

Human research ethics in the Australian Defence Force

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Our God-given mission as doctors is to challenge all varieties of disease-causing microorganisms...and to devise the most expeditious treatment possible. However, the research upon which we are now to embark is the complete opposite of these principles, and may cause us much anguish as doctors. Nevertheless, I beseech you to pursue this research based on the double medical thrill: one as a scientist to exert effort in probing for the truth in natural science; and two, as a military person, to successfully build a powerful military weapon against the enemy.¹

THE LOYAL MILITARY PHYSICIAN serving in the Japanese Army's notorious Unit 731 was apparently unconcerned by the dilemma confronting him. Indeed, he conveniently linked the goals of medical research with the military mission, despite his unit's involvement in human vivisection, biological weapons testing, and freezing experiments. Sadly, the Japanese Army was not alone in its corruption of the Hippocratic Oath. Perhaps more infamous was the state of confusion between the caduceus and swastika in Germany, where 350 physicians participated in concentration camp atrocities during World War II.²

In both these cases, physicians facilitated human rights violations through silence during and after the event.³ In fact, by treating victims of these violations while remaining silent as to the cause of their plight, physicians have aided repressive regimes by shielding their human rights violations from public scrutiny.³

Increasing concern about human rights abuses, including the safety and conduct of research involving humans, led to the Declaration of Helsinki in 1964. The National Health and Medical Research Council (NHMRC) statement on ethical conduct of research involving humans was released in Australia in 1982.

Principles of human research ethics

More recently, the Belmont Report in the United States identified three basic research ethical principles.⁴ These are respect for persons, beneficence, and justice. These principles have been described so often, for example by NHMRC⁵ and Pearn,⁶ that most medical ethicists now accept them as self-evident.



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Abstract

- ◆ The Australian Defence Human Research Ethics Committee (ADHREC) was formed in 1989 and is committed to ensuring human research involving Defence personnel or on Defence property is conducted professionally and ethically.
- ◆ Major challenges for the committee are:
 - ◆ ensuring the committee meets the needs of the ADF and that researchers do not perceive the committee as too self-righteous;
 - ◆ dealing with the issue of informed consent in the "captive population" of the ADF;
 - ◆ determining whether proposed trials are in fact trials of drug safety (which the committee does not approve because of the issues of informed consent); and
 - ◆ addressing the growing number of requests for trials that involve performance enhancement, including likely requests for trials exploiting knowledge of the human genome.

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When these principles are combined with the National Privacy Principles,⁷ it is often assumed that Australian human research, including that conducted by the Australian Defence Force, is beyond criticism. However, this is not a "given", and depends upon ethical military and scientific leadership, and close scrutiny of research protocols to prevent the exploitation of "captive subjects" for commercial, military, athletic or academic gain.

ADHREC

The Australian Defence Human Research Ethics Committee had its origins in 1989.⁸ It is committed to creating and maintaining an environment in which research on humans undertaken on or by ADF personnel, or on Defence property, is conducted both professionally and ethically. ADHREC's mission is to promote and encourage health research in the military context.

Defence research ethics involves concerns in addition to informed consent.⁹ These include *a priori* intention to publish research undertaken in the military domain. In a sense, ADHREC "completes the publication loop" with its publicly released annual report and its annual report to the Australian Health Ethics Committee.

Informed consent

Military personnel are convenient subjects in the sense that they are usually normal, healthy people who can easily be followed up

The Australian Defence Human Research Ethics Committee, 2004



Back row, left to right: Mr David Dillon, Professor John Pearn, Colonel Peter Warfe, Lieutenant Commander Tammy Thomas, Air Vice-Marshal Bruce Short (Chair), Monsignor (Air Commodore) Peter O'Keefe, Chief Justice Terence Higgins, Colonel Glenn Wells, Dr Alan Twomey. Front row, left to right: Lieutenant Colonel Rosemary Landy (Executive Secretary), Lieutenant Colonel Vicky Ross, Mrs Elizabeth Grant, Mrs Kerrie Broderick.

for data collection for years.¹⁰ However, the question arises whether members of armed forces (or subjects within any disciplined or rigidly hierarchical organisation) could ever really be considered capable of providing completely voluntary consent.

In this regard, ADHREC notes that:

Research on humans which involves servicemen and women is, in many ways, unique. As a research population, the ADF is especially attractive. It is a large population, enjoying both a high level of physical fitness and readily available expert medical care. However, members of the ADF are also a captive population, whose working lives are regimented in a way that civilian personnel rarely experience. ADF personnel are subject to order in a way that civilian personnel are not, and for them the issue of voluntary consent is a particularly important and sensitive one. ADHREC exists to safeguard the rights of these men and women, the same rights that the civilian population expects to enjoy.⁸

The NHMRC is quite explicit on this matter: “The ethical and legal requirements of consent have two aspects: the provision of information and the capacity to make voluntary choice”.⁵ These are the fundamental issues which ADHREC has had to confront in relation to safety drug trials, physiological enhancing drugs, and “not-yet licensed” vaccines.

The large number of research protocols directed towards training institutions has also concerned ADHREC. In many cases, this is desirable, for example when addressing training injury prevention strategies. However, as Kahn noted, “students are captive in a different sense because their role is inherently lesser in power than the other members of the relationship”.¹⁰ With a more ominous tone, he noted that “the potentially coercive nature of being a student may arise from a course requirement that they serve as a study subject”. In this sense, an ADF recruit may be “twice a captive” and hence may be more attractive to over-zealous researchers or superiors.

Two further case studies represent a sobering and contemporary extension of the issue of health support to captive subjects. First, there are allegations of abuses by medical personnel of prisoners in Abu Ghraib prison in Iraq.¹¹ The second disturbing case concerns the recent detention of an apparently mentally ill

woman for six months in a Queensland jail, after being found in north Queensland. She was subsequently sent to South Australia’s Baxter Detention Centre in October 2004, where she was held for four months after telling authorities she was a German woman.¹² Initial anecdotal reports indicate that attending health staff may have supported her detention.

These cases are not primary failures of the application of human research ethical principles. However, they may be considered as inevitable outcomes when the same ethical constraints are not extended to captive populations. This is the overarching issue confronting the ADF.

Human research ethics challenges for the ADF

The main human research ethics challenges for the ADF appear to fall into four broad categories. First, ADHREC must ensure that researchers do not perceive the committee as excessively assertive and self-righteous. Second, the committee must ascertain which drug research trials are in actual fact safety trials of drugs or vaccines that cannot legally be undertaken in the country of manufacture. Third, ADHREC must concern itself with practical limitations of informed consent involving individual and collective protection using non-licensed drugs and vaccines. Finally, the committee will need to address an increasing number of requests for research trials enhancing physiological or cognitive performance by organisations that are prohibited from testing these modalities on their own populations. Inevitably, this will lead to research protocols designed to exploit the human genome.

An intrusive ADHREC?

Ethics committees in general are likely to be self-assertive, and are unlikely to accept a rubber-stamping role.¹³ ADHREC is no exception. Indeed, committee members probably would wish to demonstrate that they as individuals, and the committee as a whole, do in fact make a difference. This often results in questions that researchers may find irritating, time-consuming and apparently irrelevant. In fact, these queries are usually to clarify an ethical issue or better inform the committee so it can provide ethical clearance in the full knowledge of what the researcher proposes. Unless this process is clearly understood by both the committee and the research community, the discussion tends to drift into “what constitutes human research?”. In some research institutions, steps have been taken to avoid the perceived hurdle of having to submit research protocols to “ivory-tower” human research ethics committees.

In the case of the ADF, this process may differ as the Defence Science and Technology Organisation (DSTO) is considering establishing its own human research ethics committee. Perhaps this would be the best course of action for DSTO and the ADF. However, considerations on this matter should address how ADHREC is failing to meet the needs of the ADF or DSTO. If there are deficiencies, should they be corrected or referred to a separate committee? Is ADHREC too heavily weighted towards the biological sciences? Are there concerns that ADHREC’s present composition is too skewed towards full-time service representation in the largely civilian defence organisation? The challenge for ADHREC is to maintain its

ethical focus and duty of care rather than allowing the bureaucratic tensions to prevail.

Safety trials

The NHMRC has recently addressed the ethical issues in safety trials in its Human Research Ethics Handbook.¹⁴ This document describes the hierarchy of safety trials in the development of a new drug or vaccine. These include Phase I studies involving the first administration of the drug to humans, assessment of the safety of the drug and its pharmacological activity, metabolism and adverse reactions. Phase II studies are the first trials of a drug in patients with the targeted disorder, or of a preventive vaccine in disease-susceptible subjects. The aim of these studies is to determine efficacy (effectiveness) and safety. As a principle, ADHREC endorses neither Phase I nor II trials on ADF members because of their diminished autonomy as “captive” individuals.

Phase III studies involve greater numbers of participants and aim to determine whether the drug or vaccine provides clinical benefit in relation to the disease for which effectiveness was demonstrated in Phase II studies, and whether the incidence and nature of adverse effects are acceptable. ADHREC has endorsed such studies when there has been a demonstrable benefit for individuals from earlier studies, and particularly in the case of diseases of military importance, such as malaria. ADHREC has not endorsed proposed studies where the predicted therapeutic or preventive benefit may be inferior to existing drugs or vaccines.

When considering these protocols, ADHREC must be satisfied as to the safety of research subjects, including whether an adverse effect has emerged during earlier studies. What is critically important is that potential participants are fully informed of the risks of participating before making their choice.

The recent increase in litigation in human research has resulted in regulating authorities refusing to allow some safety trials to be conducted in their respective countries. This has led to some multi-national drug manufacturers redirecting their research efforts to countries with less rigorous regulatory control. ADHREC routinely questions international drug and vaccine manufacturers who wish to conduct trials in Australia, to determine why they have chosen to conduct the research outside their own country.

It appears likely that future human subjects research will move from a very flexible form of self-regulation to a more bureaucratically orientated system of oversight.¹⁵ If so, it is unclear where the balance may lie between individual protection and their future health care.

Informed consent and non-approved drugs and medications

The media debate about the use of anthrax vaccine during an operational deployment in 2004 provides an excellent case study of the tensions that exist between the operational mission, individual and collective protection, informed consent, epidemiology and military medicine.¹⁶

Without doubt, the ADF acted in the utmost interests of its members and to maximise mission success. However, sceptics

may ask if this was a case of waiving informed consent. This question has been explored generically by Rettig, who examined the differences between “research” and “treatment”. He also questioned whether informed consent can be waived, and if so, under what circumstances, and who has the authority to grant waivers?¹⁷

These questions are not easily addressed in ethical or practical terms. Although the ADF acknowledges and abides by informed consent, it also recognises the practical difficulties this may entail. It could be extremely difficult to obtain fully informed consent from every service member during a rapid troop deployment. Perhaps more importantly, allowing military personnel to refuse preventive drugs or vaccines may jeopardise the combat mission. Deployed personnel would either have to remain in the area of operations without protection (placing themselves at risk or increasing the danger to other service personnel), or face repatriation.

The ADF publication on immunisation procedures describes the administrative steps required for anthrax vaccination.¹⁸ Anthrax vaccine requires approval from the Australian Quarantine Inspection Service for importation, and from the Therapeutics Goods Administration for its administration. Although anthrax vaccines are not currently registered in Australia, their use may be authorised by the TGA, who will delegate the authority to allow administration of anthrax vaccine to specific medical practitioners within the ADF only. Authority is conditional on the Defence Health Service agreeing to ensure that ADF members who receive anthrax vaccine are fully informed of the risks and benefits of the vaccine as outlined. The overriding ethical principle is that the vaccine will only be administered in an environment of informed consent.

Performance enhancement studies

Performance enhancement is not a new concept for defence forces, which have devoted substantial efforts to educating both the minds and bodies of their personnel for centuries.

However, the scope to enhance human performance is changing rapidly with the development of a variety of modalities which increase strength and endurance, as well as improving cognition. Their military applications are obvious and appealing, but what are the risks and ethical issues in researching these promising techniques? The ADF is involved in international collaborative research programs investigating the use of physical performance-enhancing agents termed “erogenic aids”. These include caffeine and other agents which are evaluated in large studies, and have been scrutinised by numerous ethical committees.

These studies appear relatively straightforward, but what considerations should be addressed when researchers wish to address human hormone studies? During 1998, ADHREC was asked to consider a research program investigating the development of a test to determine whether individuals had been using a hormone, erythropoietin, whose effect is to increase an individual’s red cell mass and therefore enhance oxygen carrying capacity. This has obvious applications in athletic competitions and military operations. The study was designed to develop a blood test capable of detecting erythropoietin users, thereby discouraging the use of the

hormone. The test would be used to screen out “drug cheats” from international competition. However, ADHREC was concerned that the research organisation was unwilling to develop the test in its own athletic population, as the individuals would probably become permanently biochemically labelled as having used a synthetic hormone. ADHREC declined ethical clearance as the proposed test had little military application and could have had a deleterious effect on military athletes in future.

The human genome

The sequencing of the human genome is likely to have huge economic opportunities: “... now that all 30 000 or so genes that make up the human genome have been deciphered, pharmaceutical industries are emerging to capitalise the custom-based drug treatment”.¹⁹ Clearly, understanding human genetic variation promises to unravel the cause of individual variation in response to therapeutics and, perhaps, performance-enhancing agents. The study of the association between genetics and drug response is termed pharmacogenomics.

The ethical issues associated with this new science are like those that apply to all scientific developments.²⁰ First, society, industry, special interest groups and individuals view the prospect of pharmacogenomics very differently. Second, there is a lack of research into the implications of introducing pharmacogenomic agents into individuals, groups or society as a whole. The intensity of the debate on genetically modified foods probably provides the closest indication of what may be expected as this new field develops.

The key question is whether the various regulating authorities will be able to maintain oversight and control of myriad research programs involving so many ethical challenges. Historically, we have seen how the US-based Ethical, Legal, and Social Implications Research Program at the National Human Genome Research Institute provided ethical oversight of much of the work conducted unravelling the human genome.²¹ Planners of the Human Genome Project understood from the outset that the scientific activities of mapping and sequencing the human genome would raise ethical, legal, and social issues that would require careful attention by scientists, health care professionals, government officials, and the public. In future, will the Australian Office of the Gene Regulator, or another agency, be an effective instrument in this regard?

The challenge for the ADF will be to assimilate these new developments without sacrificing the current ethical principles and regulatory mechanisms.

Conclusion

I have attempted to examine the background, current state of affairs and challenges involving human research ethics in the ADF. I have deliberately highlighted two shocking examples of human research abuse, which occurred when military forces and researchers ignored the legal, moral and ethical foundations of their military forces and nations. The predictable outcomes of ignoring ethical standards within captive populations have also been outlined.

ADHREC takes great care to inform researchers, research subjects and the defence community of the objectives and

benefits of having a rigorous and transparent human research ethics committee. Hopefully, readers will see ADHREC as a beneficent “watchdog” rather than an overbearing “mad dog”.

In future, the ADF is likely to be confronted with increasing requests to participate in human research. These protocols will often arise from unexpected research organisations that possess ambiguous motivation and incentives to conduct their various projects. Unique and ethically provocative proposals for research on captive populations are likely to continue.

The overriding challenge for the ADF will be to meet its duty of care to the welfare of people who have committed themselves to its protection.

References

1. Ryohei S. Bacteriological warfare. *Sunday Mainichi* 1952; Jan 27.
2. Astor G. The “last” Nazi. The life and times of Dr. Josef Mengele. New York: Donald I Fine, 1968.
3. Lucas T, Pross C. Caught between conscience and complicity: human rights violations and the health professions. *Med Glob Surviv* 1995; 2: 106-114.
4. The Belmont Report: ethical principles and guidelines for the protection of human subjects of research. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Department of Health, Education and Welfare Publication No (OS) 78-0012 Washington, DC: US Government Printing Office, 1978.
5. National Health and Medical Research Council. National statement on ethical conduct in research involving humans. Canberra: NHMRC, 1999. Available at: <http://www7.health.gov.au/nhmrc/publications/synopses/e35syn.htm> (accessed Feb 2005).
6. Pearn J. Medical ethics surveillance in the armed forces. *Mil Med* 2000; 165: 351-354.
7. National privacy principles. *Privacy Act 1998* (Cwlth), section 95A and Schedule 3.
8. Australian Defence Human Research Ethics Committee. About ADHREC. Available at: http://www.defence.gov.au/DPE/DHS/infocentre/research/adhrec/adhrec_about.htm (accessed Feb 2005).
9. Landy R, Pearn J. Medical ethics in the Australian Defence Force. *Prof Ethics* 2000; 8: 23-30.
10. Kahn JP, Mastroianni AC, Sugarman J. Beyond consent: seeking justice in research. Oxford: Oxford University Press, 1998.
11. How complicit are doctors in abuses of detainees? [editorial]. *Lancet* 2004; 364: 637-638.
12. Shameful case forces change. *Sydney Morning Herald* 2005; Feb 8.
13. Pettit P. Institutionalising a research ethic: chilling and cautionary tales. *Bioethics* 1992; 6: 89-112.
14. National Health and Medical Research Council. Human research ethics handbook. Canberra: NHMRC, 2001. Available at: <http://www.nhmrc.gov.au/hrecbook/index.htm> (accessed Feb 2005).
15. Mello MM, Studdert DM, Brennan TA. The rise of litigation in human subjects research. *Ann Intern Med* 2003; 139: 40-45.
16. Hawthorne M. Defence chiefs admit vaccine side effects. *The Age* (Melbourne) 2004; Feb 21. Available at: <http://www.theage.com.au/articles/2004/02/21/1077072889431.html> (accessed Feb 2005).
17. Waiving informed consent. Military use of non-FDA approved drugs in combat. Rand Research Brief 7534. Santa Monica, CA: Rand Corporation, 2000. Available at: <http://www.rand.org/publications/RB/RB7534/index.html> (accessed Feb 2005).
18. Australian Defence Force Publication 1.2.2.1. Immunisation procedures. 25 June 2003.
19. Ganguly NK, Bano R, Seth SD. Human genome project: pharmacogenomics and drug development. *Indian J Exp Biol* 2001; 39: 955-961.
20. Moldrup C. Ethical, social and legal implications of pharmacogenomics: a critical review. *Community Genet* 2001; 4: 204-214.
21. Meslin EM, Thomson EJ, Boyer JT. The Ethical, Legal, and Social Implications Research Program at the National Human Genome Research Institute. *Kennedy Inst Ethics J* 1997; 7: 291-298.

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