathing of the body in fumes, or indeed both at the same time. Many physicians doubted the efficacy of mercury, especially as it had terrible side effects and many patients died of mercury poisoning. Beck (1997) describes a typical mercury treatment:

“A patient undergoing the treatment was secluded in a hot, stuffy room, and rubbed vigorously with the mercury ointment several times a day. The massaging was done near a hot fire, which the sufferer was then left next to in order to sweat. This process went on for a week to a month or more, and would later be repeated if the disease persisted. Other toxic substances, such as vitriol and arsenic, were also employed, but their curative effects were equally in doubt.”

Mercury had terrible side effects causing neuropathies, kidney failure, and severe mouth ulcers and loss of teeth, and many patients died of mercurial poisoning rather than from the disease itself. Treatment would typically go on for years and gave rise to the saying.

“A night with Venus, and a lifetime with mercury”

Gerhard van Swieten (1700-1772), an Austrian army surgeon, introduced the internal use of corrosive sublimate, mercuric chloride, or liquor Swietenii, which stayed in use as treatment for syphilis for many years, and Guido Bacelli in 1894 developed it as an injection. In the late 19th century, calomel, mercurous chloride, a purgative and laxative, was used as an inunction and in tablet form and later as an injection. Ammoniated and salicylated mercury ointments were developed and the pharmaceutical formulae for unguentum hydrargyri ammoniate and unguentum hydrargyri salicilate were still in the Australian Pharmaceutical Formulary in 1955. Mercury stayed in favour as treatment for syphilis until 1910 when Ehrlich discovered the anti-syphilitic effects of arsenic and developed Salvarsan, popularly called the “magic bullet.”

New discoveries of the syphilis organism and its treatment

When it was realised by physicians that the toxic effects of mercury often outweighed any benefits it might have had, they looked for alternatives. The Polish surgeon-general Friedrich Zittman (1671-1757) mixed a drug consisting of the root of sarsaparilla with traces of mercury and called his elixir Decoctum Zittmani. The English surgeon William Wallace (1791-1837) introduced iodine therapy, potassium iodide with small doses of mercury. In the late 19th century various other metals such as tellurium, vanadium, platinum and gold were tried but were not effective.

In 1905, Fritz Richard Schaudinn, a German zoologist, and Erich Hoffmann, a dermatologist, discovered Spirochaeta pallida (the bacteria was spiral shaped and white under dark ground illumination, now called Treponema pallidum) to be the causative organism of syphilis. In 1906, August Paul von Wassermann, a German bacteriologist and an assistant of Robert Koch, developed a complement fixation serum antibody test for syphilis – the “Wasserman reaction.”

In 1906 Paul Ehrlich, a German histological chemist at the Robert Koch Institute who later in his life founded the sciences of chemotherapy and immunology, read of Fritz Schaudinn’s discovery. He had been experimenting for some years with the use of arsenic compounds in treating trypanosomiasis. Ehrlich then began experimenting with arsenic compounds in treating syphilis in rabbits. His experiments were not very successful as most of the earlier arsenicals he experimented with were too toxic, but in 1909 he and his assistant Sahachiro Hata, a Japanese bacteriologist, finally found success with the compound dioxy-diamino-arsenobenzol-dihydrochloride which they called drug “606”. This led in 1910 to the manufacture of arsphenamine, which subsequently became known as Salvarsan, or the “magic bullet”, and later in 1912, neoarsphenamine, Neo-salvarsan, or drug “914”. In 1908 Ehrlich was awarded the Nobel Prize for his discovery.

Albert Ludwig Neisser, a German physician specialising in dermatology and venereology and who had been using some of Ehrlich’s earlier arsenicals to treat syphilis, described Ehrlich’s new drug:
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“Arsenobenzol, designated “606,” whatever the future may bring to justify the present enthusiasm, is now actually a more or less incredible advance in the treatment of syphilis and in many ways is superior to the old mercury – as valuable as this will continue to be – because of its eminently powerful and eminently rapid spirochaeticidal property.”

LW Harrison, a medical officer in the Royal Army Medical Corps during World War I, described the effectiveness of Salvarsan and Neosalvarsan on soldiers who contracted syphilis during the war. Arsenic however, while being able to cure syphilis whereas mercury wasn’t, had many drawbacks – administration of treatment was complex requiring many injections over a long period of time, and it also produced toxic side effects. In 1916, A. Robert and Benjamin Sauton discovered the trypanocidal properties of bismuth, and in 1921, Robert Sazerac, Constantin Levaditi and Louis Fournier successfully treated syphilis with bismuth. It then became apparent that for arsenic to be effective, it had to be combined with small doses of either bismuth or mercury. Arsenic, mainly arsphenamine, neoarsphenamine, acetarsone and mapharside, in combination with bismuth or mercury, then became the mainstay of treatment for syphilis until the advent of penicillin in 1943.

In 1917 Julius Wagner-Jauregg, an Austrian physician, introduced the treatment of neurosyphilis with fever therapy by infecting the patient with malaria, then treating the malaria with quinine. The observation had been made that after a febrile illness the symptoms of neurosyphilis diminished, and the rationale was that it was easier to treat malaria with quinine than the syphilis with mercury or arsenic. Fred A. Kislig and Walter M. Simpson, two American physicians, introduced in 1936 the treatment of electropyrexia, using a short-wave apparatus to induce pyrexia in a patient to treat syphilis and gonorrhoea.

In 1943 penicillin was introduced as a treatment for syphilis by John Mahoney, Richard Arnold and AD Harris. Mahoney and his colleagues at the US Marine Hospital, Staten Island, treated four patients with primary syphilis chancrees with intramuscular injections of penicillin four-hourly for eight days for a total of 1,200,000 units by which time the syphilis had been cured. This became a turning point in the treatment for syphilis as penicillin was shown to be highly effective when administered during either its primary or secondary stages, and it had few side effects of any significance when compared to mercury or arsenic. Arnold wrote in 1986 of his early work with penicillin and syphilis:

“Syphilis was once a dreaded and dreadful disease involving millions of US citizens. Before the introduction of penicillin, the heavy-metal cure often caused thousands of deaths each year. The morbidity and mortality of the disease itself was horrendous, involving all ages from the fetus to the elderly.”

Was syphilis introduced from the New World into the Old World by Christopher Columbus in 1493? Over the past five centuries, and particularly in the last century, the origins of syphilis have caused great controversy amongst historians, physicians, anthropologists and palaeontologists. Up until the early 20th century the most popular theory on the origin of syphilis was that it was a new disease, contracted by Columbus’ men in the New World and introduced to the Old World after their return to Spain on 15th March of 1493. An alternative theory was put forward in 1934 by Richmond Cranston Holcomb that syphilis had already existed in the Old World before Columbus’ time, and in the latter part of last century palaeopathologists found possible evidence that this may have been so. A recent analysis of the evidence however by Kristin N. Harper, George J. Armelagos and other US anthropologists in 2011 has swung back to the “Columbian hypothesis” of the origin of syphilis.

There have been three main hypotheses on the origin of syphilis – the Columbian hypothesis that Columbus brought syphilis from the New World, the pre-Columbian theory that syphilis had already existed in the Old World and had evolved into a more virulent form around the time of Columbus, and the Unitarian theory that all treponematoses are a single disease with syphilis being an environmentally determined variant where social and environmental conditions in the late 15th century favoured its transmission by sexual intercourse.

Because the Naples syphilis epidemic appeared two years after Columbus returned in 1493 from Hispaniola, the belief that Columbus’ crew had contacted the disease in the New World arose in the scholarly and medical literature by the early 16th century. When Charles VIII invaded and seized Naples in 1495, Naples was populated by Spanish immigrants and was defended largely by Spanish mercenaries who had probably already contracted the disease in Spain and who then passed the disease onto Charles’ soldiers and followers when they invaded Naples. Schreiber and Mathys (1987) describe that the disease had first appeared
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in Barcelona in 1493 and had spread throughout Spain that year. Castiglioni (1946)26, Wills (1996)6 and Harper et al (2011)24 state that the Columbian hypothesis is supported by descriptions by several 15th and 16th century scholars such as Fernandez de Oviedo y Valdes in 1526, Bartolome de las Casas in 1530. Ruy Diaz de Isla in 1539, the latter a Barcelona physician who claimed to have treated Columbus’ men for the disease, and Gabriele Fallopius (1523-1562), all of whom stated that Columbus’ crew had a new disease and that a similar disease had been present on the island of Hispaniola for many centuries before Columbus.

The Columbian hypothesis that syphilis was brought to Europe from America in 1492 was reaffirmed in the 1950s and 1960s by a number of historians and physicians such as Harrison (1959), Dennie (1962), Goff (1967), and Crosby (1969).27 Crosby (1969) and Harrison (1959) state that the two most important historians of the time, Fernandez de Oviedo y Valdes and Bartolome de las Casas, were eyewitness to conditions in Hispaniola when Columbus was there and both considered that Columbus brought the disease back from the New World to Europe.28,29 Crosby states that both Ulrich von Hutton and Ruy Diaz de Isla identified 1493 as the year the disease first appeared in Europe. Crosby quotes Ulrich von Hutton as saying, “In the yere of Chryst 1493 or there aboute this most foule and most grievous disease beganne to sprede amonsthe people.” Crosby’s view was that treponematosis was originally a single disease which evolved into several related but distinct diseases and that venereal syphilis is the variant that developed in America, from which it probably was introduced to Europe with the return of Columbus.28

A third important scholar of the time who believed in the Columbian origin of syphilis was Ruiz Diaz de Isla, a Barcelona physician, who published in a book in 1539 that Columbus’ men contracted the disease in Hispaniola in 1492 and that he had observed its rapid spread through Barcelona after Columbus’ return. De Isla wrote that he had treated the men for the disease but hadn’t realised it was the same disease that had been ravaging Europe until many years later. He called it Morbo serpentine, ‘the hideous, dangerous, terrible disease’.28

The pre-Columbian theory arose in the early 20th century. Garrison11 refers to a 1912 publication by Karl Sudhoff, a German medical historian from the University of Leipzig, who stated that the Naples epidemic was typhoid or paratyphoid fever. That syphilis was present in Europe before Columbus’ return from Hispaniola was supported by the facts that many literary works and religious edicts referred to syphilis before the Naples siege of 1495, and also that mercury treatment had been used since the 12th century for a diversity of infectious disorders that were probably syphilis. Garrison himself says “That sporadic syphilis existed in antiquity and even in prehistoric times is quite within the range of probability.”11

An editorial article in JAMA in 193525 cited Capper (1926) as stating that many historical descriptions of leprosy were in fact syphilis, and that syphilis among the Romans was described by Celsus, Aetius and Aetius. The article also cited Butler (1933) as stating that historical evidence of aortic aneurysm being treated by Antyllus, a contemporary of Galen in Romans times, was evidence of the existence at that time of syphilis, and that Celsus accurately described a genital syphilitic chancre. Richard Holcomb’s argument in 1935 that syphilis was of pre-Columbian origin was based on a description by Michael Angelus Blondus, a 16th century Italian surgeon, who identified it with a disease described by Aurelius Cornelius Celsus, a 2nd century Greek philosopher, and Paul of Aegina, a 7th century Greek physician.25 In 1974, two anthropologists, John Lobdell and Douglas Owsley, stated “syphilis can probably not be “blamed”, as it often is, on any geographical area or specific race. The evidence suggests that the disease existed in both hemispheres of the world from prehistoric times. It is probably only coincidental with the Columbus expeditions that the syphilis previously thought of as “lepra” in Europe flared into virulence at the end of the fifteenth century.”30

Several medical historians over the last century have postulated other reasons for syphilis being a pre-Columbian Old World disease – a greater lay and medical recognition of syphilis developed in recent eras, and that syphilis had evolved from other treponemal diseases into a more virulent form due to a combination of social, cultural and environmental changes around the time of Columbus. In the last several decades development of palaeopathology has enabled close evaluation of Old World skeletons and many studies have published their findings of evidence for syphilitic bone disease.24,27

The Unitarian hypothesis, proposed by EH Hudson in 192829, that treponematoses are environmentally determined expressions of the same disease of which syphilis is one variant, with syphilis being hindered from skin to skin transmission because of development of hygiene and changing to become a sexually transmitted disease, has been refuted by genetic studies which show the different trepeneum
subspecies are genetically distinct and evolved along different paths.24

Critics of recent palaeopathological studies have pointed out the difficulties in distinguishing syphilis from other diseases that had similar symptoms and left similar bone scars such as leprosy, osteomyelitis, hypertrophic osteoarthropathy, and histiocytosis.31,32 In 2005 Bruce M. Rothschild published a review of the historical and palaeopathological record of syphilis. Rothschild found that the pathological osseotype features of syphilis were absent in human specimens from re-Columbian Europe, Africa and Asia. However specimens with evidence of treponemal disease were identified from North America dating back some 8,000 years. Bruce Rothschild as co-author with Christine Rothschild in their review study in 2000 found that somewhere between 2000 and 1800 years ago the first identified osseotype evidence of syphilis occurred in North America and it appeared that syphilis had transmuted from yaws.33 Rothschild (2005) states that it is clear syphilis was present in the New World at the time of Columbus’ arrival, perhaps in a milder or a non-venereal form, and there is evidence it existed in the same area of the Dominican Republic at which he landed. Rothschild also states that all evidence for treponemal disease existing in re-Columbian Europe represents isolated cases for which alternative diagnoses are more likely.35

A review of palaeopathological studies of treponemal disease in the New and Old World by Baker and Armelagos in 1988 documented an abundance of pre-Columbian New World finds, but an absence of Old World finds, a finding that was reaffirmed by Powell and Cook and by Rothschild in 2005.24,27,32 Baker and Armelagos (1988) concluded that pre-Columbian American skeletal analyses reflect a treponematosis that spread to the Old World through non-venereal contact, and that European social and environmental conditions at the time favoured the development of venereal transmission. They also stated that the rapid spread of syphilis throughout Europe around 1500 reflected the introduction of a virulent disease into a population that had not been previously exposed and had no immunity to it.27 In 2008 Harper et al published a comprehensive phylogenetic analysis of 26 geographically disparate strains of pathogenic Treponema, which found that the venereal syphilis strains originated recently and were more closely related to yaws strains from South America than to other non-venereal strains, further supporting the hypothesis that syphilis, or a progenitor of the bacteria, came from the New World.24

In 2011 Harper et al evaluated all published reports of pre-Columbian Old World treponemal disease, using a systematic approach involving diagnostic criteria, certainty of diagnosis, and the accuracy and reliability of palaeopathological dating and radiocarbon dating. The authors concluded that among the 54 reports they evaluated using their criteria they did not find a single case of Old World treponemal disease that had both a certain diagnosis and a secure pre-Columbian date. They came to the overall conclusion that evidence for an Old World origin for syphilis remains absent, and that this further supported the hypothesis that syphilis, or its progenitor, came from the New World.24

Syphilis was a terrible disease because of its propensity to mimic many medical disorders, and its importance to medicine was emphasised by Sir William Osler who in an address given to the New York Academy of Medicine in 1897 titled Internal Medicine as a Vocation said:

“I often tell my students that it is the only disease which they require to know thoroughly. Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you.”

From its beginning, syphilis was greatly feared by society—because of the repulsiveness of its symptoms, the pain and disfigurement that was endured, the severe after effects of the mercury treatment, but most of all, because it was transmitted and spread by an inescapable facet of human behaviour, sexual intercourse. The origin of syphilis is still a topic of debate and research, believed by physicians and scholars up until early last century to have been brought to the Old World from America by Christopher Columbus. In recent times, archaeologists and palaeontologists had found possible evidence it existed in the Old World before Columbus. This has been disputed by other researchers however and it seems that it is still possible that Columbus did bring syphilis, or its progenitor, to the New World.

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References


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Army Malaria Institute – its Evolution and Achievements
Third Decade (1st Half): 1985-1990

Karl H. Rieckmann, Anthony W. Sweeney, Michael D. Edstein, Robert D. Cooper, Stephen P. Frances

Abstract
The first half of the third decade (1985-1990) after the establishment of the Malaria Research Unit was characterised by a substantial increase in laboratory and field activities. Various new procedures were developed to discover and counter the increasing problem of parasite resistance to established antimalarial drug regimens. After early findings that the currently-used pyrimethamine/dapsone (Maloprim®) prophylaxis was no longer effective against *Plasmodium falciparum* malaria, *in vitro*, *ex vivo* and pharmacological investigations were undertaken with proguanil and a low dose of dapsone. This led to a field study in Papua New Guinea (PNG) which indicated that such a drug combination might be more effective than Maloprim®. Before the effectiveness of this combination could be determined further, it became obvious that Maloprim®/chloroquine had become inadequate for the protection of ADF soldiers on exercises in PNG. During one of these exercises, the landmark discovery that *P. vivax* had developed resistance to chloroquine was the first documented evidence that this previously successful standard medication had lost its efficacy against vivax malaria. These findings in 1988/1989 led to the evaluation of mefloquine and doxycycline as alternative prophylactic regimens for ADF personnel serving in malarious areas. In efforts to identify and assess other potential antimalarial drugs, *in vitro* studies were continued with various strains of *P. falciparum*. These studies were supplemented by investigations with *P. falciparum* and *P. vivax* in non-human primates and by malaria transmission studies with *Anopheles farauti* mosquitoes. The survey of anopheline mosquitoes in northern Australia indicated the widespread presence of three isomorphic species of *An. farauti* and the ever-present possibility of re-introducing malaria into northern Australia. Investigations relating to the biological control of mosquitoes were gradually phased out and emphasis was given to the assessment of novel mosquito repellent measures for improved personal protection against malaria.

Background
The global malaria situation had generally not improved during the previous decade. Following the principles of primary health care outlined at the Alma Ata Conference in 1978, increasing emphasis was given to applying strategies of malaria control tailored more specifically for different epidemiological conditions. Although basically an eminently sensible approach, lack of funding and decreased prioritisation of malaria activities in many malarious countries meant that there was generally little or no improvement in the malaria situation. The extension of chloroquine-resistant falciparum malaria to other areas, including Africa and the Southwest Pacific region was a contributing factor hindering malaria control activities. In some countries, a combination of pyrimethamine and sulfadoxine (Fansidar®) had largely replaced chloroquine for malaria treatment. However, since most infections still responded clinically to chloroquine and related drugs, they continued to be used as first-line treatment because they were affordable and largely effective in suppressing malaria in populations with some degree of background immunity to malaria. In a few areas, though, travellers or residents with little or no immunity to malaria were not responding adequately to prophylaxis or treatment with standard drugs. This raised the possibility of using alternative drugs, such as the tetracyclines and mefloquine, for malaria prophylaxis and treatment.

Research activities at the Army Malaria Research Unit (AMRU), commenced in the mid-1960s, were able to be increased following its relocation from the University of Sydney to the Ingleburn military facility in 1974. This was possible because improved housing facilities enabled the gradual acquisition of more suitable equipment for the laboratories, the establishment of an appropriate mosquito insectary and animal quarters, and a gradual increase in staff from 9 to 23 positions by the end of the decade. Significant progress was made in assessing *in vitro* drug resistance and screening potential antimalarial
Drugs by short-term and long-term culture of *Plasmodium falciparum*, in determining the synergistic activity of antifolate drug combinations in rodent malaria, and in developing sensitive methods for estimating drug concentrations in body fluids with a view to optimising drug doses used for malaria prophylaxis and treatment.6 Following the Unit’s documentation of chloroquine-resistant falciparum malaria in Papua New Guinea (PNG) at the start of the second decade, increasing attention was given to the investigation of various antifolate drug combinations. Although studies with dapsone/proguanil combinations continued for a while, greater attention was placed on dapsone combined with another dihydrofolate reductase (DHFR) inhibitor – pyrimethamine. This pyrimethamine/dapsone combination, widely known as Maloprim®, was registered and approved for malaria prophylaxis in Australia in 1979.

By 1980, standard malaria prophylaxis for Australian military personnel consisted of weekly Maloprim® and chloroquine while on deployment overseas and for 4 weeks after return to Australia to suppress falciparum and vivax malaria. In addition, a 14-day course of primaquine (7.5 mg base 3 times a day) was taken to eradicate any residual liver stages of vivax malaria. With good drug compliance, these regimens appeared to be largely effective in preventing malaria in the rather limited number of military personnel deployed overseas during this period.

The accidental discovery of a fungus killing mosquito larvae in the Unit insectary generated considerable interest in the possible use of *Culicinomyces clavisporus* as a potential fungal larvicide to control mosquito breeding, although its practical application in the field remained in doubt. In addition to preliminary studies with another mosquito pathogen, other entomological activities included speciation and malaria transmission studies with *Anopheles farauti*, the major malaria vector in the Southwest Pacific region, and the initiation of annual surveys to map the distribution of this vector in northern Australia.6

### Staff and facilities

In January 1985, Colonel Eric Donaldson became Director of AMRU, following the promotion of Colonel Graham Maynard to Brigadier and his transfer to Army Headquarters in Canberra. Colonel Donaldson inherited a unit which had grown considerably since its inception about 20 years earlier and which was destined to contribute significantly to international efforts to control drug-resistant malaria. During 1985 and 1986, there was a substantial extension of primate, mosquito and parasitology facilities. In addition, office space was acquired from 2nd Military Hospital to accommodate a refurbished library, staff offices and a small laboratory. In late 1985, Professor Karl Rieckmann was recruited as Director of Medical Research, following a 25-year absence from Australia during which he conducted laboratory and field investigations to control the increasing problem of parasite resistance to antimalarial drugs. After the transfer of Lieutenant Colonel John Twartz to 2nd Military Hospital in 1986, Major Andrew Taylor was posted to the Unit as medical officer for 12 months. Following Colonel Donaldson’s re-assignment to the Army Aviation Centre at Oakey, Queensland, in August 1987, Lieutenant Colonel Sweeney became Commanding Officer and Acting Director of the Unit. In 1988, Ms Barbara Kotecka was appointed Parasitologist following the resignation of Dr Haydn Scott, and Lieutenant Colonel Donald Davis was posted to the Unit as Medical Officer for a short period of time.

**Figure 1: Army Malaria Research Unit Staff (1986).**

*Standing (L to R): Mr H. Scott, PTE A. Topping, SGT C. Rogers, SGT J. Staley, CAPT R. Cooper, CPL M. Baker, Mr T. Haddon, CPL M. Sellars, SGT K. Neuman, CPL G. Owen, Mrs J. Turl, LT S. Frances.***


In 1988, Emeritus Professor (Colonel) Black died after a distinguished career in tropical medicine during which he was also the motivating force in re-establishing the Army’s active participation in malaria research activities. In the same year, Karl Rieckmann was appointed Professor of Medicine at the University of Sydney. After his appointment as Director of AMRU in 1989, the long-standing association with the University of Sydney was strengthened when AMRU was accorded departmental status within the Faculty of Medicine during the following year. In
1989, Major Michael Edstein commenced a 3-year posting to the Armed Forces Research Institute of Medical Research (AFRIMS), Thailand, and contributed to joint efforts by AMRU and US and Thai Army scientists to counter the increasing problem of drug-resistant malaria.

Malaria situation

**Upsurge in malaria during military exercises in PNG.** Current malaria prophylaxis appeared to control malaria in the ADF quite well until the deployment of 163 members of the Special Air Services (SAS) regiment to PNG for 3 to 4 weeks during 1988 and 1989. Five soldiers developed malaria (3 *P. falciparum*, 2 *P. vivax*) while taking prophylaxis and 36 of them had attacks of malaria (6 *P. falciparum*, 30 *P. vivax*) after completing prophylaxis.\(^7\) The malaria attack rates were similar to those observed during the Pacific campaign of World War II and higher than those observed during the Malayan emergency or the Vietnam conflict. This suggested very strongly that weekly Maloprim®/chloroquine prophylaxis was no longer able to protect soldiers adequately against falciparum and vivax malaria and that the current primaquine eradication regime was becoming less effective in preventing relapses of vivax malaria. The gravity of the situation was heightened even further by the documentation that chloroquine was unable to suppress vivax malaria in 2 soldiers who were treated with chloroquine after their return from PNG.\(^8\) There was obviously an urgent need for improved protection of soldiers against malaria.

**Drug resistance**

**In vitro test for drug resistance.** The increased likelihood of ADF personnel acquiring drug-resistant infections highlighted the importance of forwarding parasitised blood samples to AMRU to assess the *in vitro* sensitivity of parasites to chloroquine and other drugs.\(^9\) By determining the presence and degree of drug resistance in patients with falciparum malaria, medical personnel could modify their treatment regimens, if necessary, for patients whose infections had been acquired in the same geographical area. These tests could also be helpful in formulating more effective prophylactic and therapeutic drug regimens for particular areas of deployment.

**P. falciparum** resistance to pyrimethamine/dapsone (Maloprim®). The first documented evidence that *P. falciparum* was becoming resistant to Maloprim® was in 1987 when high performance liquid chromatography (HPLC) analysis revealed that high plasma concentrations of pyrimethamine and dapsone did not prevent an Australian soldier from developing falciparum malaria while on prophylaxis in PNG.\(^10\) Furthermore, adequate plasma concentrations of pyrimethamine, dapsone and chloroquine were observed in 3 of the men who developed falciparum malaria while they were still on weekly prophylaxis following the 1988/1989 SAS exercise in PNG.\(^7\) Six other men became ill with falciparum malaria within 4 weeks after completing prophylaxis, suggesting that parasites were only partially suppressed by Maloprim®/chloroquine prophylaxis.

**P. vivax** resistance to chloroquine. Following the 26-day deployment of SAS soldiers to PNG during 1989, 2 soldiers developed acute attacks of vivax malaria 3 to 15 days after return to Australia.\(^8\) Both men were still on weekly chloroquine and Maloprim® prophylaxis, and their plasma chloroquine levels were considerably higher than those generally regarded as therapeutically effective against *P. vivax*. About 30 years after the emergence of chloroquine-resistant *P. falciparum*, this was the first documented evidence that *P. vivax* was also capable of developing resistance to chloroquine. Chloroquine-resistant *P. vivax* was also observed in a traveller returning to Australia from PNG and the Solomon Islands.\(^11\)

**P. vivax** tolerance to primaquine. Relapses of vivax malaria acquired in the southwest Pacific area have traditionally been treated with a total daily primaquine dose of 22.5 mg base, rather than 15 mg base, because parasites from this area were considered to be more tolerant to the drug than in other parts of the world. The unacceptably high number of vivax infections observed in the SAS soldiers after their return to Australia suggested that the parasites were becoming even more tolerant to primaquine than previously reported.\(^7\)

**Malaria diagnosis.** The increasing problem of drug resistance highlighted the importance of early microscopic diagnosis of malaria and correct identification of malaria species. The diagnostic verification service provided by the Unit revealed that the wrong plasmodial species was being identified in up to one in 5 military personnel, raising the likelihood that some military personnel had received inappropriate treatment. This emphasised the need to forward duplicate blood films to AMRU as quickly as possible to enable treatment to be modified if necessary. As species identification by microscopic examination of blood films can sometimes be notoriously difficult, it was hoped that this problem could be partly resolved by reviving 2–4 week training courses for pathology technicians working at defence and other laboratories.
Proguanil/Dapsone as a possible alternative to pyrimethamine/dapsone (Maloprim®)

Earlier favourable field and laboratory findings with proguanil/dapsone led to a reconsideration of using proguanil in combination with a low-dose of dapsone, for malaria prophylaxis. Further studies were carried out with proguanil, chlorproguanil, and their active triazine metabolites to gain a better understanding of the pharmacokinetics of these drugs. Addition of proguanil, dapsone or monoacetyl-dapsone (principal metabolite of dapsone) to the pyrimethamine-resistant K1 isolate of P. falciparum showed little or no antimalarial activity in vitro. On the other hand, cycloguanil (active metabolite of proguanil) was several orders of magnitude more active than its parent compound, with 90% parasite growth of the drug-resistant K1 isolate being inhibited at a concentration of 80 ng/mL. However, only 20 ng/mL cycloguanil was required to inhibit parasite growth when 40 ng/mL dapsone was added to the culture. Parasite growth was also inhibited when 20 ng/mL cycloguanil was added to sera collected from volunteers 24 hours after administration of a low dose of 10 mg dapsone.

These encouraging results led to the use of a bioassay (see below) to assess the activity of proguanil and dapsone by incubating sera, collected at various times after drug administration, with in vitro cultured parasites. By determining serum antimalarial activity in vitro, preliminary information about the duration and synergy of drug activity could be obtained ex vivo, before proceeding to in vivo assessment of such activity in individuals exposed to or infected with malaria. Thus, 6 healthy Army volunteers, not serving in a malarious area, received 200 mg proguanil daily for 7 days and, after an interval of at least a month, 10 mg dapsone daily for 7 days.

Serum specimens were collected at various intervals up to 24 hours after the end of proguanil or dapsone administration. None of the dapsone sera showed any antimalarial activity against the K1 isolate and, although sera from a few of the proguanil-treated volunteers (containing cycloguanil) showed partial inhibition of parasite growth for up to 12 hours, none of them did so 24 hours after drug administration. On the other hand, when dapsone- and cycloguanil-containing sera were combined with each other, parasite inhibition varied between 77% and 99% in the samples collected from volunteers 24 hours after medication.

The favourable ex vivo antimalarial activity of proguanil combined with dapsone prompted a further study to determine the steady-state pharmacokinetics of 200 mg proguanil co-administered daily with 10 mg dapsone in 6 healthy male soldiers. After the seventh and last daily dose, mean plasma maximum (minimum) concentrations of proguanil, cycloguanil and dapsone were 151 (21), 56 (15) and 285 (125) ng/mL, respectively. Respective elimination half-lives were 23, 15 and 18 hours. When serum samples collected between 4 and 24 hours were incubated with parasites of the K1 isolate, no parasite growth was observed in any of the cultures.

The complete inhibition of parasite growth following daily co-administration of proguanil and dapsone was in marked contrast to observations in 6 soldiers following weekly administration of pyrimethamine/dapsone (Maloprim®). Although sera collected from the 6 volunteers inhibited parasite growth of the drug-sensitive FC27 isolate completely at trough concentrations of both drugs, even maximum serum concentrations failed to inhibit the growth of K1 parasites. Infections with less resistant parasites might still be able to be suppressed at peak concentrations, but this would be unlikely for serum samples collected towards the end of the weekly dose of Maloprim. This is due to the ill-matched elimination half-lives and clearance of pyrimethamine and dapsone, with mean half-lives in the volunteers being 105 hours and 23 hours, respectively. The considerably more rapid elimination of dapsone implied that residual levels of pyrimethamine would not be able to suppress parasites without the synergistic activity of dapsone. This very significant difference in the pharmacokinetics of the two drugs probably explained the decreasing effectiveness of Maloprim in areas where parasites were becoming increasingly resistant to pyrimethamine.

Field study with proguanil and low-dose dapsone.

The results of these findings were shared with the PNG Medical Research Advisory Committee and it approved a joint proposal by Ramu Sugar Limited (RSL) and AMRU to evaluate the effectiveness of proguanil/dapsone among seasonal workers at RSL, PNG. Some consideration had been given by RSL to using proguanil alone for malaria prophylaxis because chloroquine prophylaxis was not protecting their relatively non-immune workers from highland provinces against malaria. However, because in vitro tests in 1987 had shown parasites in this malarious area to have a degree of resistance to cycloguanil similar to that observed during studies at AMRU, the sugar company was keen to evaluate the effectiveness of a 12-week supervised course of proguanil in combination with a low dose of dapsone. As a result, 280 out of 1800 workers living in highly malarious villages indicated their willingness to participate in a supervised 12-week course of proguanil/dapsone.
Three weeks after receiving a standard 3-day course of amodiaquine to eliminate any circulating asexual parasites, they received 200 mg proguanil once a day and 25 mg dapsone twice a week (10 mg tablets for daily administration were unavailable). Finger-tip blood specimens were collected every two weeks for examination of malaria parasites and white cell counts. In addition, blood specimens were examined for malaria parasites from any villagers (participants and non-participants) who developed fever or reported to the RSL medical clinic with any illness. None of the 225 participants who completed the 12-week proguanil/dapsone course showed any parasites in their blood films during the period of drug administration, but 16 of them developed symptomatic infections 2 to 12 weeks after the end of drug administration. During the 12-week proguanil/dapsone course, 72 symptomatic infections were detected in the 1,500 or so non-participants, indicating continuous malaria transmission during the period of the trial.\textsuperscript{16}

These findings suggested that this prophylactic regimen was effective in preventing malaria in an area with proven resistance to chloroquine and proguanil. The cumulative weekly dose of dapsone (50 mg) was one-half the weekly dose of dapsone (100 mg) in Maloprim\textsuperscript{®} and less than one-third the cumulative weekly dose given to Australian and American soldiers during the Vietnam conflict (175 mg).\textsuperscript{3} No decrease in white blood cells was observed throughout the course of the study and, in reality, agranulocytosis would be unlikely to manifest itself after such low doses of dapsone. Due to the marked drop in malaria cases and no discernible drug toxicity, the company expressed its interest in promoting the wider use of this drug combination among its workers to enhance their health and to reduce the number of man-hours lost by malaria illness.

Although favourable results were obtained at Ramu, further studies were obviously required before this drug combination could be considered for use as an alternative to Maloprim\textsuperscript{®}. Therefore, field studies were started in 1989 with two possible alternative drugs – doxycycline (a tetracycline drug) and mefloquine.

**Doxycycline prophylaxis**

In 1970, the tetracyclines had been found to be effective against both the pre-erythrocytic and asexual erythrocytic stages of chloroquine-resistant \textit{P. falciparum} malaria.\textsuperscript{19} Following that early discovery, clinical and field studies with various tetracyclines, including doxycycline, had confirmed that this group of drugs, when given in combination with a rapidly-acting blood schizontocide, was highly effective in curing drug-resistant falciparum malaria.\textsuperscript{20} However, despite indications that the selective use of the tetracyclines might be beneficial for “personal prophylaxis by non-immune individuals visiting or working temporarily in areas with a high transmission of multidrug resistant strains”,\textsuperscript{20} the first field study to determine the prophylactic effectiveness of doxycycline had not been conducted until 1986.\textsuperscript{21, 22}

During 1989, 184 Australian soldiers volunteered to take 100 mg doxycycline daily during their deployments to PNG for 3 to 6 weeks. In addition to doxycycline prophylaxis, 69 men also took a daily dose of 7.5 mg primaquine base. Medication was generally well-tolerated and, although about 1 in 20 soldiers experienced some photosensitivity, the incidence of gastrointestinal disturbances was similar to that observed with mefloquine or Maloprim\textsuperscript{®}/chloroquine prophylaxis.\textsuperscript{7} All of the men were protected against \textit{P. falciparum} and \textit{P. vivax} while they were on medication. None of them developed falciparum malaria after returning to Australia but, despite a 14-day primaquine eradication course, 13% (15 out of 115) of the soldiers taking doxycycline alone experienced delayed primary attacks of vivax malaria, usually within 2 to 3 weeks after returning to Australia. On the other hand, none of the 69 soldiers taking doxycycline, in combination with a low-dose of primaquine, developed vivax malaria.\textsuperscript{7} Leaving aside these preliminary findings with primaquine, it seemed likely that short-term administration of doxycycline might play a useful role in protecting healthy non-pregnant adults against falciparum malaria and in suppressing vivax malaria during medication with this drug.

**Mefloquine (Lariam\textsuperscript{®}) prophylaxis**

Mefloquine is a 4-quinolinemethanol drug which had been developed under the auspices of the antimalarial drug development program of the US Army. Initial clinical studies with this drug in 1974 had shown it to be very effective in the prophylaxis and treatment of multidrug-resistant falciparum malaria.\textsuperscript{23, 24} After extensive field studies over the next decade, this long-acting drug had progressively been approved for use as an antimalarial by various countries, and was registered in Australia in 1988. The following year, 40 soldiers agreed to take a weekly dose of 250 mg mefloquine for 4 weeks during their deployment to PNG; all of them remained well and the medication was tolerated as well as Maloprim\textsuperscript{®}/chloroquine prophylaxis.\textsuperscript{7} After return to Australia, despite taking the primaquine eradication course, 10% (4 out of 40) of the soldiers suffered acute attacks of vivax malaria. As expected, mefloquine had acted against
the asexual erythrocytic stages of *P. falciparum* and *P. vivax* but not against the liver stages of *P. vivax*. These results provided further evidence that 22.5 mg primaquine a day for 2 weeks was not always able to eliminate the latent tissue stages (hypnozoites) of *P. vivax* acquired in PNG.

**Assessment of other potential antimalarial drugs**

*In vitro assessment of drug activity against drug-resistant isolates of P. falciparum.* Additional studies were performed with various pyrimidine and purine antimetabolites in collaboration with the Department of Biochemistry, University of New South Wales. Some synergistic activity against *P. falciparum* was observed between pyrazofurin and tuberculcin, but none was observed in most combinations of these compounds or when they were combined with dihydrofolate reductase (DHFR) inhibitors such as pyrimethamine or cycloguanil (active metabolite of proguanil).25 These investigations were followed by collaborative studies with the Department of Biochemistry at the University of Sydney to determine the activity of TDHO-Me, BW566C80 (a new antimalarial undergoing clinical trials), and pyrazofurin, which inhibit the third, fourth and sixth step of the de novo pyrimidine pathway, respectively. Unfortunately, no synergism was observed between any of these compounds nor between them and dihydrofolate reductase (DHFR) inhibitors, such as cycloguanil. This was in marked contrast to the intense synergistic activity observed between DHFR inhibitors and dapsone.25 Because of these findings, further studies with pyrimidine and purine antimetabolites were discontinued. By contrast, collaborative studies with the Australian National University started in 1984, continued to show that Mannich bases exerted significant antimalarial activity against drug-resistant isolates of *P. falciparum*.26,27

**Bioassay for assessing drug activity.** After establishing the continuous culture of several different strains of *P. falciparum*, it became possible to use a bioassay method28 to complement HPLC drug analysis of serum specimens. In addition to estimating the concentration of some drugs, such as the active metabolite of proguanil (cycloguanil),29 the bioassay could provide comparative data of biological activity against parasite strains with defined drug susceptibilities. The bioassay could also be used to detect the presence of unrecognised active drug metabolites not yet detectable by HPLC analysis. But perhaps the most important contribution of the bioassay was that now the synergistic antimalarial activity of various serum concentrations could be assessed against different strains of *P. falciparum* after drug administration to either uninfected non-human primates or human volunteers. Thus, vital information about the potential value of various drug combinations could be obtained before formulating drug regimens for malaria prophylaxis and treatment.15

**Effectiveness of amodiaquine against chloroquine-resistant P. vivax.** Historically, chloroquine and amodiaquine had been used interchangeably for malaria prophylaxis and treatment because it was considered that malaria parasites were equally susceptible to both these 4-aminoquinoline drugs. However, in 1969, amodiaquine was shown to be more effective than chloroquine in treating multidrug-resistant infections of *P. falciparum*.30 Would chloroquine-resistant *P. vivax* respond in the same way? The findings in 2 Aotus monkeys inoculated with the AMRU 1 isolate indicated that this isolate was also more susceptible to amodiaquine and that this 4-aminoquinoline drug could play a useful role in the treatment of chloroquine-resistant *vivax* infections.31

**Malaria transmission studies**

**Malaria transmission via mosquitoes using cultured parasites**

As part of AMRU’s collaboration with the Walter and Eliza Hall Institute (WEHI) and the Australian Malaria Vaccine Joint Venture (Saramane Pty Ltd), colony specimens of *An. farauti* needed to be infected with *in vitro* cultured *P. falciparum* gametocytes. This would enable immunisation studies to assess potential vaccine candidates as well as future trials to evaluate the efficacy of antimalarial drugs. The *An. farauti* colony was chosen for this work as, unlike the *An. farauti* 2 and *An. farauti* 3 colonies, it was self-mating and sufficient numbers to support the work could be readily maintained. The procedure of producing cultured gametocytes and infecting anophelines was being routinely carried out by Dr Imogene Schneider’s team at Walter Reed Army Institute of Research (WRAIR) using the NF54 (WR) strain of *P. falciparum* and *An. stephensi*. During February and March 1987 Captain Bob Cooper learnt the technique at WRAIR and then transferred it to AMRU. Despite being able to induce *P. falciparum* cultures to produce healthy gametocytes, there was a persistent failure to infect *An. farauti* 1 past the ookinete stage. To determine whether *An. farauti* 1 was indeed refractory to cultured *P. falciparum* gametocytes, colony *An. farauti* 1 material was sent to Dr Schneider who ran parallel infection studies with the same batch of gametocytes fed to both *An. farauti* and *An. stephensi*. The results showed that while 70% of *An. stephensi* became infected to the
sporozoite stage, only 2.1% of *An. farauti* 1 were infected and this only to the oocyst stage.\(^{32}\) The importation of *An. stephensi* into Australia was not possible due to quarantine regulations and, in the absence of a competent vector, these studies were abandoned pending changes in the quarantine regulations.

**Malaria transmission in *Saimiri* and *Aotus* monkeys**

*Aotus* monkeys, first received at the Unit in 1982, continued to be regarded as the best experimental host for human malaria parasites. Although breeding pairs of *Aotus* monkeys were producing live births, older monkeys were dying from old age, so that the colony was not increasing in size. As further *Aotus* monkeys could not be obtained from overseas, *Saimiri sciureus* monkeys were acquired from the Commonwealth Serum Laboratories (CSL), Melbourne, to determine whether they could be used as an alternative host for human malaria parasites, especially *P. vivax*.

Commencing in 1989 attempts were made to infect *Saimiri* and *Aotus* monkeys with various strains of *P. vivax* (Chesson and Salvador 1). Following isolation of the chloroquine resistant strain - designated as AMRU 1 - from an ADF soldier exercising in Papua New Guinea, studies using this strain became the main focus of the work. The aim was to adapt and characterise the natural course of infection of this strain in *Saimiri* and *Aotus* monkeys so that a monkey malaria model could be used to evaluate the efficacy of antimalarial drugs.

Studies with *Saimiri* monkeys showed that these animals were refractory to the chloroquine resistant AMRU 1 strain of *P. vivax*, though they were infected with the AMRU 2 strain which was a chloroquine sensitive strain isolated from another ADF soldier who had become infected in PNG.\(^{33}\)

*Aotus* monkeys, on the other hand, could be infected quite readily with the AMRU 1 strain. Over a period of a year 12 monkeys were inoculated with AMRU 1 parasites, either by blood passage or using cryopreserved parasites. Parasites appeared in the peripheral blood of all monkeys within 3-18 days (mean 7.5 days) following inoculation, with maximum parasitaemias (range 1200 - 68800/µL; mean 20587) being achieved within 19 days of inoculation. However, within 13 days, parasitaemias in all monkeys fell to less than 500/µL. Gametocytes were produced during the course of the infection and appeared to be most infective 3-4 days prior to peak parasitaemia. Infection rates in *An. farauti* 1, *An. farauti* 2, and *An. farauti* 3 were 16.8%, 8.9%, and 16.9%, respectively, though rates as high as 96% were observed in some batches. Attempts to transmit infections via the bites of these infective mosquitoes were achieved in 9 out of 15 monkeys, with an average prepatent period of 32 days (range 15-79 days).\(^{34}\) The ability to use sporozoites to initiate infections in monkeys offered the potential to develop a cyclical model for the evaluation of antimalarial drugs against the liver stages of *P. vivax*.

**Distribution of Anopheline mosquitoes in northern Australia**

Operation Anopheles, initiated in 1984 to determine the distribution of the *An. farauti* sibling species in northern Queensland, was extended during 1985-1990 to cover all of northern Australia where malaria outbreaks had previously occurred and to include all species of anophelines. Cape York Peninsula was surveyed in 1985 and 1986, the Gulf of Carpentaria in 1987 and 1988, and the Northern Territory in 1989 and 1990. The work was supported by members of the 1st Preventive Medicine Company, Kiowa light observation helicopters from 162 Reconnaissance Squadron, Army Aviation, provided access to the remote and isolated areas of the region. Adult anophelines, collected by using CO2 baited light traps, were identified morphologically. This was also done with adult mosquitoes which were reared from larvae that had been collected from breeding sites throughout the survey area.

Specimens identified as *An. farauti* were cryopreserved and transported back to AMRU where the isomorphic species were separated using isoenzyme electrophoresis or\(^{35}\) DNA labelled probes. The isoenzyme electrophoresis method, developed by Dr Rod Mahon (Division of Entomology, CSIRO, Canberra), worked well for specimens collected in northern Queensland but failed to identify *An. farauti* specimens collected in the Northern Territory. The latter specimens were examined using species specific DNA probes designed to separate the isomorphic species - *An. farauti* 1, *An. farauti* 2, and *An. farauti* 3.\(^{36}\) This method, developed in collaboration with Dr Tom Burkot and Leanne Cooper of the Queensland Institute of Medical Research, does not require field specimens to be preserved as stringently as those collected for analysis by isoenzyme electrophoresis. This is due to the DNA molecule being quite robust and less susceptible to degradation than enzymes.

*An. farauti* 1 could also be identified by a simple field technique not requiring the sophisticated equipment used for isoenzyme electrophoresis and DNA hybridisation. It relied on the fact that larvae of this species breed in brackish water and can tolerate higher levels of salinity than either *An. farauti* 2 or 3. Thus, exposure of first instar larvae to sea water for 1 hour killed 0.5% of *An. farauti* 1 larvae but >99.1% of *An. farauti* 2 and 3 larvae.\(^{36}\)
Of the 12 species of anophelines collected from 620 sites, the 9 most common were *An. farauti* 1 (128 sites), *An. farauti* 2 (67 sites), *An. farauti* 3 (93 sites), *An. annulipes* (335 sites), *An. bancroftii* (181 sites), *An. meranaukensis* (162 sites), *An. hilli* (88 sites), *An. amictus* (93 sites), and *An. novaguinensis* (70 sites). All species were found in areas with rainfall above the 1200 mm p.a. isohyet, but only *An. annulipes* and *An. amictus* were found below the 1000 mm p.a. isohyet. While the breeding of most species was dependent on adequate rainfall, *An. farauti* 1 and *An. hilli* also required brackish water. Geographically, the distribution of the three isomorphic species of *An. farauti* varied from one area to another. *An. farauti* 1 was common along all coastal areas of northern Australia. *An. farauti* 2 was the most common and widespread of the three isomorphic species in Cape York Peninsula, while *An. farauti* 3 was the most abundant species in inland areas of the Northern Territory.\(^{27-30}\)

Operation Anopheles indicated the wide distribution of various species of the *An. farauti* taxon, the main malaria vectors in northern Australia. As vast tracts of the Northern Territory and northern Queensland within the range of these species are frequently used by the ADF for training exercises, they remain a potential threat to ADF personnel if malaria is reintroduced into Australia. In 1989-1990, about 1000 malaria cases were imported annually into Australia, of which about 1 in 20 were in Army personnel returning from overseas exercises. A small malaria outbreak did, in fact, occur in northern Queensland. Although it was not related to any movement of military personnel, it illustrated the importance of prompt malaria diagnosis and treatment to decrease the likelihood of gametocytes infecting local vector mosquitoes.

Potential of Microsporidia for mosquito control. Earlier field observations at Mildura conducted by AMRU had discovered a microsporidian – *Amblyospora annulirostris* mosquitoes in Mildura, Victoria.\(^5\) With the support of research grants from the National Health and Medical Research Council and the World Health Organization, the complete life cycle of *Amblyospora* in mosquitoes and the copepod intermediate host was established. This provided the opportunity to evaluate the potential value of these parasites as biological control agents of mosquitoes.

The particular *Amblyospora* species infecting *Cx. annulirostris* mosquitoes and *Mesocyclops albicans* copepods was described as *Amblyospora dyxenoides*.\(^{42}\) Its infection rates in copepods were directly proportional to the concentration of spores (derived from dead infected mosquito larvae) to which they were exposed.\(^{41}\)

Subsequent studies with another microsporidium - *Amblyospora indica* – infecting *Culex sitiens* (with *Apocyclops* as the copepod intermediate host) showed that its life cycle was similar to that of *Amblyospora dyxenoides*. Furthermore, the developmental stages of these two microsporidia looked to be the same in both mosquito hosts and also in the different copepod species.

The possibility that these two microsporidia were the same species was investigated by host specificity experiments in which spores produced in both mosquitoes were exposed separately to the two copepods. The results indicated that spores from *Cx. annulirostris* were not able to infect *Apocyclops* sp. copepods and that spores from *Cx. sitiens* were not infectious to *M. albicans*. Further experiments showed that copepod spores produced in *M. albicans* were infectious to *Cx. annulirostris* larvae but not to *Cx. sitiens* larvae. Similarly, spores from *Apocyclops* copepods were infectious to *Cx. sitiens* but not to *Cx. annulirostris* larvae. These findings suggested that there was a high level of specificity of these microsporidia in their invertebrate hosts.\(^{42}\)

A computer simulation model of the dynamics of *A. dyxenoides* in its mosquito and copepod hosts showed that the biological complexity of this host-parasite system made it difficult to adequately assess its potential for control of mosquito populations.\(^{43}\) Moreover, there were technical problems in the production of inocula for field release that would have to be solved before this approach could be implemented, including the artificial culture of microsporidia and the mass laboratory rearing of spores in copepods or mosquito larvae.\(^{44}\) Even though the specificity experiments were based on only two mosquito/copepod combinations, each *Amblyospora* species probably only infects a single mosquito host species, thereby preventing its biocontrol potential against a range of disease vectors. For these reasons it was concluded that, on the basis of current knowledge, such parasites could not be considered as promising biological control candidates of mosquitoes.

No further investigations with any other potential biological agents were carried out, including some that were discovered accidentally during Operation Anopheles in northern Queensland. They included *Culcinonemes bisporalis*, *Crypticola clavulifera* and *Lagenidium giganteum*; observed in mosquito and biting midge larvae living in water contained in plant leaf axils near Millaa Millaa.\(^{45-46}\)
Insect repellents

Deet – applied to skin. The topical application of mosquito repellents was (and continues to be) an important means of protecting oneself against malaria. The ADF mosquito repellent, a liquid formulation containing 95% diethylmethylbenzamide (also known as diethyltoluamide, commonly called deet) in ethanol, felt oily when applied to skin and was not particularly well accepted by soldiers in the field. As there was also some concern about the safety of using such high concentrations of deet, studies were undertaken by AMRU to evaluate alternate approaches to reducing vector-human contact.

A novel approach, developed by a chemist in Melbourne, was to incorporate 20% deet and 0.5% permethrin in a bar of soap, and using it as a repellent by rubbing moistened soap onto the surface of the skin. When field studies were undertaken at Homebush Bay, Sydney and the Cowley Beach Training Area in Queensland, the soap formulation provided protection against mosquitoes for only one hour, much shorter than the ADF mosquito repellent.

Permethrin – impregnated in uniforms and bednets. Another field study at Cowley Beach was conducted using an alternative approach for repelling mosquitoes – the impregnation of clothing with permethrin, a synthetic pyrethroid compound. The results showed that impregnated jungle green uniforms prevented more mosquitoes from biting than untreated ones.

In 1989, permethrin-impregnated uniforms and bednets were first used by ADF personnel during their service with the UNTAG Mission to Namibia. The effectiveness of permethrin impregnation was monitored by placing swatches of fabric in the pockets of Disruptive Pattern Combat Uniforms (DPCU) and by attaching them to ADF bednets before treatment. Samples returned to AMRU by the health officer for chemical analysis showed that the treatment was carried out successfully. Furthermore, bioassay of the samples showed a marked knockdown and mortality of An. farauti mosquitoes. However, due to operational limitations, it was not possible to determine how long the permethrin treatment persisted in DPCU.

Also in 1989, the persistence of permethrin in bednets was investigated in collaboration with the World Health Organization entomologist in Honiara, Solomon Islands. Net samples used in the field evaluation of impregnated nets on Guadalcanal were sent to AMRU before treatment and 2, 5, and 8 months after treatment. Chemical analysis and bioassays showed that permethrin persisted in treated nets for 8 months, but was lost more readily from the bottom of nets, probably due to abrasion after handling.

Deet combined with permethrin. In a collaborative project with the Letterman Army Institute of Research, US Army, the efficacy of 2 new ‘controlled release’ formulations of deet and the US Army’s standard repellent (75% deet in ethanol) were compared with each other at the Cowley Beach Training Area. In addition, mosquito biting activity was determined when each of these topical skin applications were used in combination with permethrin-impregnated uniforms. This was the first US Army/ Australian Army entomological research undertaken since World War II. The 3 deet formulations and the impregnated uniforms had similar repellent activity. However, when any of the deet repellents were used in combination with the impregnated uniforms, there was a marked decrease in mosquito biting activity.

Repellents against “Chiggers”. Studies were also carried out to evaluate the activity of various repellents against the chigger mite, Eutrombicula hirsti. Trombiculid mites can transmit scrub typhus, a potential public health problem for soldiers in northern Australia. They are also responsible for ‘Scrub Itch’, a painful condition which is often encountered by soldiers in the wet tropics. After establishing a colony of these mites and studying their biology, repellent studies showed that low concentrations of deet, dimethylphthlate, benyl benzoate and permethrin were highly toxic to chiggers. A subsequent field study conducted in 1990 at Cowley Beach Training Area showed that Disruptive Pattern Combat Uniforms treated with permethrin and dibutylphthalate provided excellent protection against E. hirsti chiggers.
These investigations represented the first Australian research in this field since World War II.

Conclusion

The first half of the third decade (1985-1990) was characterised by greater emphasis on practical problems facing ADF personnel in malarious areas. *In vitro*, *in vivo* and *ex vivo* tests and procedures were used successfully to investigate the increasing prevalence of *P. falciparum* and *P. vivax* to standard antimalarial drugs. These investigations revealed, for the first time, that *P. vivax* could develop resistance to chloroquine, the standard drug used world-wide for the prevention and treatment of vivax malaria. Laboratory and field studies were also able to identify potentially useful drugs and drug combinations for preventing drug-resistant malaria infections. Although wider biological control of mosquitoes proved difficult, significant advances were made in identifying repellent formulations and procedures for providing better personal protection against mosquitoes and other arthropods. As northern Australia remains receptive to malaria, the Unit conducted the most extensive survey of anopheline mosquitoes and characterisation of malaria vectors ever performed in that region.

Acknowledgement

The opinions expressed are those of the authors and do not necessarily reflect those of the Joint Health Command or any extant Australian Defence Force Policy.

Highlights

1985
• Colonel Eric Donaldson appointed fourth Director (up to 1987).
• Professor Karl Rieckmann appointed Director of Medical Research.

1986
• *Plasmodium falciparum* *in vitro* studies with Mannich base compounds (up to 1990).
• Annual surveys and characterisation of anopheline mosquitoes in northern Australia (up to 1990).
• Experiments with microsporidia (*Amblyospora*) for biocontrol of mosquitoes (up to 1990).

1987
• *Ex vivo* and pharmacological studies with proguanil and low-dose dapsone.
• Trials with topical mosquito repellents and insecticide-impregnated clothing and bed nets (up to 1990).

1988
• First documented evidence of *P. falciparum* resistance to Maloprim in PNG.
• Attempts at transmission of cultured *P. falciparum* via mosquitoes (up to 1988).

1989
• Professor Karl Rieckmann appointed fifth Director (up to 2006).
• Discovery that *P. vivax* is able to develop resistance to chloroquine.
• Course of chloroquine-resistant *P. vivax* infections in non-human primates and their cure by amodiaquine.
• Evaluation of doxycycline and mefloquine for malaria prophylaxis.

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Aspiration Risk Increases With Healthy Ageing as Determined by a Novel Technique

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Purpose
Difficulty swallowing (dysphagia) is common and becomes more prevalent with advancing age. It affects over 40% of otherwise healthy individuals over 70 years old and 60% of patients in aged care facilities\(^1\). The Swallowing Risk Index (SRI) is a novel approach that provides objective information regarding swallowing function without the use of x-rays. SRI is derived from measurements taken in the throat (pharynx) during swallowing using a manometry device that measures pressure and flow simultaneously. Correlation of SRI with x-ray swallowing studies shows a score of over 15 indicates a high risk for aspiration of swallowed contents into the lungs\(^2\). We investigated the effect of ageing on SRI.

Methods
Studies were performed in 29 healthy adults aged 20-59 (mean 36±2 years) and 33 aged 60-93 (mean 75±2 years). No participant reported swallowing difficulties. Measurements were made by swallowing liquid and jelly boluses (5x5ml and 5x10ml) using a solid-state manometry-impedance catheter (OD 3.2mm, 25 pressure sensors at 1cm, 12 impedance segments at 2cm). Computer based software was used to derive swallow functional variables. These included the upper and lower pressures reached within the throat, as well as the time taken for the boluses to pass through the throat and into the upper oesophagus. The amount of material that remains behind after swallowing was also determined. The SRI was derived by using a validated formula\(^2\).

Results
Older age was associated with increased SRI, although the mean SRI remained below the significant cut-off value of 15 for all age groups (Figure 1). Increasing age was associated with lengthening the pharyngeal flow interval variable, indicative of reduced clearance of material after swallowing. Other swallowing variables were not affected by increasing age. Larger bolus volumes increased movement strength and speed through the throat area, leading to a lower risk of aspiration.

Conclusions
SRI increases with increasing age, but can reach the cut-off value indicative of aspiration set previously at 15. As the majority of patients with swallowing difficulties are older, this data forms an important baseline for comparison for subjects affected by swallowing difficulties. SRI potentially shows subtle deterioration in swallowing function can be quickly, objectively and non-radiologically assessed, allowing for early intervention before major symptoms develop.

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Figure 1: Mean Swallowing Risk Index (SRI) in healthy participants

*p<0.05 when compared to healthy participants aged less than 60 years

The Rate of Upgrading of Trus Biopsy Results in Intermediate Risk Prostate Cancer
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Purpose
Prostate cancer is the most common newly diagnosed cancer in Australia, with males under 75 years old having a 1 in 7 risk of developing prostate cancer, rising to 1 in 5 before the age of 85 \(1\). As of March 2012, there are approximately 116771 males over the age of 55 who are Veterans Gold and White card holders, which comprises 49.3% of all Gold and White card holders, including females\(^6\). Therefore prostate cancer is a significant and
prevalent health issue for both the Veteran and wider Australian community.

There are a variety of treatment options available for prostate cancer, including radiotherapy, active surveillance and watchful waiting. These may avoid the significant risks of surgery which include incontinence and impotence, and may in some cases avoid treating patients who may not have required treatment for their prostate cancer.

Currently Transrectal Ultrasound (TRUS) guided biopsy is the standard method of diagnosing prostate cancer. It is known that this is associated with false negative results (missed cancers) as well as false ‘true positive’ results, which represent under grading.

Under grading is a significant issue when considering non-surgical treatment options because:

- The true grade and extent of the prostate cancer is usually never determined as the entire prostate is not removed for pathological examination.
- Higher grade prostate cancer may not be suitable for less invasive treatment options, potentially compromising patient survival and outcomes.
- Gleason 7, Intermediate risk prostate cancer is an important group because these patients are generally considered for Surgical, Non-extirpative and Active Surveillance treatment options.

Method

This study utilises the South Australian Prostate Cancer Clinical Outcomes Collaborative (SA-PCCOC) database which is located at the Repatriation General Hospital. The SA-PCCOC database collects prostate cancer information from approximately 50% of all new prostate cancer patients in South Australia.

During the time period of 1996-2010, a total of 531 patients with Gleason 7 prostate cancer who subsequently underwent a radical prostatectomy were identified.

Multivariate and univariate analysis were also performed to assess factors involved with upgrading.

Results

The incidence of the TRUS biopsy correctly reflecting the grade of prostate cancer in the radical prostatectomy specimen was only 62%. Depending on Gleason grade subtype, between 16-27% of patients had their prostate cancer upgraded after their radical prostatectomy.

Conclusions

This research indicates that upgrading of prostate cancer in intermediate risk patients is substantial. This has implications for the counseling of patients, especially when considering non-extirpative treatment, as these options may not be suitable for a proportion of patients. However it must be appreciated that prostate cancer grade is only one aspect in treatment choice and a holistic approach including patient expectations, comorbidities and lifestyle must be utilised.

Currently further research utilising the SA-PCCOC database is being undertaken to determine methods through which the rate of prostate cancer upgrading may be able to be reduced.

References


Predicting bladder cancer death amongst veterans

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Purpose

The association between smoking and bladder cancer is well established.1 Due to the high incidence of smoking, bladder cancer is a disease more prevalent in the veteran population than the civilian population.2 The Repatriation General Hospital currently maintains a Bladder Cancer Outcomes Database which collects data relating to all newly diagnosed cases of bladder cancer in veterans and non-veterans, including patient characteristics, histological grade, staging and disease progression. The purpose of this study was to compare characteristics between veteran and non-veteran subjects diagnosed with bladder cancer, to identify independent predictors of death in these populations and to explore the potential for reducing bladder cancer deaths.

Methods

Using the established Bladder Cancer Outcomes Database, all cases between 1st January 1978 and 19th December 2011 were identified. There were a total of 1466 patients identified, 1177 of which were matched to veteran status. The data was analysed using SPSS software. Kaplan Meier and Cox’s Regression models were used for univariate and multivariate survival analysis respectively.
Results

Overall, there was no significant difference in outcome between veteran and non-veteran subjects. The five year survival rate of veterans was 82.5% compared with 85.3% for non-veterans. In both groups, the staging of disease at diagnosis was the strongest independent predictor of outcome. Patients with T1 disease had 5 times (HR 5.8, 95% CI 2.9, 11.8) the risk of bladder cancer death compared with Ta disease, whilst patients with T2 at diagnosis had over 14 times the risk of death (HR 14.8, 95%CI 6.8, 32.1). Stage at diagnosis was a stronger independent predictor than either grade or age at diagnosis in a multivariate model including veteran status.

Conclusion

The Bladder Cancer Outcomes Database is a useful tool for assessing and benchmarking the outcomes for the mixed veteran and civilian population in the Repatriation General Hospital. Given that stage at diagnosis is the strongest independent predictor of bladder cancer death, a program aimed at early detection for those groups at high risk, such as veterans and others with extended smoking histories, may be successful in improving outcomes from bladder cancer.

References


The Impact of Commonly Used Medicines on Urinary Incontinence: An Example of Using Administrative Health Claims Data to Improve Primary Care Practice.

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Purpose

To demonstrate how a health promotion based quality improvement program utilises routinely collected administrative claims data to identify medicine related problems in an elderly population, then uses this data to bridge the evidence-practice gap to improve use of medicines and health outcomes.

Methods

Retrospective analysis of the Australian Government Department of Veterans’ Affairs health claims database identified veterans dispensed a continence aid and/oxybutynin or propantheline between 1st January to 31st December 2009. The Australian Medicines Handbook, Meyler’s Side Effects of Drugs, MIMS online and published reviews were searched to identify medicines with the potential to worsen urinary incontinence. Prescription symmetry and event analyses were conducted to determine the extent to which initiation of these medicines was associated with initiation of oxybutynin. The Australian Government Department of Veterans’ Affairs Veterans’ MATES program then utilised the administrative claims data to provide direct patient-based feedback to medical practitioners about dispensed medicines associated with urinary incontinence. Supporting educational material developed by a clinical panel was provided to medical practitioners, continence nurses and pharmacists. Veterans who met the target criteria were mailed educational brochures.

Results

25,301 veterans were included in the initial study. 90% (n=22,858) were dispensed a medicine with the potential to aggravate incontinence during the study period, with 47% dispensed three or more. Commonly dispensed medicines that could cause or aggravate incontinence included diuretics (42%, n=10,558), sedatives (35%, n=8,857) and calcium channel blockers (31%, n=7,718). Increased rate of initiation of oxybutynin occurred after initiation of hypnotic and sedative benzodiazepines (adjusted sequence ratio (ASR) 1.16; 95% CI 1.07-1.26), SSRIs (ASR 1.12; 95% CI 1.03-1.23) and calcium channel blockers (ASR 1.40; 95% CI 1.28-1.55).

Direct patient-based feedback and supporting educational materials were distributed to 10,588 medical practitioners. Supporting educational material was distributed to 7,988 pharmacies, 282 continence nurses and 27,414 veterans. Preliminary evaluation revealed that the percentage of targeted veterans who discontinued a medicine with the potential to aggravate urinary incontinence, was higher than historical comparison groups following the intervention. Discontinuation of medicines appeared to be attributable to the cessation of anticholinesterases and typical antipsychotics. The data-driven intervention appeared to be well received.
with 91% of responding medical officers reporting the material to be useful and 81% indicating that at least one of their identified patients required a review.

Conclusion
The use of pharmacoepidemiologic data can aid the design, delivery and evaluation of interventions to improve the use of medicines and health outcomes for patients.

Patient and Caregiver Satisfaction of the ‘Initial Assessment Psychosocial Clinic Palliative Care’
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Introduction
The evaluation of the Initial Assessment Psychosocial Clinic Palliative Care is a model that has been introduced as a quality improvement exercise after the palliative care service underwent a process of self assessment against the National Standards Assessment Program (NSAP). The palliative care service was unable to demonstrate a systematic way in which patients and caregivers receive an interdisciplinary assessment focusing on all the domains of ‘total’ care. The palliative care service is very strong in attending to physical issues and signs of obvious distress, however a process that enables early identification of issues across the whole domain can now be delivered through this new model of care.

Inclusion for the clinic
New referrals to palliative care which are triaged as ‘clinic only’ will be eligible for this service. This triage criteria means that the patient has a high functional score and is well enough to attend a clinic setting for a duration of approximately 90 minutes. The focus of service delivery is based on initial assessment, education and health promotion especially for the primary caregiver.

Methodology
Patient and caregiver satisfaction surveys were developed based on existing tools from the Palliative Care Outcomes Collaborative, and the Palliative Care National Standards Assessment Program. These questionnaires were posted out with a reply paid envelope to patients and their caregivers.

Results
41 patients attended the GP Plus clinic between September 2011 and February 2012. Of those 41 patients that attended 4 attended alone without a caregiver. Of a possible 78 questionnaires sent out to both patient and caregiver we had 36 returned which gave us a 50% return rate.

24 questionnaires were from both patient and caregiver, 4 questionnaires were from carers only, 6 were from patients only, and 2 were from bereaved caregivers.

6 patients died within the study time, and 2 patients died within 3 weeks of attending the clinic.

Outcomes
Overall there were very positive responses to the nature of the clinic. Patients provided a satisfaction rate of 82% - 89% for time with the Nurse Practitioner, 82%-94% for time with the Social Worker and 80%-94% for time with the Psycho-Oncology Nurse. With the exception of the Social Work Clinic caregiver satisfaction scores were generally a little lower with 79%-83% satisfaction with the Nurse Practitioner, 82%-93% satisfaction with the Social Worker and 83%-87% satisfaction with the Caregiver Network Facilitator. Patients appreciated the opportunity for privacy to discuss their own fears and concerns related to the illness in 94% of responses which compared to 83% of caregivers. Qualitative comments support the structure and value of the clinic however further evaluation is proposed to assess the benefit to the referring health care providers.

Suicidality in the Australian Defence Force: Results from the 2010 ADF Mental Health Prevalence and Wellbeing Survey
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Background and Aims
The prevalence of suicide in the US military is increasing and may soon surpass general population rates. Predominantly, non-fatal suicidality precedes completed suicide, thus focusing on non-lethal suicidality among personnel presents an important intervention opportunity. However, comparisons across existing studies are made difficult as a result of differing methodologies, differing military service populations, currency of service and small female sample sizes.

This study aims to investigate prevalence and likelihood of mild and serious ideation, suicide plans and attempts in a representative sample of the entire Australian Defence Force (ADF). Likelihood of non-lethal suicidality is also examined by sex, service, rank, deployment, psychiatric disorder, and trauma.
Methods
The ADF Mental Health Prevalence and Wellbeing Study obtained a representative sample of 24,481 currently serving regular personnel in the Navy, Army and Air Force. Self-report questionnaires were utilised. A subsample also consented to CIDI telephone interviews.

Results
Mild and serious ideation, suicide plans and attempts were reported by 6.7% [95% CI 6.4-7.0], 3.9% [95% CI 3.7-4.1], 1.1% [95% CI 1.0-1.2], and 0.4% [95% CI 0.3-0.5] ADF personnel, respectively. Likelihood of non-lethal suicidality varied in relation to sex, service, rank, trauma, occupational factors and psychiatric diagnoses.

Conclusions
Rates of non-lethal suicidality among ADF personnel are significantly higher than prevalence found in the Australian civilian community, except suicide attempt. Elevated likelihood of suicidality among personnel with psychiatric diagnoses and/or trauma underscores the relevance of identification and support services.

Effectiveness of Screening for Chronic Obstructive Pulmonary Disease (COPD) in Royal Australian Air Force Aircrew
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Purpose of study
COPD has the potential to impact upon fitness for flying duties. Over a ten-year period between 2000 and 2010 no cases of COPD within the RAAF aircrew population were notified to AVMED as the regulatory authority, thus theoretically denoting a zero prevalence of disease across an approximate 20 000 person-year observation period. Such a low reported prevalence is in stark contrast to the prevalence of COPD in the general community.

This study aimed to validate the effectiveness of extant screening occupational medical examinations for RAAF aircrew in early detection of COPD. A secondary objective of this study was to ascertain the prevalence of cigarette smoking (as the primary risk factor for development of COPD) within the RAAF aircrew population.

Methodology
Eligible aircrew subjects (≥ 35yrs age) were screened using a simple proprietary questionnaire for COPD, followed by office spirometry (PiKo-6TM) if a positive questionnaire response was declared. Positive PiKo-6TM spirometry results were further assessed against results of previous spirometry as undertaken at time of prior routine occupational medical examination.

Results
141 out of an eligible 205 (68.8%) subjects participated in the study, with 27% of participants being current or former smokers. 11 positive PiKo-6TM spirometry results were observed, with review of past spirometry records for these subjects demonstrating one highly-probable case of COPD. A further 6 subjects had markedly abnormal spirometry results not thought likely to reflect COPD, but for which further investigation was recommended.

Conclusions
Whilst the true prevalence of COPD within the RAAF aircrew population is not thought to be as high as the general population, this study has demonstrated that the true prevalence is unlikely to be zero. Results from this study highlight several areas for improvement in routine spirometric screening of RAAF aircrew.

Identifying Psychological Disorder in the Australian Defence Force: The Diagnostic Validity of Three Screening Scales
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Purpose
Depressive, alcohol and post-traumatic stress disorders are the most prevalent disorders among Australian Defence Force (ADF) members. The ADF routinely screens for these disorders using three well-known psychological scales – the Kessler Psychological Distress Scale (K10), the Alcohol Use Disorders Identification Test (AUDIT), and the Post-traumatic Stress Disorder Checklist (PCL). However, it is unknown whether their established cut-off scores are applicable to ADF members. This has important implications given that ADF members’ scores may ultimately result in receipt of much-needed treatment, or conversely, social stigma or harm to members’ careers (through the inability to deploy, being made inactive, or discharged). This study is the first to test the diagnostic utility of these scales in a large and representative defence population (the ADF).
Methods

In the ADF Mental Health Prevalence and Wellbeing Study, a large and representative sample of currently-serving Navy, Army and Air Force members (n = 24,481) completed the K10, AUDIT and PCL scales. Then, a carefully-selected subsample (n = 1798) completed a structured diagnostic interview to detect 30-day disorder. Using demographic information from military records, data were then weighted up to represent the entire ADF population of 50,049 members.

Results

Results of ROC analyses showed that all three scales had adequate levels of sensitivity and specificity, with overall diagnostic efficiency ranging from .75 to .91. Optimal screening cut-offs for the K10, AUDIT and PCL were 17, 8, and 29, respectively. AUDIT and K10 cut-offs closely paralleled those established in the general population, whereas the optimal PCL cut-off more closely resembled that recommended for US military personnel, rather than the established general population cut-off. All optimal cut-offs were very similar to those already used by the ADF.

Conclusions

These three brief self-report scales represent a cost-effective and clinically useful means of screening for psychological disorder in the ADF. Results also support the assertion that defence populations may need a less-stringent cut-off than civilian populations to screen for post-traumatic stress disorder.

Mild Traumatic Brain Injury (mTBI) in the Australian Defence Force (ADF): Results from the 2010 ADF Mental Health Prevalence and Wellbeing Dataset

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Purpose

The occurrence of mild traumatic brain injury (mTBI) has attracted much attention in recent years. This has emerged due to a suspected increase in mTBI, thought to be the result of increased use of explosive devices in combat in the last decade. Accurate prevalence estimates of mTBI are extremely difficult to ascertain given the non-specific nature of post-concussive symptoms, measurement issues (to determine the degree of combat exposure), variation in deployment length as well as cultural differences such as compensation practices and healthcare systems across countries. Understanding mTBI in the context of deployment is important owing to the implications for healthcare provision, deployability status and compensation for affected veterans. As such, there is a distinct lack of epidemiological estimates of mTBI in military populations, including the Australian Defence Force that needs to be addressed. This presentation will examine the lifetime prevalence of self-reported head injury in a representative sample of the ADF.

Methods

Using data from the 2010 ADF Mental Health Prevalence and Wellbeing Study, this study examines the prevalence of mTBI in the context of mechanisms of injury, frequency of reported post-injury symptoms, differences between deployed and non-deployed groups, and relationships between injury and various psychiatric disorders.

Results

In total, 28.3% of ADF personnel have experienced at least one mTBI in their lifetime. Over twelve per cent of the ADF reported being exposed to a blast or explosion IED, and 14.0% reported being exposed to an RPG. The most prevalent cause of mTBI was motor vehicle accidents (MVA) with MVAs and falls carrying a greater risk of mTBI than blast exposure. ADF members with a lifetime mTBI were more likely to be male, in the Army, older in age, junior in rank and less likely to have been on operational deployment. mTBI was associated with a significantly increased risk of all domains of psychological disorder.

Conclusions

Given the evidence of increasing risk of permanent sequelae associated with repeated mTBI, solely focusing on the deployment exposures will miss the fact that many ADF members are likely to have had mTBI prior to deployment from non-combat related causes. From a public health perspective, the prevention of motor accident trauma in the ADF needs to be addressed in any policy about mTBI. The high prevalence of falls as a cause of mTBI suggests the risks associated with training and should not be underestimated from an occupational health and safety perspective.
Off-Label Prescribing in Palliative Care – a Cross-Sectional National Survey of Australian Palliative Medicine Doctors

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Introduction
Regulatory bodies such as the Food and Drug Administration (United States) register specific medications (formulation and strength) in specific doses (range, frequency and duration) for specific indications (population and disease). Once registered, medications may be prescribed at clinician discretion. Off-label use is beyond the registered (licensed) uses. Whilst off-label prescribing is prevalent and may be clinically appropriate, such prescribing may expose the patient to uncertain efficacies and increased risks of toxicities.

Purpose
To examine the understanding and practice of off-label prescribing in Australian palliative medicine clinicians.

Methods
A cross-sectional survey of palliative medicine clinicians examined understanding and practice of off-label prescribing. Participants were asked about off-label prescribing, consent and commonly used off-label medication/indication dyads. These were classified into off-license, off- and on-label, and whether medications were reimbursed.

Results
105 clinicians responded (53% response rate). The majority had poor documentation of consent. 236 medication/indication dyads were proposed, covering 36 medications. 45 dyads (19%) involving two medications were unlicensed. 118 dyads (50%) involving 26 medications were off-label, and the remaining 73 dyads (31%) involving 12 medications were actually on-label.

Conclusion
Off-label prescribing is common, not guided by clearly defined policy, and is often poorly recognised. This has clinical, legal and ethical implications for the management of complex palliative care patients. Further research is required to determine the prevalence, clinical benefit and resultant iatrogenic morbidity and premature mortality, particularly of commonly used off-label medications. System level policy on off-label prescribing is required to protect patients and clinicians.
A Randomised, Double-Blind Placebo Controlled Study to Assess the Efficacy and Toxicity of Subcutaneous Ketamine in the Management of Cancer Pain


Southern Adelaide Palliative Services, Repatriation General Hospital

Background
The dissociative anaesthetic ketamine is widely used for pain related to cancer, usually in conjunction with opioids. The evidence to support its use in this setting has come primarily from uncontrolled studies. A Cochrane review was able to include only two small studies and concluded that insufficient evidence was available to support its use.

Methods
This phase III, multi-site double-blind, dose escalation, placebo randomised controlled study aimed to determine whether ketamine, delivered subcutaneously over three to five days is more effective than placebo, when used in conjunction with opioids and standard adjuvant therapy in the management of chronic uncontrolled cancer pain. Ketamine would be considered to be of net benefit if it provided clinically relevant improvement in pain, defined as a reduction in average pain scores by ≥2/10 points from baseline, with limited breakthrough analgesia and acceptable toxicity.

Findings
One hundred and eighty five participants were included in the primary analysis. There was no significant difference between the proportion of positive outcomes (0.04 (-0.10, 0.18) p=0.55) in the placebo and intervention arms (response rates 27% (25/92) and 31% (29/93)). Pain type (nociceptive versus neuropathic) was not a predictor of response. There was almost twice the incidence of adverse events worse than baseline in the ketamine group after day one (IRR = 1.95 (1.46, 2.61), p<0.001) and throughout the study. Those receiving ketamine were more likely to experience a more severe grade of adverse event/day (OR=1.09 (1.00, 1.18), p=0.039). The number needed to treat for one additional patient to get a positive outcome from ketamine was 25 (6, ∞). The number needed to harm, because of toxicity-related withdrawal was 6 (4, 19).

Interpretation
Ketamine does not have net clinical benefit when used as an adjunct to opioids and standard co-analgesics in cancer pain.

Funding
Palliative Care Branch, Australian Government Department of Health and Ageing.

Influence of the Ipsilateral Motor Cortex on Functional Performance in Unilateral Transtibial Amputees

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Purpose of Study
Each year approximately 35 lower-limb amputees undertake prosthetic rehabilitation at the Repatriation General Hospital (Hordacre et al. 2012). The aim of prosthetic rehabilitation is to restore function and mobility to ensure a safe re-integration into the community. Contemporary rehabilitation practices are based on restitution of function using neuroscientific principles of promoting adaptive neuroplasticity in the human brain.

The primary motor cortex (M1) in both hemispheres undergoes extensive neural reorganisation following amputation of a peripheral limb (Chen et al. 1998; Kaas & Qi 2004; Schwenkreis et al. 2003). Up-regulation of the M1 ipsilateral to the amputation may increase descending drive to the residual limb via ipsilateral projections. It is unclear whether an increase in excitability of ipsilateral M1 is adaptive or maladaptive. Furthermore, the effect of current rehabilitation practices on neural reorganisation after amputation has not been elucidated and may or may not be optimum to drive adaptive neuroplasticity within M1.

The purpose of this study was to investigate if the balance in excitability between ipsilateral and contralateral M1 innervating the quadriceps muscle of the amputated limb is related to lower-limb function. This was assessed using transcranial magnetic stimulation (TMS) to quantify M1 activity bilaterally, and calculate ratios reflecting interhemispheric excitability. These measures were then correlated with validated assessments of gait and function in unilateral transtibial amputees.

Methods
Community dwelling unilateral transtibial amputees with varying levels of function and time since amputation were recruited from a satellite prosthetic service located at the Repatriation General Hospital. Single-pulse TMS was used to evoke motor evoked potentials and generate stimulus-response curves from M1 contralateral and ipsilateral to the amputated limb, and M1 contralateral to the non-amputated limb.
The slope from the steepest part of the curves was determined and used to calculate an Index of Corticospinal Excitability (ICE) for the amputated limb and a Laterality Index (LI) for both limbs.

General amputee function was assessed with a standardised amputee assessment (AMP-PRO), and gait parameters were assessed using a Gait Rite walkway system. Linear regression was used to assess relationships between neurophysiological and functional measures.

Results
Preliminary results indicate that unilateral transtibial amputees with negative ICE (more lateralised to ipsilateral M1) were associated with less step time variability on the amputated limb, and a greater asymmetry in step length between amputated and non-amputated sides. Amputees with negative LI values (more lateralised to M1 innervating the non-amputated limb) were associated with greater step time variability on the non-amputated limb and lower functional scores on the AMP-PRO assessment.

Conclusions
Greater excitability of ipsilateral corticomotor projections to the quadriceps muscle on the amputated limb negatively influences features of gait in transtibial amputees. These results require further investigation, but may have implications for targeted neurophysiological interventions during rehabilitation aimed at improving function and mobility in these patients.
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