RMA DVA ESO

10th YEAR 10th YEAR 10th YEAR

Proceedings of
2004 CANBERRA FORUM

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Table of Contents:

APPENDICES

Technical/scientific papers presented at the forum by invited speakers but not reproduced in this publication

Military Rehabilitation & Compensation (MRC) Bill
Mr Bill Maxwell. Division Head, Compensation and Support, DVA
Mr John Douglas, Director, Compensation and Support, DVA
Mr Andrew Moorhead, Director, Compensation and Support, DVA

Korean War Cancer and Mortality Study
Dr Keith Horsley, Director of Research Studies, DVA

Recent Initiatives in the ADF
Air Commodore Tony Austin, Director-General of Defence Health Service, ADF
Colonel Stephan Rudzki, Director of Preventive Health, Defence Health Services Branch, ADF

Foreword

The 2004 RMA/DVA/ESO forum was held in Canberra on the 30 and 31st March. The objectives of the forum were to: restate RMA processes; inform representatives of the Veteran community; address issues of concern to the Veteran community; provide a forum for Department of Veterans' Affairs (DVA) and Department of Defence (DoD) representatives to address current issues; and to provide the opportunity to identify future challenges.

The forum was attended by around 45 representatives of Ex-Service Organisations (ESOs) and representatives of DoD, DVA, the Repatriation Commission, the Veterans' Review Board and the Specialist Medical Review Council, as well as the members of the RMA and the RMA secretariat. It was opened by the Hon. Danna Vale, MP, Minister for Veterans' Affairs.

The format of the forum involved presentations, a workshop on critical appraisal and causal inference, and question and answer sessions. Opportunity for the latter was provided at the end of each presentation as well as at specific sessions dedicated to answering questions submitted prior to the forum. There were thus opportunities for active participation by ESO representatives.

The topics of the various presentations were chosen to explain RMA processes, elaborate on the legislative and scientific constraints under which the RMA operates and to reflect current issues of concern.

The purpose of this document is both to record the content of the proceedings and to provide veterans or their advocates with a helpful reference for matters which arise when dealing with the Statements of Principles (SOPs). The principles and processes by which the RMA operates, as outlined in the proceedings of the 1998 forum, are essentially reconfirmed in this document.

All presentations given by members of the RMA are included, either as a paper or as edited versions of the audio transcript. Presentations given by guest speakers are listed but not included because they provided background information of a topical nature which was only indirectly related to RMA functions. All questions and answers from throughout the forum have been brought together from the audio transcripts, grouped in broad categories and edited for clarity. Additional useful general material is provided in the Appendix.

Formal and informal feedback received by the RMA about the forum has been very positive. Delegates felt that the forum met its objectives and was relevant and useful. We hope therefore that this document will be a relevant and useful resource, both to those who were present and those who, in the future, need to gain a greater understanding of the RMA and the SOP system.

Professor Ken Donald
Chairperson
Repatriation Medical Authority

Abbreviations and Acronyms

APPVA	Australian Peacekeepers & Peacemakers Veterans Association
ASASA	Australian Special Air Service Association
AVADSC	Australian Veterans & Defence Services Council
BMI	Body Mass Index = W/H^2 (W = weight in kg, H = height in metres)
DDT	Dichlorodiphenyltrichloroethane
DoD	Department of Defence
DVA	Department of Veterans' Affairs
ESO	Ex-Service Organisation
GARP	Guide to the assessment of rates of veterans' pensions
MET	A unit of measurement of the level of physical exertion. 1 MET = 3.5 ml of oxygen/kg of body weight per minute or, 1.0 kcal/kg of body weight per hour, or resting metabolic rate
MRCA	Military Rehabilitation and Compensation Act
PTSD	Post-traumatic stress disorder
RDFWA	Regular Defence Force Welfare Association
RMA	Repatriation Medical Authority (the Authority)
RSL	Returned & Services League of Australia Limited
SMRC	Specialist Medical Review Council
SMSE	Sound medical-scientific evidence
SOP	Statement of Principles
TPI	Australian Federation of Totally & Permanently Incapacitated Ex-Servicemen and Women
VEA	Veterans' Entitlements Act
VRB	Veterans' Review Board
VVAA	Vietnam Veterans Association of Australia
VVFA	Vietnam Veterans' Federation of Australia

Ministerial Opening Address

The Hon Danna Vale MP
Minister for Veterans' Affairs

Repatriation Medical Authority Forum
30 March 2004
Canberra

Good morning, everyone. I'd like to acknowledge Professor Ken Donald and members of the Repatriation Medical Authority and the RMA Secretariat staff, Dr Jonathan Phillips and members of the Specialist Medical Review Council, Dr Neil Johnston and members of the Repatriation Commission, Brigadier Bill Rolfe, Principal Member of the Veterans' Review Board, Ex-Service Organisation leaders, and ladies and gentlemen. It is a great privilege for me to join you today, to celebrate the achievements of the Repatriation Medical Authority.

This year marks the 10th anniversary of the establishment of the RMA. In just a decade the Authority has established itself as an integral and respected agency in our world class repatriation system.

The RMA was established in 1994 in response to audit findings that the veteran disability compensation system was suffering from a lack of consistency in its decision-making.

The introduction of Statements of Principles in 1994 by the RMA, was intended to provide a firm foundation to ensure not only that payments were generous, but that veterans were treated consistently and fairly.

The RMA has developed SOPs based on sound scientific evidence and has worked to ensure the SOPs evolve as new studies emerge on the health factors affecting our servicemen and women.

Ten years on, the combination of the SOPs, expert computer systems developed by DVA – and a commitment to training staff and ex-service pensions officers – has delivered an enviable system for delivering compensation that meets the needs of disabled veterans.

Processing times for primary claims have fallen and processing costs are down – both an indication that the job is being done more efficiently.

There has been a significant improvement in the quality of decision-making and a notable reduction in rates of appeal for review of decisions – meaning that the job is being done more effectively.

Importantly, the partnership between the RMA, DVA and Ex-Service Organisations also has strengthened veteran confidence in the integrity and fairness of the compensation claims system.

When caring for veterans it is necessary to strike a balance between the generous support that the community expects for those who have served our nation, and a certain amount of rigour in applying legislative provisions.

While no system can be perfect, the arrangements we have in place today mean that veterans can have high levels of confidence that they are being treated consistently.

A great deal of credit for the RMA's success must go to Professor Ken Donald.

Professor Donald has chaired the authority since its inception and his expertise, experience and dedication to the RMA's work are greatly valued by the Government.

I would also like to express my appreciation to the RMA members and their Secretariat staff, many of whom are also celebrating their 10th anniversary with the authority this year.

But while we are celebrating a significant milestone, that doesn't mean that we will be resting on our laurels.

In 2004, the repatriation system is poised to enter a new stage of its evolution, with the establishment of the Military Rehabilitation and Compensation Scheme.

This will be a landmark moment in the history of Australian repatriation – the

creation of a single scheme designed to meet the care and compensation needs of both serving members of the Australian Defence Force and the next generation of veterans.

I am looking forward to its speedy passage so that we can carry forward our intention to commence the new scheme from the

1 July 2004.

The new scheme will bring together the best elements of the Veterans' Entitlements Act and the Safety, Rehabilitation and Compensation Act.

One of the most important elements of the scheme will be the inclusion of the RMA's Statements of Principles as the determining instrument for compensation claims.

The inclusion of SOPs in the new scheme followed extensive consultation with veterans and serving members and reflects their successful use under the VEA.

While this decision has generally been welcomed by those who have played an active role in the development of the legislation, I would like to address concerns raised recently in the legal profession that the use of SOPs will make it more difficult for ADF members to obtain compensation for injuries suffered on peacetime service.

This quite clearly is not the case.

Statements of Principles already deal with all forms of service, from peacetime to warlike service. They could even be used in civilian compensation cases, as the RMA investigates all possible causal factors for diseases and conditions that are covered by SOPs.

The legal concerns raised also overlook the fact that Statements of Principals are not static documents. They are subject to review to ensure they are kept up to date with the latest scientific evidence.

And, where a condition is not covered by an existing SOP, the connection between service, of whatever kind, and the injury or disease is made on the basis of the medical evidence available.

Obviously, some changes may be necessary in applying Statements of Principles to the health and compensation needs of serving personnel.

We have no intention of just superimposing the existing system onto the ADF profile, without testing the adequacy of the SOPs for that purpose and satisfying serving members of their comprehensiveness.

The RMA has an excellent track record of consultation and of responding to the genuine needs of ex-servicemen and women.

Professor Donald has already indicated to me the authority's intention to consult widely with the defence force community once the legislation has passed Parliament, to ensure that the Statements of Principles effectively meet the needs of ADF members under the new scheme.

I might say that this is not the first time that legal arguments have been raised claiming that Statements of Principles would make it harder for veterans to access their entitlements.

I expect those involved in the establishment of the Repatriation Medical Authority will recall that similar concerns were raised about the move to SOPs to determine veterans' claims under the VEA.

In this 10th anniversary year we can look back and see the proof to the contrary.

I look forward to the Repatriation Medical Authority continuing its dedicated work on behalf of all those who serve in the defence of Australia.

The RMA – Ten Years On & Its Evolving Role

Professor John Kearsley, RMA Member

Paper prepared from edited transcripts of the RMA Forum
March 2004

The RMA – Ten Years On & 1998 Canberra Forum Publication

My role, as the first RMA speaker, is really to set the scene for this conference, to offer an overview, to review our achievements and to review the limitations under which we also work as the Repatriation Medical Authority. I'd also like to provide a sense of the journey that has led us to these achievements.

When the RMA was first created 10 years ago, the SOP concept was a largely foreign area. There was no template, there was no blueprint and there was no history that the fledging RMA could reflect upon. What we had was the Veterans' Entitlements Act and some very skilled people.

At this point I would like to pay tribute to our Chairman, Professor Ken Donald, because I think he has been an amazing example of how to make an organisation forge ahead. Where there was nothing, there now is something substantial, and Professor Donald has been, in significant part, responsible for that achievement. One of the things Professor Donald has always implored to RMA members is that we need to act lawfully. It is important to understand the framework in which we've had to work.

The first part of my talk is really an overview or a review of our achievements, and I will highlight seven achievements. The second part of my talk will be to review some of the limitations that really are, to a great extent, not in the RMA's direct control. It is important because sometimes individuals, and members of Ex-Service Organisations, do not agree with us or our views. It's important to understand that a lot of this tension is actually not our fault. We are often restricted by either the poor quality of the science, the poor quality of the published peer reviewed literature, or sometimes the legislation itself in respect of occasional unrealistic expectations.

The first RMA achievement is the establishment and refinement of the SOP system. Back in 1994, we didn't really have a history and we didn't know what a SOP would look like. By the end of the year 2003, the RMA had produced nearly 1200 instruments, covering a total of 276 individual conditions and the percentage of conditions covered by SOPs at the primary level in 2003 was 93.2%. The RMA has covered the vast majority of the important SOPs.

Initially, of course, the first priority was to determine as many SOPs as possible. We chose those SOPs for which we thought there were likely to be many claims and for which there was good and reliable peer-reviewed published evidence. In the first three years after the inception of the RMA, 229 conditions were covered, and 667 instruments were determined. The emphasis now has changed in that, while we are still creating SOPs, we now spend most our time reviewing SOPs because the nature of the peer reviewed literature is that it is always changing and being refined.

In each investigation the evidence for all potential factors is reviewed. We have become very particular about how we write the factors because, as you will be aware, there are a large number of very sophisticated SOP users. These include the veteran community, Ex-Service Organisations, the courts, the AAT, the VRB, the SMRC and the wider community.

The SOPs are now readily available on the RMA Website, and so there is a lot more scrutiny as to what we write and the factors that are created. I will come back to that issue of interpretation afterwards. Currently, of course, there's a steady and increasing flow of requests for investigations, or review.

As I have said, new information accumulates rapidly, so that most requests require a review of the whole evidence and therefore an investigation is advertised. Requests for investigations can also be received from the SMRC. There is now an expanding role for SOPs for serving personnel because of the new MRC Act.

I might just go back to this point about reviews and the thoroughness of the SOPs. The current review of Malignant Neoplasm of the Prostate gland for instance will take in excess of eight months to fully and properly re-examine. So these reviews do take time. We review the whole SOP and all the factors just to ensure that no new factor has emerged or existing factors have changed.

Now, why do SOPs change? I want to clarify first of all that, in fact, existing SOPs do not of themselves change. If we want to change a SOP, the SOP needs to be revoked and then reissued. SOPs change for a number of reasons. One, as I've said, is that there is new sound medical-scientific evidence. Upon review a change may or may not be required, depending on the evolution of that information in peer reviewed journals. There may be administrative reasons for change- someone may have left out a semi-colon, there might be an alteration in the format, or at times there might be just too many amendments.

Sometimes also, there are problems in interpreting the factors, or what we mean by a disease entity. I recall that there was great argument at one stage of what we meant by the "large intestine". Now, for most people the large intestine is the large intestine, but when we have to define it so carefully in SOPs we have to make sure that we know exactly where the ileo-caecal valve fits. Is it part of the large or small intestine? And does the recto-sigmoid include the large intestine? These are issues about clarity of disease definitions.

Sometimes, we know what we think and what we meant, but other people think that we meant something different. The courts, ESOs and veterans are extremely helpful in helping to clarify factors, because sometimes what we write as a factor in terms of the exposure or the amount of the exposure is open to interpretation. We certainly thank the ESOs and other people who have pointed out variable interpretations of our factors to us.

The RMA flowchart on Determination of SOPs shows the step by step process by which the RMA acts to produce a SOP (see Appendix 1). When we receive a request from an ESO, the Repatriation Commission, other organisations, or veterans, the RMA goes through a process. The first step is; is the condition under consideration a disease? If it's not then we are unable, under the legislation, to create a SOP.

The RMA has discussed the condition of hiatus hernia, and this is just provided as an illustration of how hard it is sometimes to know if an entity is a disease or not. Hiatus hernia is where part of the stomach slides up into the chest. We know from radiology studies that at least 60% of the normal population have a sliding hiatus hernia without symptoms, and sometimes it's an incidental finding. The problem for us sometimes is knowing whether a common condition can actually be considered a disease. What people come to the general practitioner with are symptoms, but if you have a sliding hiatus hernia you may have reflux, and that reflux may cause symptoms. However, there are some people who have a hiatus hernia, no reflux and no symptoms, and other people can have symptoms without reflux. Whether the "disease" is hiatus hernia, or whether the entity is "reflux", occupies our time in discussion. In a large number of cases the literature on particular entities is unhelpful and

sometimes it's hard to separate in the published literature reflux and symptoms from hiatus hernia itself.

The next step, after we have considered whether a condition is a disease under the Act, is to ask, "Is there published peer reviewed evidence?". If there is, we then collate a range of factors which can be potentially implicated in the causation of disease X with potential for military service exposure. This is a huge task and our Secretariat is involved heavily in this area. RMA members then view the evidence. Each RMA member brings with them their own experience on whether a factor identified can be considered "causative".

We tend to use the option of clinical judgment if we are considering a relatively rare condition for which there is no peer reviewed published evidence on causation. One that I had personal experience with years ago is Merkel cell tumour of the skin. You will never, ever, ever see a published paper looking at causation in a strictly scientific fashion because the tumour is so rare. However, because I've had experience and seen patients with that condition, to me, it was fairly obvious that this particularly rare skin condition is highly related to sun exposure even though there is very little published evidence. You will see that in the skin cancer SOP, Merkel cell cancer therefore appears.

Once we have assessed causation, we then apply the two standards of proof, either at the reasonable hypothesis level or at the balance of probabilities level. I will discuss those particular issues afterwards.

The second major achievement is the development of an RMA website which contains an introduction to the RMA, a short history, profiles of the RMA members and a list of current investigations and reviews. The various RMA publications are published and there are useful links provided.

The third achievement is a more efficient review process. Back in the year 2000 new powers were introduced in amendments to the VEA (section 196CA). The RMA is now allowed to decline a request for formal review if there is no new evidence provided. An investigation is a laborious process and it tends to tie up an enormous amount of RMA time. This amendment means that we don't need to look at reviewing SOPs if there is little in the way of new evidence. There is also the power to collate requests so that they can all be folded into the one investigation. In addition, we have had additional medical research officers appointed to the RMA because of the volume of work.

The fourth achievement is independence from the Department of Veteran Affairs. That has been maintained, and we have separate legal advice and staff.

The fifth achievement is that the expertise of the RMA membership has been maintained. We have always had an epidemiologist and most of us have epidemiology experience. The subject matter expertise of RMA members ranges across most diseases and we all have a broad experience, whether that be in public health, public administration, research and/or clinical practice.

RMA members have varying periods of appointment to avoid all of us retiring at the same time and therefore a loss of corporate memory. It's very important that we calibrate with each other so that the mind of the RMA in five years is the same mind of the RMA as it currently is, assuming no change in the Veterans' Entitlements Act.

The sixth achievement is our pro-active approach to communication between the RMA and the community of SOP users. There's never a sense that we have, in creating SOPs, tried to slip one in under cover. Any proposed change is always advertised. We always have that transparency

so that people know what is happening with the factors. In fact, ESO representatives are always consulted if there is a potential to make a factor harder to meet in a Statement of Principle or in deed, if a factor is to be removed.

There are regular mail outs and publication of annual reports and explanatory notes. Forums and conferences have been held and RMA members and the Secretariat attend relevant conferences and meetings. People also understand that when they ring the RMA they will get a good informal hearing by either the Registrar or by other members of the Secretariat.

The seventh and final achievement relates to the RMA's other roles. The RMA is not always the RMA in that we have occasionally, as individuals, been appointed to various expert committees, and most of these expert committees or working parties have been followed by publications and proceedings. We have looked at spina bifida occurrence in children of Vietnam veterans; the health effects of depleted uranium; radiation exposure; and the health of SAS veterans. In the mid 90s there were big conference, on smoking and malignant neoplasm of the prostate gland; and stress and health. There are some negatives in that the expert groups and conferences do take up a lot of time for the RMA and the Secretariat.

The second half of my talk is an attempt to illustrate some of the legislative and scientific limitations which affect the RMA processes. I think most people understand that the remit of the RMA is not to carry out research so I will not discuss that any further.

We will consider these limitations under three headings. The first is: "What constitutes sound medical-scientific evidence (SMSE)?". The second limitation is, "How we define disease?". The third limitation is the standards of proof which apply to particular types of service.

Section 5AB(2) of the VEA specifies what constitutes SMSE. SMSE is taken to be information that has been published in a medical or scientific publication and has been subjected to a peer review process. It can also be information which, in accordance with generally-accepted medical practice, would serve as a basis for diagnosis and management of a medical condition. Material on the Internet is often not peer-reviewed unless published by a reputable organisation, so generally we don't accept Internet material as SMSE. Expert opinions also don't usually count as SMSE, unless they are supported by published evidence.

I should expand on the word "hypothesis", because there has always been some confusion about that word. In the Veterans' Entitlements Act, "hypothesis" is used in a legal sense, whereas scientists think of "hypothesis" more in a scientific sense. In the legal sense, "hypothesis" means that there is substantial evidence that points towards a causal association between a factor or an exposure and a disease. The linkage must not be fanciful, and it has sometimes been quantified by people outside the RMA as roughly a 1 in 20 probability that factor X is linked with disease Y.

However, in the scientific sense a hypothesis is really a hunch and when scientists conduct experiments they have to state their hypothesis: "We think this is what happens. This is such and this is what we intend to prove". In the legal sense, for the purposes of the RMA, the evidence needs to be there first.

I will now give some examples of the problems with expert opinions. It would be possible to pay an expert witness, I suspect,

to show that cannon fire causes haemorrhoids. If you think about it, cannon fire is a shock that could increase straining or increase pelvic pressure, and if repeated over a time, could lead to haemorrhoids. That might have happened in the past, but if you look up the scientific literature, I doubt whether there will be any evidence of cannon fire as a causative agent in haemorrhoids in the legal sense that we work with.

Another example of expert opinion is a letter which came from an eminent heart specialist. The issue at hand was whether smoking was related to thrombosis, or clotting in the veins, and the cardiologist said:

> *"A specific cause for the thrombosis in this person was not found, but there is a well-established connection between cigarette smoking and venous thrombosis and it seems that cigarette smoking was a factor in its causation. In summary, then, this person has a history of femoral vein clotting and coronary artery disease. There is little doubt that cigarette smoking is causally related to both of these conditions."*

That opinion was sent in as a letter without any supporting evidence. A review of the literature between cigarette smoking and venous thrombus, showed that:

> *".. few controlled studies that dealt with venous clotting alone were found that supported a positive association with smoking, hence a smoking factor has not been suggested for the SOP on deep venous thrombosis."*

The RMA takes seriously the opinion of a medical colleague. We would look up the literature to see whether any literature had changed, but as people can see in this instance, the literature had not changed and there was still insufficient peer-reviewed published evidence to support that link.

In the scientific literature it is part of the methodology of a study to clearly define exposures and outcomes, whereas the RMA is often asked to investigate chemicals or groups of exposures. We find out that veterans are concerned about aircraft exhaust, or petroleum fumes or smoke as being causative factors for disease or illness. Our understanding, as the RMA, is that we need to actually drill into what the chemical compounds are rather than just make a factor that says "exposed to smoke". It is our understanding that we need to know the chemicals that cause harm, rather than just a mixture of chemical substances.

Similarly, it is neither legally nor scientifically correct to make factors for groups of veterans. In the past the RMA has made a factor for prisoners of war. That factor was made very early in the history of the RMA because it was almost impossible to tease out what the noxious exposure really was. There were very few prisoners of war and, of course, they were subject to appalling conditions. Since then we have tried to stay away from including groups of veterans in the SOP factors.

We come now to the definition of "disease", which is defined in section 5D(1) of the legislation. I have already described the issue with hiatus hernia and tried to highlight the problems that the RMA faces in dealing with conditions that are common in apparently normal people. It is important to understand that a disease does not include a temporary departure from normal physiological state or the accepted ranges of physiological or biochemical measures that result from normal physiological stress.

Another limitation related to 5D is the inability to make a SOP for a condition that is not recognised as a disease. For instance,

studies of Gulf War veterans in Australia and overseas have found an excess of self-reported symptoms, but these are not able to be classified as a disease under the Act. Constellations of symptoms do not always cluster in a consistent way to enable a syndrome or disease to be defined.

It is not clear sometimes when a risk factor becomes a disease. For many years within the RMA, we have debated whether conditions like obesity, hypertension or high serum cholesterol actually constitute a disease or whether they are simply a continuum of normal life. The issue with hypertension has cropped up over many years and people will understand that hypertension, obesity and hypercholesterolaemia are certainly risk factors for other diseases such as stroke. These are bad prognostic factors but whether the risk factors themselves actually constitute a disease is open to some debate.

Of course, most of these risk factors are treated, and so if you go to your GP and you have high blood pressure or you are obese, or you have hypercholesterolaemia, you will almost certainly be treated. Take hypertension as an example. In the past, a blood pressure of 140 on 90 has been considered to be "normal", but if you have a blood pressure of 140 on 90, you can still suffer one of the side effects or one of the sequelae from hypertension. The lower your blood pressure is, it is claimed, the longer you will live, and blood pressure or hypertension is seen as a continuum rather than a fixed disease entity. The mind of the RMA in relation to this issue is still in a state of flux. However, as uou would be aware, we do in fact have SOPs for hypertension and morbid obesity.

The next legislative issue relates to Sections 196B(2) and 196B(3) which specify the two standards of proof. The RMA must determine the Statement of Principles in respect of injuries, disease or death, setting out the factors that must, or must as a minimum, exist and which of those factors must be related to service. Our view is that any factor, or any circumstance, can be related to service, apart from genetic factors.

The RMA is not able to include a factor unless the body of SMSE points to or supports a reasonable hypothesis of a causal association between the factor and the outcome. This standard of proof applies to injury, disease or death incurred on operational, hazardous or peacekeeping service. For the balance of probabilities standard, which applies to eligible war service and defence service, the SMSE has to show that it is more probable than not that the factor in question is causally related to the disease. For many diseases, despite extensive review of the literature and a very generous standard of proof, few or no causes can be identified. Sometimes factors related to service cannot be included due to lack of evidence.

In looking at causation, the RMA starts with a particular disease rather than starting with a particular symptom or exposure. In general, the RMA is not required to examine risk factors or exposures and consider all their potential adverse health effects. The RMA is required to focus on particular kinds of injury, disease, or death, as they relate to service. The starting point is a disease rather than a risk factor or exposure. In addition, the RMA is not required to determine matters of fact concerning an individual veterans' service record and the link between his or her service and a factor. That is the role of DVA.

Synergistic effects are not usually considered. Let us take cancers of the tongue as an example. If you smoke, then you are at risk of cancer of the tongue. If you drink

alcohol, you are at risk of developing cancer of the tongue. If you both smoke and drink, then you are at a much greater risk of developing cancer of the tongue. The problem here is that the literature often is not of sufficient quality that we can tease out exactly how much of a contribution smoking and alcohol consumption may contribute to a given condition.

Likewise, the RMA does not consider positive effects of exposures, only the negative effects. That is in accord with the legislation. Our remit is to consider exposures that are responsible for illness, not protective effects. In looking through factors causative for illness or disease we sometimes find protective factors, such as DDT in relation to breast cancer and alcohol in low doses in relation to heart attacks, but they do not enter into our consideration when we create factors for SOPs. We may however, consider inability to undertake protective actions, such as exercise or consumption of dietary fibre.

The last issue is that of idiosyncratic factors in disease causation. These are largely genetic factors which we don't take into consideration. One example is UV light exposure and skin cancer. It is obvious that a person's skin has an impact on whether they are predisposed to developing skin cancer. Some people have fairer skin than others, but this is again not a consideration that we take into account.

In concluding my talk, I hope that I have been able to set the scene for speakers who will follow. I have attempted to provide an overview of the journey that the RMA has taken over these 10 years, and also to point out to you our achievements over that period of time. As the RMA we will continue to act appropriately, carefully and, most of all, lawfully. We will continue to seek sound medical-scientific evidence for causation and we will continue to be open to surprises in our work. Thank you.

Stress and Stressors

Professor Beverley Raphael, RMA Member

Paper prepared from edited transcripts of the RMA Forum
March 2004

Stress and Stressors

Even though my topic was psychiatric conditions and stress, the core issue which comes before the RMA repeatedly relates to the whole issue of stressors, stress and the relationship to health. I think it's very fitting that this follows on from the discussion of both the strengths and the barriers to how the RMA functions, because in the area of stress, the confusions that exist in the scientific literature and the advances that come progressively through a scientific expansion in this field, have to inform what we do. Yet this has still left us with things that may appear nebulous and difficult when we try to relate them to the real life experience of veterans for matching against SOPs.

Now, stress is a broad concept. In the English language and probably in many other languages there are similar or different concepts related to cultural perceptions. However, in the scientific literature it is often very poorly defined and variably measured. That has to be on the table from the beginning because, as indicated in the earlier presentation, we have to base our decisions for the SOPs on the scientific and medical literature.

We think it is useful to consider separately the stressors, the things that happen, events or ongoing circumstances, and stress, the reaction. The reaction may have psychological, physiological, biological, social or cultural components.

When we think about stress and its effects, stress may range from something like being in a motor vehicle accident to the fact that stress is part of everyday life. From the moment a baby is born and indeed from the moment a baby is conceived, there are stressor effects which may impact on development either biologically, psychologically or socially. The adaptations made, the coping strategies evolved and the psycho-physiological mechanisms of response may be linked to genetic predispositions as well as to learning processes. These are all part of the fact that stress is part of life.

In our earlier conference on stress we also looked at stress as challenge because it is quite clear that without adequate stimulus, which may be stressful at times, there is an inadequate process of development. The response to the challenge component of stressor exposures is often a critical aspect of development and, as has been suggested increasingly by some research, it's necessary for personal growth. There are now questionnaires that are looking at personal growth as a consequence of what might be called psychologically traumatic stress.

Stress exposures, stress and individual reactivity can be influenced by genetic factors and there's a body of research which has looked at behavioural genetics and the relationships between reactivity to stress and patterns of genetic connection. Learning can also affect the response to stressors. If you grow up in a very anxious environment; say for example you have a parent who is worried and anxious about how some threat may hurt you, you may learn to be more reactive to external stressor exposures.

We know from a range of studies in the literature that people are variously exposed to stressful exposures. When we look at the end of the spectrum of what might be seen as potentially psychologically traumatic exposures, we know that while everybody gets some exposures in those circumstances, certain groups in the population may have excessive exposures. The question that then arises is what part of that individual or that group might seek or be vulnerable to greater exposures to stressors for a variety of potential reasons.

There are social and cultural factors which affect the responses to stressors. We would define something as bad for example if someone attacked you savagely as you walked out of a social venue. On the other hand, if you were tackled the same way on the football field everyone would be saying, "This is great." Whether or not you ended up with the same wounds, you might perceive it differently and its cultural and social context would be quite different. You would be seen, if your team won, as a victorious person and the significance of the stressors and the stress effects would be seen as a great contribution to your team's positive achievements. In the other situation you might be seen as a victim.

People's perceptions of stressors come up in the discussions about criterion A in post-traumatic stress disorder (PTSD). Perception is frequently part of what we try to take into account if we can measure the impact it might have as reported in the scientific literature.

We also know that it is critical, if we are being fair to science, to bear in mind protective influences, resilience and personal strengths. These factors might also influence how we respond to stress. Studies of children and others in very adverse and highly stressful environments have shown that there are personal and other characteristics that favour resilience so that there is not a negative outcome from the exposure.

Positive support from the environment both before, during and after an exposure, may influence outcome as may learning and training. For example, in my work in the field of disaster (which also relates to the military) we have found that people who are prepared and exercised in handling certain stressors or exposures are likely to have better outcomes in terms of their mental health. Much of this may relate to the degree to which we perceive or learn or develop control over the potential stressor, our capacity to have some control in our reaction to it, and the skills and a sense of mastery which may come from past experience. Past experience may make you vulnerable but it may also give you skills and strengths in handling the next exposure.

Another important factor in stressor reactions is that when we look back we often attribute things to particular life experiences. How we separate real causes from that attribution is a difficult thing in science, as it is clinically. We know, for example, that significant events in our lives are often remembered very clearly. Whether that memory is on a spectrum with the traumatic memories of a psychologically traumatising experience often remains to be identified in the process of assessing its impact as well as the relationship of the memories to it.

Recent research has suggested that even with wartime experiences, which may seem to be quite clear cut, there may be change over time in the memory of what actually happened. So, what actually happened, one's perception of the event and the impact of memory progressively changing and dealing with it in different ways, may mean that in retrospect the event takes on a greater or a lesser significance as a potential causative factor.

We know there are often quite significant differences between an acute exposure to a one-off, major, horrendous life event and more chronic stressors which may seem to be at a lower level and yet nevertheless may seem to impact in a range of ways on health and mental health. These differentiations are often not clearly distinguished in the literature and yet the science may point to one or other of these components as being critical in aetiology. How many, how

frequently and how often we are exposed as well as how sudden, unexpected and uncontrollable stressor exposures are, may contribute to their impact. However we know that we may actually attribute something to a life experience as a cause when it may or may not be a cause.

Some years ago, some researchers looking at people who had a range of psychiatric illnesses asked them what they thought were the causes. Most people attributed their illnesses to stressor exposures. It is a strong, social attribution that we believe ourselves, if we've been stressed, that it may make us sick. It may certainly make us psychiatrically unwell but we may believe that stress might have contributed to our illness, very often without the science that can support our contention.

There is nobody in this room, including myself, who would not agree that war is stressful for all involved and all who watch and all who know anything about it. I started my life as a young general practitioner in a veterans' practice. The principal in the practice had survived Changi so I grew up as a doctor working with veterans and I ended up a psychiatrist, I am sure, because I kept saying, "What happened to them in the war?". Nobody else seemed to be asking those questions.

Dr Lars WeisÊth, who is a Professor of Disaster and Military Psychiatry at the University of Oslo and a consultant to NATO, suggested that there are three forms of war stress: shock traumas of brief duration, repetitive or serial trauma and prolonged exposure to danger characterised by varying degrees of predictability and control. Marshall, another researcher in this field, again talks about a range of low intensity events which people might see as coming into play in what is sometimes called the malevolent environment. This consists of the more chronic type of events as opposed to high magnitude events and conditions where people's lives are threatened. So, even when people have tried to look at stress and war, operational definitions of what stress might be have varied between researchers who are extensively experienced in looking at this field.

Not all stressor exposures lead to problems of illness and we know now from a large number of studies of soldiers and many other exposed populations that even with severe exposures to horrendous traumas, not everybody is likely to either develop PTSD or to have a psychiatric condition as a consequence. For example, in a US study of Vietnam veterans, 15% were reported to have PTSD.

In the general community in Australia the level of post-traumatic stress disorder found by a national epidemiological study was 3.5%, which is quite high. It is linked to a range of exposures to trauma in the community. We know too that while combat exposure might be one of the high risk factors for developing an illness like post-traumatic stress disorder, military service also has positive effects. There are a range of studies which suggest that these might be to do with learning, development of personal strengths, being part of a team, coping skills and a sense of independence and maturity.

Many young men and now young women come in to the services at a time of personal maturation- late adolescence and young adult life. It is a time of development and growth, where there are particular vulnerabilities but opportunities for strength. Social cohesion, mastering the experience, personal characteristics, training, experience, and recognition and response from others, are critical factors for coping with an exposure.

If other people respond to you by saying, "It

was nothing" or "It's your fault", it tends to make it more likely that this will be a difficult issue for you. When I was a general practitioner working with veterans I could never understand why their entitlement cards were labelled, "Inadequate Personality Disorder," because it seemed to me going to war meant you were adequate in the first place. There was a sense that people often felt they were blamed for what had happened to them, or that it was some reflection on them as people. We know that better recognition is critical.

We are well aware that the RMA have a range of definitions of severe stressors. These have evolved in different ways because of the literature relevant to the particular conditions and the science that was available at the time that the SOPs were being prepared. We understand this does not make things easy, and indeed in some instances we may not have adequately clarified some of these things because the literature was uncertain. This will lead us to look much more closely in a review of these stressor exposures.

This links to the work that's been done for DSM-IV, and before it DSM-III, in trying to define better what a stressor exposure is. Encompassed in the DSM-IV definition of an acute stressor is the reaction to the stressor: "Which event or events might evoke intense fear, helplessness or horror" The need for a reaction in the definition has been debated frequently. Some scientific literature suggests that there can be a dissociation from reactions in which it's as though you weren't there. This dissociation may be indicative of heightened risk of developing a condition later. So, sometimes the definition includes the response and sometimes it doesn't.

Where there has been exposure to catastrophic stress a consequence may be enduring personality change. This may reflect part of a spectrum of PTSD. The term "psychosocial stressors" refers to a different level of stress, and can be related to the broader range of conditions than the very specific type of stressor identified for post-traumatic stress disorder. Here we look at the range of things that could occur that would be extremely distressing for us.

In our own attempt to be more scientific, there is often a complexity between describing the exposure and the reaction to it. In the scientific literature there is often no clear separation of the exposure and the reaction to it and there is a broad, ill defined use of the word "stress". The confusion in the literature makes it difficult for the RMA to make conclusions which can be applied in a SOP.

Some of the questions that have arisen from ESOs, from veterans and from the courts are included here. I'm putting these up, not because there are sound scientific answers to these, but because they are common questions that come up across the spectrum.

The first question is, does the stressor component for PTSD have to be an actual threat of death or serious injury? Does it have to be a threat which anyone could objectively judge, or is it really to do with perceptions? What do we mean when we say the person was confronted by an event? If you're rung up and told about an event, is this stressful? What about your individual perceptions? If you thought it meant you or a loved one were going to die, is that objective or is that a perception? What if you found out later that there wasn't really a basis for the perception of threat?

Another question is what types of events might constitute stressors, and how severe might they be? People have made many attempts over the years to grade life event stressors. In the early work of Holmes and

Rahe the death of a spouse rated the highest on the scale and we have to go from this to trying to identify the rating corresponding to being exposed to a terrorist threat, or indeed to any other horrific life threatening experience. It's interesting to note in the aftermath of September 11 there have been a very large number of studies in the US looking at the rates of PTSD in the population. New York hotels were booked out as soon as September 11 happened with people coming in to do trauma counselling for everybody.

As it turns out, the better literature is highlighting the fact that resilience was strong and early high levels have settled down to quite low levels in the general population. We have to be very careful that in our understanding of stressor exposure we are both appropriately recognising the potential impacts as perceived by members of the armed services and veterans, as well as protecting people from developing a disabling view of the experience.

The RMA is committed to understanding and supporting the reality of the nature of the conditions described, and veterans' experiences, but also making sure that we do this properly. To do it properly we have to provide the scientific basis and in our ongoing review we have to answer some of the questions that have arisen and been put to us by veterans or the courts. We have to take into account what evidence there is about subjective and objective realities.

The question of the malevolent environment as a more profound and ongoing stressor has come up but is still in the early stages of study in the scientific literature. Other questions being studied are the nature of the different stressor exposures and experiences, how memory may alter and change these in adaptive and non-adaptive ways, and how exposures may lead to different outcomes and disorders. Our work, of course, then has to be picked up in the clinical side for the assessment and diagnosis of individual veterans. Thank you.

"Normal" Population Abnormalities Versus Risk Factors

Professor Andrew Wilson, RMA Member

Paper prepared from edited transcripts of the RMA Forum
March 2004

"Normal" Population Abnormalities Versus Risk Factors

When does something which is basically fairly normal for our society become something which is abnormal? This issue goes back quite a long way, and perhaps the easiest way to look at it is to take the example of blood pressure. When people first started to think about high blood pressure as being a medical problem, back in the pre-60s days, there was a thing called "malignant hypertension", which was a disease in which the blood pressure was very high.

These people had systolic blood pressures which were over the two hundreds, which was frequently rapidly fatal. People would have strokes or renal failure within years of the development of this condition. There were medications that were available to treat it, but they were very limited in terms of what they could do, and they had quite serious side-effects.

Over time various studies started to point to the fact that you didn't have to have malignant hypertension, but having high blood pressure which was something less than that malignant hypertension also placed you at increased risk of heart disease, stroke and renal disease. The development of new medications which didn't have quite the same side-effect profile meant that people with high blood pressure could be treated at a lower level. The level at which we've been prepared to treat high blood pressure, the level which is called hypertension, has progressively decreased, and we now accept a level of around 120 systolic as being a level above which we think somebody has hypertension.

We now know from studies of over a million people, studies from countries all around the world, China, Australia, the UK, US and Europe, that even as you go below those levels that we call hypertension, people who have higher levels of blood pressure have a higher risk of stroke and heart attack than people who have lower levels of blood pressure. However, there is still only one group that we're calling hypertensive, that is those people whose blood pressure is above this magic mark of 120, which is the point when we start to treat it.

A similar problem exists in relation to blood lipids, or cholesterol levels. I am part of a committee which is being convened for the third time in 10 years to look at what levels of blood cholesterol we should treat with drugs. Progressively over that 10 year period we have seen a lowering of the threshold as we started to understand that lower levels of cholesterol seem to be associated with increased protection from heart disease and stroke. One in seven dollars of a budget of about $7 billion for the Pharmaceutical Benefits Scheme in Australia now goes towards supporting cholesterol lowering therapy.

What is more, the most recent data suggests that you can treat people down to a level of at least 3.5 and probably even get people's cholesterols down to a level of about 2.7, and they'll still gain some benefit for it. Now, if we look in the Australian population there's virtually nobody who has a cholesterol level of 3.5 or lower. It's the exceptional person, perhaps elite athletes or SAS serving members, who would have cholesterol level which might get down that low, and even many of them will have levels which are higher than that.

So, we're going to have to make a decision – do we give everybody in Australia cholesterol lowering therapy? Do we consider that everybody has an abnormal cholesterol as the case may be? Clearly, as a society, that's a fairly significant issue that

we're going to have to come to grips with.

That brings me on to the last item that I want to talk about, and that's weight. In the Australian population weight is increasing. It increases with age across the population, and it's unfortunate that we are now also seeing an epidemic of obesity in young children.

What do we mean by obesity? There is one set of definitions which have come out from the World Health Organisation which state that a BMI of 25 to 29 will be called overweight and a BMI of 30 or over will be called obese. In and of itself being overweight or obese is not unhealthy. I don't consider myself to be sick just because I carry an extra 10 kilos of weight. I will start to think of myself as sick if I develop some complications as a result of that, and I'd probably think of myself as sick if I was mad enough to let somebody try and treat that in some way.

The difficulty that the RMA is facing in trying to deal with this is that by the basis of our legislation we are required to make SOPs for diseases. How do we handle these things which are almost normal patterns in our community and how do we try and think about the association between that and some exposure that may or may not have occurred during service?

That's a challenge, and it's one that we're going to have to continually keep under review. We've tended to take a view that if a doctor diagnoses it as a treatable problem or if there is some complication, then we'll call it a disease. Some examples are hypertension and sliding hiatus hernia.

Will it stop there? Is it going to stop with weight? Is that the last thing that we're going to have to look at? No, there are other things that are already here that we're going to have to consider in the same way. Another issue that we're going to have to consider, for instance, is low bone density or osteoporosis.

Osteoporosis is a disease defined by reaching a certain threshold of bone density, much in the same way as hypertension. There's a lot of argument going on in the medical community about the cut-off point at which we define osteoporosis. It is being argued that perhaps it is too high. Again, we are dealing with a condition which will affect virtually all women once they become post-menopausal, and which is increasingly being recognised as a common problem for men, particularly as men survive longer.

Although we don't necessarily have any answers, we felt we needed to discuss these issues, to try and give you an idea of the type of thinking that we have to go through. As a society we are trying to face this problem which is in almost plague-like proportions, but which is not easily understood in the traditional way that we think about disease and abnormality physiologically. Thank you very much.

Critical Appraisal and Causal Inference

Professor John Kaldor, RMA Member

Paper prepared from edited transcripts of the RMA Forum
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Critical Appraisal and Causal Inference

Introduction

The primary purpose of this presentation is to convey the main scientific ideas behind critical appraisal and causal inference, the two fundamental processes involved in the creation of a Statement of Principles by the RMA.

The development of the SOP always begins with a literature search. The RMA Secretariat uses computer databases and a range of other mechanisms to identify all publications that might conceivably qualify as "sound medical-scientific evidence" of relevance to the SOP. Each publication generally reports the results of a single study that investigated the role of one or more factors in causing the disease referred to by the SOP.

Once these publications have been gathered together, the process of critical appraisal is applied to each one in turn. Critical appraisal is a systematic method developed in the field of health research for reviewing the results of published studies. Although it demands a good understanding of the principles of epidemiology and statistics, critical appraisal can be undertaken by people who are not specialised in the content area of the research being reviewed. Indeed, the whole premise of critical appraisal is that a general reader can identify standard features of studies from their published reports, and that consideration of these features can then allow a judgement to be made on the quality of the study and the implications of its findings.

At the RMA, the literature search and critical appraisal steps are undertaken between the regular monthly meetings, and result in what is known as the submission relating to a proposed SOP. At the monthly meetings, the RMA members jointly examine the submission, and use the methods of causal inference to determine which, if any, of the various factors that have been considered in relation to a particular disease are causal. Causation can be determined at the reasonable hypothesis or balance of probabilities level.

What is a cause?

Before discussing critical appraisal and causal inference in more detail, it will be useful to consider what we actually mean by the cause of a disease or an injury. For some conditions, causes seem obvious: for example, a vehicle crashes, a person who was perfectly healthy before the crash is rescued and is found to have a fracture. In this situation, it seems indisputable that the crash caused the fracture. There is no reason to look for other causes, even though there is a remote probability of another factor having been responsible. Nor do we feel compelled to do a literature search to find whether there are any published studies that compare the numbers of fractures in people who have just experienced a road crash with the numbers in those who have not!

Similarly, if a person goes on a long march on a hot day and at the end of the day has blistered feet and a headache, there is little doubt about the causal pathways. It is entirely reasonable to conclude that ill-fitting footwear caused the blisters and dehydration from sun exposure caused the headache. Causation is unequivocally demonstrated by the close proximity in time of the causal factor and its effect, in combination with the obvious physical pathways that provide the connection between the two.

Defining a factor as a cause of a disease is much more complicated for diseases that occur a long time after exposure to the

factor. If a person is exposed to herbicide in the context of Vietnam service, or some other situation, and then 20 years later develops leukaemia, was exposure to the herbicide the cause?

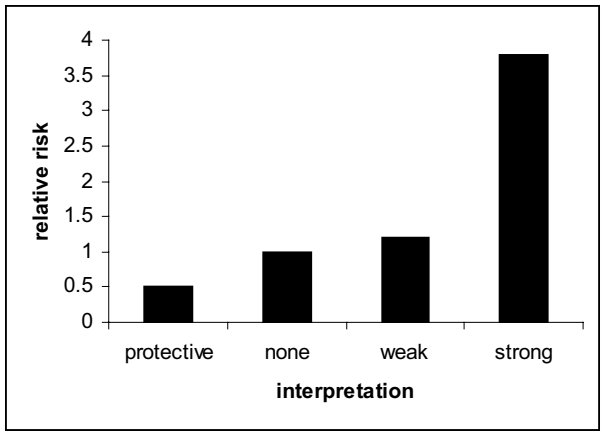
We know little about the causes of leukaemia, and the person could have been exposed to many other factors both before and after the herbicide exposure. In these situations, a factor can only be determined to be a cause of the disease in question if there is corroborating evidence from epidemiological studies. Specifically, we need studies that determine whether there was a higher rate of disease occurrence in those exposed to the factor than in those who were not. Although "clinical judgment" and animal experiments may play some role, we rely almost entirely on the human epidemiological studies to tell us whether there was a difference in the disease rates between those exposed and unexposed to the factor.

These studies are essentially measuring the relative probability of the disease occurring in people who are exposed, compared to those who are unexposed. If the probability of disease is higher in the exposed group, then we can say there may be an association between the factor and the disease. Once an association has been established, we can then go to the next step and consider whether it likely to be causal. It is important to note that a factor may be associated with a disease, without actually being a cause.

Through the science of epidemiology, a number of different methods have been devised for comparing people who are exposed to a factor with those who are not, and determining whether exposure is associated with the development of disease. The various methods have various strengths and weaknesses, and none is perfect, nor applicable in all situations. They do, nevertheless, generally result in the estimate of a measure of association, usually one known as the relative risk.

If there is no association at all between the factor and disease, the resulting relative risk is one (Figure 1). Simply stated, the amount of disease in the exposed group is the same as in the unexposed group, and the ratio resulting from dividing one by the other is one. A relative risk substantially above one provides a strong suggestion that exposure may be causally related to the disease. For example, a relative risk of three means that people in the exposed group were found to have the disease three times more often than those in the comparison group.

Figure 1. Relative risk



Sometimes studies show that the amount of disease in the exposed group is less than the amount in the unexposed group. This finding suggests that exposure to the factor may actually be protective, in the sense that it reduces the chance that the disease will occur.

The RMA does consider protective factors, but more often is faced with studies that report factors that seem to have a weak or moderate effect, in that the relative risk is increased above 1.0, but not by very much. Most often, relative risks are reported in the range 1.25 up to about 1.75 (indicating increases in risk from 25 up to 75%), providing some suggestion of causality, but

still leaving room for doubt unless the studies are of very high quality, or there are a number or studies of reasonable quality all showing a consistent result. Relative risks that are well above two are hard to dispute as providing strong evidence of causality. There would usually have to be some major weaknesses or inconsistencies in available studies for the RMA not to draw a conclusion of causality in this circumstance.

Steps in critical appraisal

Evaluation of study quality is the role of critical appraisal. The published record of each study provides the raw material, and a systematic approach to reading the paper is taken to examine exactly what methods were used to conduct the study, and thereby assess the likelihood that the published relative risk is valid.

In carrying out its critical appraisal, the RMA depends crucially on the quality of published reports. Even if a study was of fundamentally high quality and published in a prestigious journal, it is not always clearly described in the written report. A considerable amount of experience in critical appraisal is required before a practitioner can confidently decide what has been left unsaid or partially stated in a published report.

When conducting a critical appraisal of a published report, the first step is to determine what the author of the paper was investigating. Usually there will be a stated research question, such as "does exposure to herbicides cause leukaemia?", stated either in the title of the paper, the abstract, or the introduction.

Next, it is essential to decide what particular study design is being used by the researchers to answer the question. Generally, the design will be a randomised trial, a cohort study, a case control study, a cross-sectional study or a correlational study. Many publications will state the design, but a number do not, and specialised knowledge is required to be able to infer what design was used.

Each type of study has different qualities and weaknesses as an epidemiological information gathering device. Some of them have strengths in being able to measure the levels of exposure, while others are more suited to accurate assessment of disease rates. They all have fundamental limitations, and none is perfect.

Having identified the study design, we proceed to considering what factors are being investigated as possible causes of the disease, and how they are being measured. Ideally, a study has been able to measure the exposure to the factors directly but, more often, epidemiological investigation relies on surrogate measures of exposure. For example, to determine whether a person was exposed to a herbicide, the most direct approach would be direct measurement of air or blood levels at the time of exposure, but such information is rarely available. The study may therefore have relied on indirect measures, such as the self-report of the study participants (often years after exposure occurred).

Critical appraisal also requires that the reviewer of a paper determine how the study assessed the presence or absence of the disease of interest. Again, the ideal will be direct, objective determination by the research team, but there are some diseases that can only be assessed indirectly. For example, a study of headache relies on self-report to make the diagnosis.

The main results of a study are generally presented as relative risks, accompanied by some measure of their statistical precision. For this purpose we use confidence intervals, which give an indication of the range that there might be around the

estimate of the relative risk. Another statistical adjunct is the P-value, which assists in judging whether any observed association may be a chance finding.

Once the basic elements of the study have been established as clearly as possible from the published report, the process of critical appraisal then involves assessing the extent to which chance, bias and confounding may have operated as alternative explanations of the reported findings.

If we see a relative risk that is clearly increased above one, there are generally three broad alternatives that must be excluded.

First, it could be a chance finding. Perhaps the people exposed to the factor were at risk of getting the disease more than the people who were not exposed, for reasons completely unrelated to the presence of the factor, for example their genetic makeup. Although generally impossible to prove, when studies are very small, chance can never be ruled out as the reason for the observed difference.

A second explanation is that the study was subject to some form of methodological bias. Ideally study measurements are carried out in an objective way, but in practice, a subjective element is often introduced as a result of the study design. Consider, for example, studies that collect information on past exposure from people who have a serious illness and a comparison group of people without the illness. It is entirely plausible that the recollections and perceptions of the two groups may differ, even if they in fact had identical exposure histories.

The third circumstance that might give rise to apparent associations is the phenomenon of confounding, whereby people exposed to the factor of interest differ systematically from those unexposed, with regard to some other factor that is actually a cause of the disease. Critical appraisal provides a standard framework for reviewing published reports of studies, and determining the potential role of one or more of these alternative explanations. With so many papers published in so many journals, by so many different authors using so many different approaches, critical appraisal has become an essential tool for reducing the resulting information to a common, comparable form that allows it to be synthesised in an objective manner.

Evidence for causation

Finally, the RMA takes the information resulting from the critical appraisals of all available studies, and forms a judgement as to whether there is a basis for determining causal relationships between specific factors and the disease under consideration. At this point, there are a number of criteria that can be considered, but there is no simple formula for making the determination.

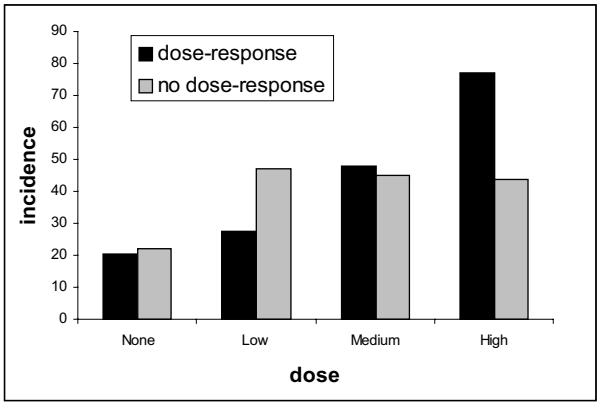
Most important seems to be the strength and consistency of an association. If ten studies of the relationship between a factor and a disease all show a relative risk of four or five, it is very likely to be identified as a causal factor, at both the reasonable hypothesis and balance of probabilities level.

Big relative risks are hard to dismiss as having alternative explanations, and generally provide strong support for causality, but they are not necessary for the determination of causality. A factor can increase the probability of disease by twenty per cent or less, and still be a true cause. In this situation, other criteria are often assessed to support causality.

If a study has been able to quantify exposure in some way, rather than simply classifying participants as exposed or unexposed, then it

may be possible to examine the relationship between exposure levels and the relative risk. A steady increase in risk with increasing exposure, sometimes referred to as a dose-response, provides evidence in favour of a causal relationship (Figure 2).

Figure 2. Dose-response effect



It is also crucial to assess whether the studies provide clear evidence that the exposure was present before the disease. Although this criterion seems obvious, several study designs (case-control and cross-sectional) involve assessing exposure at the same time as the disease is diagnosed. It is not always possible to determine from the information presented that exposure indeed occurred before the onset of disease.

Another important aspect of judging causality is the plausibility of the linkage in terms of the known biology of the disease, and its overall coherence with the reported epidemiological findings. Although we clearly do not understand the biological basis of all relationships that we observe, we would be very cautious about attributing causation in circumstances that directly contradicted our understanding of biology.

Conclusion

The RMA draws on its ever-accumulating experience to try to establish some consistency in the process of drawing together critical appraisals of published literature and making causal inferences about the relationships between specific factors and diseases. As you will be aware, we work under legislation that suggests that we should look for reasons to attribute causality if we can and that is indeed what we do.

As a result of this underlying philosophy, we tend to make judgements of causality, particularly at the reasonable hypothesis level, on the basis of somewhat weaker evidence than might be accepted in other contexts. Nevertheless, we aim to do so in a consistent manner, using comprehensive and systematic reviews of all the information available. There is no compromise to the overall scientific integrity of the process.

The Expectations from Health Studies

Summary of presentation by:
Professor Ken Donald, RMA Chairman

Paper prepared from edited transcripts of the RMA Forum
March 2004

The Expectations from Health Studies

This talk is about health studies and the way in which they may or may not be of use to the RMA and the SOP system. The first thing to note is that the compensation system in Australia depends upon causes of diseases as defined by exposures. It does not depend upon classes of veterans. In fact, factors in SOPs made on classes of veterans are not covered by the legislation.

The RMA has had a lot of requests over the years to make factors for groups of veterans, everything from groups down to less than a dozen men, through to whole theatres. If we did go down that path, we would actually finish up with hundreds of factors based around increasingly smaller and smaller groups, and that's not what the parliament, to this point in time, has decided.

One example is provided by the Korean War veterans' cancer study, which showed an excess of smoking related cancers. Although there is no factor for Korean War veterans, they can make claims under the SOP system. Korean Veterans who have lung cancer can claim under a number of factors that already exist in lung cancer – smoking, diesel fumes – just to name a couple. If they have cirrhosis of the liver, they can claim under the alcohol factor.

It comes back to the point that not all people in a deployment have the same exposures. There is a tendency for a health study to assume that a particular group of soldiers, whether they be Korean veterans or whether they be a smaller group, have all had the same exposures when in fact they haven't.

Furthermore, it is sometimes quite difficult to sort out even what the exposures were 50 years ago, or 20 years ago, let alone which individuals were exposed to which particular exposures. It has been our experience that quite often health studies have raised expectations that the RMA is in no position, legally, to meet. The current F-111 deseal/reseal study brings up – from looking at what we have received so far- it brings up another issue about exposures. For a significant proportion of the chemicals that appear to have been part of the exposure, there is no sound medical-scientific evidence, no published literature, about what the effects of those chemicals might be. Again, for the RMA, that's a blind alley because we can't guess at what might be the effects of a chemical. Occasionally, if a chemical were very closely related to a molecule that has been extensively investigated, we might be able to draw some conclusions about potential effects.

Another issue that has come up in the Gulf War 1 study, is that the outcomes measured by the study don't fit the definition of "disease" in the legislation or, for that matter, don't fit the definition of "disease" in the standard medical text books. The Gulf War study turned up a constellation of symptoms but no specific identifiable disease. And looking at the F-111 study, it's clear that people have a lot of symptoms and they also sometimes appear to have signs, but unless there is a definable disease, legally we have no starting point.

Those are two of the problems with retrospective health studies, the problem of measuring exposures and the problem of the sorts of outcomes that health studies sometimes produce. Retrospective studies depend to a significant extent on people's recall and there is really very little opportunity to measure exposures. It is not that the health studies are not as well done as possible, it is that the retrospectivity and the nature of the data preclude some of the outcomes that you would get from a hypothesis driven prospective study. The general principle is that retrospective studies often only really raise problems, they don't solve them.

Another problem with health studies is the finding of many different symptoms, which could just be a chance finding or a finding of unknown significance. If you look at the general practices around Australia on any particular day, there's a percentage of Australians who go to see their GP, say 5%. Now, that 5% who go to see their GP on any one day, bring with them about a dozen different symptoms and many of them never get a diagnosis specifically attached to them. On that same day, 20% of the community had those same symptoms and did not go to a doctor. If you go to the next day, 5% go to their GP again, but it's a different 5%. When you're dealing with human beings and their symptoms, the facts of the matter are that many of the symptoms that human beings have mean nothing, because the next day they're gone and another group of people have got the same symptom. It raises a lot of false alarms, particularly if people have got a heightened susceptibility to observing their own symptoms.

There can even be problems with abnormalities detected by laboratory tests. It is well-known that if you do blood tests on everybody in the room here, you find abnormalities by chance, and if you do that same level of blood tests a week or a month later, you get false positive results on a different group of the population. An enormous amount of health resources in this country is wasted following false trails of what are chance laboratory findings in somebody who has got absolutely nothing wrong with them. Laboratories in general have got a false positive rate, so by definition, some of the results you get out of a laboratory are going to be wrong. Some of the ones that are wrong are going to be high, by chance.

These are the sorts of background issues that impact upon retrospective non-hypothesis driven studies. They raise problems that actually don't exist, and you finish up with these constellations of symptoms which often don't add up to anything more than what's going on in the average community, day in and day out. It is hard to untangle when you've got something real, and when you've got something that is just one of these false positives.

In retrospective studies exposure to risks from medical interventions are often studied. In every situation in treating a patient, or deciding on a vaccination regime for children or soldiers or anybody else, you are balancing the risks against the benefits. All immunisation has a complication rate. Aspirin has a complication rate- if you take aspirin, you're more likely to die of haemorrhagic stroke than you are if you don't take aspirin. There is no medical intervention that does not have a risk. The safest and most cost effective medical intervention ever invented is still aspirin, in economic terms, but it still has a down side. It is important to compare the risk of intervention with what would have happened if there had been no intervention. Because the risks occurred a long time ago they can be difficult to assess.

Many retrospective health studies – not just retrospective studies in veterans, but retrospective studies in general – are often under-powered. What happens is that even if you start with a large number, by the time you get down to specific disease entities, or specific findings, or specific syndromes, the number of people left in that category do not give you the statistical power to calculate a statistically significant outcome.

When studying small groups another danger is that when the number of cases of a particular disease is measured, instead of finding three cases of cancer X, they find seven. That is two and a half times what is expected and it looks like something is really

going on. What you don't know is that in the next 500 people, there are going to be no cases because the statistics will catch up and the rate will balance out over time. The lack of statistical power means that the results are unreliable, and could be purely due to chance.

Some ethics committees actually view a study that has small sample size and therefore has low power as being unethical in its own right. They might produce a non-finding and create more questions than you actually answer. That is considered by some ethics committees who do their homework to actually be an unethical thing to ask people to approve.

One of the other problems of health studies is that they aren't that, they are actually sickness studies. They ignore the fact that, quite often the group that is being studied has a number of things that positively affect their health. One of the concerns of public health practitioners about these sorts of studies is they have a great propensity to make a group of people who are well become sick, because they overlook the positive effects of whatever the exposures might have been.

Those are the main issues that impact upon the RMA's ability to use retrospective studies, whether they be retrospective health studies of veterans; or whether they be retrospective studies of bus drivers in Denmark; or occupational studies of lead workers in factories. That is not to say that retrospective health studies are not capable of providing key information. A lot of the RMA's findings in health have come from retrospective studies when there has been no other option. The limitations- small sample sizes, poor exposure documentation and lack of a predefined hypothesis- restrict their usefulness.

Certainly, retrospective studies will be the only way you're going to get efficient collection of information about rare forms of cancer or motor neurone disease or other diseases that don't occur very much. On the other hand, prospective studies give you the opportunity to study the symptomatology that you see in a reasonably short amount of time after deployment.

The RMA is very pleased that Defence is moving towards being able to prospectively look at exposures of troops in the field. Some of our allies appear to be far ahead of us in doing it, and are actually plotting where each individual soldier was and his or her particular exposures. I think in the future, those sorts of prospective studies will actually be able to produce some outcomes which may well be more useful to the RMA than the retrospective studies have tended to be.

Soldiers will be prospectively tagged for their exposures, not necessarily their deployments. That will mean that a soldier over a lifetime, or over his/her period of service, will build up an exposure profile which may not necessarily reflect the deployment arrangements. Scientifically that is a more powerful tool than trying to measure diseases by deployments because not every soldier on the same deployment has the same exposures. Also, soldiers in the current Defence Force will go on many deployments. I think when you look at exposures rather than geographic parts of the world or different particular conflicts, there are going to be a whole different set of questions and a whole different set of outcomes that potentially might be more useful in the future.

Prospective studies can give us, in an evolving way, responsiveness to a whole different set of needs and ways of doing more. It is only through those types of studies that we will be able to discover the

evolution of problems, whether they start as constellations of symptoms or whatever, and know if there is going to be a progression to illness and have the opportunity to influence that course in a more positive way.

We also shouldn't forget that the most powerful use of this research is not looking at health effects or claims for compensation, but the question of duty of care to make sure that people are not exposed unnecessarily to harmful things during deployments.

Protective Effects of Exposures

Professor John Kaldor, RMA Member

Paper prepared from edited transcripts of the RMA Forum
March 2004

Protective Effects of Exposures

In the course of reviewing the medical scientific literature for a SOP, most factors that emerge as potentially causally related to the disease that is the subject of the SOP show a positive association; in other words, exposure to the factor is associated with an increased likelihood that the disease will occur. Nevertheless, we are increasingly faced with data on factors that show an inverse association with the disease, in that exposure is associated with a lower risk.

As with positive associations, we need to exclude chance, bias and confounding as alternative explanations, before we can translate an inverse association into a claim that the exposure is protective, in that it is causally related to reducing the likelihood of disease occurrence.

At first glance, it might seem that protective factors would not need to be considered in a SOP on causal factors, given that the purpose of the SOP is to describe causes of disease. In fact, if exposure to a factor can reduce the risk of disease, it is reasonable to conclude that a reduction in the exposure level may actually increase the likelihood of the disease occurring. The absence of any factor that is established as being protective can therefore be transformed into a causal factor if a person is unable to maintain exposure to the normal or beneficial level of the factor.

For example, a number of studies have now shown that exercise protects against colorectal cancer. Therefore, the circumstance of being unable to exercise could be interpreted as being a causal factor for colorectal cancer.

For a causal factor, we would generally expect to see consistent estimates of the relative risk that were above about 1.25, such that exposure to the factor gives a 25 per cent increase in the chance of getting the disease, compared to people not exposed to the factor. Similarly, it would be appropriate to define a factor based on inability to maintain protective levels of exposure, provided the estimated relative risk associated with the absence of exposure was consistently observed to be greater than about 1.25.

For factors in the RH instrument, the RMA has accepted relative risks as low as 1.1, in circumstances where the combined evidence from epidemiological studies provides particularly strong evidence for causality. While the RMA is encouraged to be generous in its interpretation of the evidence for causation, it clearly cannot go beyond the limits of scientific credibility.

When a person develops a disease that is covered by a SOP, the relevance of any factor included in the SOP depends on the threshold level of exposure specified in the SOP. This level is determined from the available published literature, as being associated with a measurable increment in risk.

For some factors, the increase in risk associated with exposure is calculated in published studies by making comparisons with people who were considered to have little or no exposure. For example, in studies of exposure to herbicide, it is generally assumed that comparison groups were unexposed, and that any increment in risk associated with exposure is with reference to this background.

On the other hand, there are factors for which exposure is ubiquitous in human populations, and the calculation of risk increments in published studies must be made with reference to people whose exposure was below a specified level, rather than being zero. Consider fat consumption, or sunlight exposure as examples. In these

situations, the true relative risk associated with the threshold level of exposure specified in the SOP will vary from person to person, depending on the individual levels of exposure arising from sources other than service.

To illustrate this point, think of two individuals, one of whom had been exposed to 90% of the specified threshold level of a factor prior to the start of qualifying service, and another who had been exposed to 10%. If each of these individuals then has service related exposure that takes the cumulative level exactly to the threshold specified in the SOP, they will both qualify for acceptance of the factor. However, the service-related exposure will clearly have been associated with a much smaller increment in risk for the first individual than the second.

To illustrate the point in another way, take the hypothetical circumstance that our SOP system covered not just Australia but a number of countries of our region, and consider a SOP for malaria.

If a person lives predominantly in Australia and develops malaria following deployment to a malaria endemic area, the relative risk associated with the deployment would be very high. On the other hand, for a person who lives in an endemic area, and is then deployed in an endemic area, the increment in risk associated with service may be quite small. Thus the background risk of an individual can substantially influence a person's real relative risk.

The current system is effectively based on averages, in that it makes acceptance of a factor more difficult for people who have a very low background, while it advantages people who actually have a very high background.

Formally, the legislation governing the SOPs does not make provision for taking account of the levels of exposure experienced by an individual outside service, although there is one major factor for which such considerations have been built into the operation of the corresponding SOPs.

Exposures that become SOP factors through their absence or the inability to maintain protective levels would be of this second kind. Clearly if removal of the exposure is to be judged to cause an increase in disease risk, there must be widespread exposure to the factor under normal circumstances. Consider exercise levels or fruit and vegetable consumptions as illustrations. Thus individuals who qualify under factors for which it is the absence that increases risk are doing so at a variety of relative risks, because of the variation in their background levels of exposure.

The incorporation of protective factors (or at least their absence or reduction) in SOPs is thus an evolving area of interest for the RMA. It has encouraged us to look more closely at some key methodological issues underpinning the calculation of threshold levels for exposure, and will certainly provide a wider range of factors for consideration in SOPs.

Syndromes and Causes – Illness and Disease

Dr Justine Ward, RMA Secretariat

Paper presented at the RMA Forum
March 2004

Syndromes and Causes – Illness and Disease

Introduction

The health problems of veterans of the first Gulf War have been extensively studied by various governments. The difficulty of defining and finding the causes of the diverse symptoms reported by veterans of the Gulf War has once again highlighted the problem of war syndromes and their evaluation. The Repatriation Medical Authority has a statutory responsibility to make Statements of Principles for syndromes, provided that they meet the legal requirements for definition of a disease under Section 5D of the Veterans' Entitlements Act (VEA). The problems with defining syndromes and evaluating their causes as they relate to the functions of the RMA will be outlined in this paper. The broader question of understanding health and illness will also be considered, as this question relates to how disease is defined and how symptoms are understood by individuals.

Defining a Syndrome and Potential Consequences

A syndrome is defined in Dorland's Medical dictionary as "a set of symptoms which occur together; the sum of signs of any morbid state; a symptom complex". To be able to recognise a syndrome there needs to be a repeatable grouping of particular symptoms. Often there is no known cause of a syndrome and sometimes a cause will subsequently be discovered. For example, acquired immune deficiency syndrome (AIDS) was initially described by a set of symptoms recognised by an astute group of clinicians and study of the syndrome eventually led to the discovery of a new virus.

Illnesses that are well defined as diseases have more status than symptoms and this leads to a pressure to find a cause or at least define a syndrome. The naming of a syndrome, while providing the comfort of validation to sufferers, also has potential consequences which may be both adverse or beneficial to individuals. It essentially medicalises a set of symptoms, with major potential medical, legal, political and social consequences because of flow on effects to approaches to treatment, compensation and patient's lives.

Giving a set of symptoms a medical name can place people in the sick role and actually impede their recovery. This was realised as far back as World Wars I and II, when it was found that soldiers with acute combat stress reaction were more likely to return to duty if they were treated quickly and near their combat units than if they were treated as patients in a hospital (Hyams, Wignall and Roswell 1996).

An individual's expectations of his/her prognosis can have the effect of self-fulfilling prophecy. A poor self-rated health status has been found to be a predictor of mortality in longitudinal studies and this phenomenon is not entirely explained by existing illnesses and symptoms (Idler and Benyamini 1997). Self-rated health can influence behaviours that influence health status, for example smoking, alcohol use, less engagement in preventive practices such as physical activity and screening and poor compliance with medications. Reduced expectations may be reinforced by social factors, such as reduced employment opportunities for those with disabilities, financial incentives and behaviour of peers (Lupton and Najman 1989). Concerns about potential reproductive effects may make people worry about their children's health or even decide not to have children. Because of such potential adverse consequences, it is important that syndromes are not defined unless there is a sound scientific basis for doing so.

Exposures and Possible Causes

The problem of post combat syndromes has prompted considerable research and debate as to their aetiology. One possibility is that post combat syndromes are physiological diseases caused by unique environmental exposures. In every conflict there are unique exposures related to the place, the time and the conditions of war. In the Vietnam War there was Agent Orange/dioxin; in the Bosnian conflict there was depleted uranium; and in the Gulf Wars unique exposures have included smoke and oil cloud, vaccinations against plague and anthrax and the anti-nerve agent pyridostigmine bromide.

Each conflict also has distinctive psychological stressors, such as heavy shelling of trenches in World War 1; not knowing which villagers were Viet Cong in the Vietnam conflict; and threat of being exposed to chemical, biological or radiological weapons in the Gulf War conflicts. Pervasive, unknown threats can be very hard to cope with psychologically. One veteran wrote in a letter home: "I can deal with getting shot at, because even if I got hit, I can be put back together- a missile, I can even accept that. But gas scares the hell out of me..." (Berstein and Kelley, 1995)

There has been a great deal of effort made towards attempting to discover possible associations with exposures and various diseases. Despite this large research effort, chronic somatic symptoms have not consistently been linked to any particular exposure (Hyams, Wignell and Roswell 1996, Sim et al 2003).

For more recent conflicts, there is a possibility that symptoms represent the early stage of disease or diseases which have yet to manifest fully with demonstrable physical signs or changes in laboratory tests. Further follow up is needed to ensure that diseases do not develop. Sufferers of the so called "effort syndrome" in World War I were followed up but did not show an increased mortality (Hyams, Wignell and Roswell 1996, Jones et al 2002). Studies of mortality in Gulf War veterans have not so far shown an increase in overall mortality relative to non-deployed veterans and no disease categories were significantly elevated in veterans (Research Working Group of Military and Veterans Health Coordination Board 2002). Although follow up will inevitably demonstrate the development of diseases over time, a link to exposures still needs to be made to establish causation.

Another possible explanation for post combat symptoms is that, despite some unique war experiences, there is something about the overall war experience that produces a common response. It is interesting to examine the historical record relating to post-combat syndromes. Hyams et al (1996) has described war syndromes characterised by similar symptoms after every conflict since the US civil war. These symptoms include fatigue, shortness of breath, headache, sleep disturbance, forgetfulness and impaired concentration. These war syndromes were given different names after each conflict: "irritable heart syndrome" in the US Civil War; "effort syndrome" in World War I; "battle fatigue" in World War II; posttraumatic stress disorder after the Vietnam; and "Gulf War syndrome" after the first Gulf War. US, UK and Australian Gulf veterans report suffering from more symptoms than non-Gulf veterans. A range of neuropsychological symptoms was most commonly reported despite markedly different exposures of each veteran.

Jones et al (2002) attempted to characterise post-combat syndromes by doing a historical cluster analysis of symptoms using war pension files from the Boer War to the first

Gulf War. In this study the authors examined the veterans' own attribution of symptoms. Boer war and First World War servicemen with disordered action of the heart believed it to be due to physical illness or physical exertion. First World War veterans with neurasthenia attributed their symptoms to both physical exertion and the psychological stress of military service. Gulf War servicemen with predominantly debility symptomatalogy tended to attribute illness to physical illness, injury or environmental conditions, whereas those with neuropsychiatric symptoms tended to attribute symptoms to the psychological stress of war.

This historical examination shows that experiences of symptoms, diagnostic labels and beliefs about causation are linked but change according the nature of combat, contemporary medical knowledge and prevailing health beliefs. These authors conclude that what has changed is not the symptoms themselves but the way in which they have been reported by veterans and doctors. It highlights the potential danger of allowing preconceptions to get in the way of scientific hypothesis formation and testing.

Shared symptoms may represent a common reaction to stressors or other exposures whether they occur in military or civilian life. Australian Gulf War I veterans reported all fatigue related outcomes more commonly than the comparison group and had elevated amounts of symptoms in the groupings of psychophysiological, cognitive and athro-neuro-muscular (Sim et al 2003). There is an overlap in these symptoms and those experienced by civilians affected by multiple chemical sensitivities, fibromyalgia and chronic fatigue syndrome. Unexplained symptoms have also been reported by civilians after the World Trade Centre attacks (Clauw et al 2003).

All these conditions or postulated conditions have in common that they are based on self-reported symptoms, lack objective verification of exposures and proven causative exposures, lack consistent abnormal physical findings and cannot be confirmed with any clinical test (American College of Occupational and Environmental Medicine 1999, Working group chronic fatigue syndrome 2002). It has been suggested that, rather than apply specific labels to groups of symptoms, particularly ones that imply a pathogenesis, a more clear and unbiased terminology should be used, for example "medically unexplained symptoms" (Clauw 2003).

To add to the confusion, there is also an overlap of symptom based conditions with various psychiatric disorders which often manifest with somatic complaints, including anxiety, depression and somatoform disorders (Hyams 1998). This is not to suggest that the diagnosis of a psychiatric condition is in doubt, but it can be difficult to establish whether the psychiatric disorder is the primary cause of symptoms or a result of debilitating fatigue or pain.

Methodological Problems With Studying Syndromes

A syndrome is sometimes defined primarily for the purposes of study. Having a definition does not necessarily mean that a condition exists. Study designs require that people with a condition (cases) are compared to people without a condition (controls) for the prevalence of particular risk factors, or that exposed and unexposed groups of people are compared to see what proportion develop into cases. It is therefore necessary to develop at least a working definition of a case. However, the lack of specificity of such definitions means that they may not be reliable in distinguishing cases from non-cases (Hyams 1998). This

reduces the power of the study to detect a difference in exposures between the two groups. When cases cannot be reliably identified it is also difficult to recognize the influence of bias and confounding (Hyams and Roswell 1998). It is hoped that progress in the study of symptom based conditions will eventually identify some consistent distinguishing laboratory features and make case definitions much more specific, at least in some instances.

Chronic fatigue syndrome has been able to be characterised by a common set of diagnostic criteria (Fukuda 1994). In contrast, while the level of symptom reporting among Gulf War veterans was higher than in the comparison group, statistical analysis showed that the pattern of symptom reporting in the two groups was similar. This has suggested that the Gulf War veterans do not have a unique symptom complex or cluster (Sim et al 2003). Similarly, no consensus for proposed definitions for multiple chemical sensitivities has been able to be reached in the scientific community, in a large part because of the lack of ability to identify a specific group of symptoms.

There were many methodological problems associated with studying Gulf War illnesses, especially problems with objectively measuring exposures and recall bias. The latter is a potential problem with all retrospective studies. People who are concerned about their symptoms or who have a disease are more likely to ascribe to a particular exposure or experience than people who feel well. Sufferers of symptom-based conditions have ascribed their symptoms to various temporally associated environmental exposures, including modern offices, chemicals, food allergies and silicone implants (Hyams 1998). Extensive questioning of veterans for health studies or health assessments has the potential to remind them of traumatic events and provoke symptoms.

The authors of the Australian Gulf War health study state that some, but not all, symptom reporting could be explained by recall bias (Sim et al 2003). Their analysis also suggested a possible problem with recall bias in reporting of exposures. A study of recall of military hazards showed that reporting of military exposures can change over time, although consistency of reporting is better for some exposures than others (Wessely et al 2003). Furthermore, reporting new exposures was associated with worsening health perception while forgetting previous exposures was associated with improved perception.

Ill-defined symptoms are common presenting complaints to primary care physicians.

As many general practitioners can attest, it is not always easy to diagnose a disease because many diseases present with similar symptoms and signs. Without the ability to distinguish between them on the basis of signs or pathological tests, some diseases would be impossible to diagnose. Even if a physiological correlate of disease is found, it does not necessarily establish that it is causally related, as the abnormality could also be an effect of symptoms rather than the cause of them.

Illness and Disease

Part of the difficulty with dealing with medically unexplained symptoms may be due to an artificial dichotomy between disease and health. Dorland's medical dictionary defines disease as "any deviation from or interruption of the normal structure or function of a part, organ, or system of the body as manifested by characteristic symptoms and signs; the etiology, pathology, and prognosis may be known or unknown."

The VEA has a slightly broader definition:

(a) any physical or mental ailment, disorder, defect or morbid condition (whether of sudden onset or gradual development); or

(b) the recurrence of such an ailment, disorder, defect or morbid condition.

Disease definitions are useful for various purposes: for researchers to establish causation, for governments to base policies on compensation and for the medical profession to make decisions about treatment, especially if symptom clusters consistently respond to specific clinical strategies. However, disease definitions do not necessarily give an accurate reflection of how people experience their health on a day to day basis. Health is defined as a state of optimal physical, mental, and social well-being, and not merely the absence of disease and infirmity.

In a review of the scientific literature pertaining to stressors and the Gulf War, Marshall (1999)pointed out that:

> *"Illness and disease are overlapping, but distinct, constructs. Whereas disease refers to constellations of symptoms that define a diagnosable physical or psychiatric disorder, illness refers to the subjective experience of poor health. Illness manifests itself as somatic (bodily) or psychological symptoms, but may stem from multiple sources—including cognitive and social processes—and may or may not reflect the presence of an underlying disease (Kleinman, 1988). The relationship of illness to disease is complex. A person may experience ill health with no underlying disease. Conversely, he or she may suffer from an underlying disease without perceiving himself or herself as ill (Weiner, 1992)."*

Sociologists argue that it is not possible to separate the experience of health or ill health from its social context. Much poor health is a function of social circumstances and events (eg broken marriages, boring and repetitive work) and may have no pathophysiological basis (Lupton and Najman 1989). The traditional disease model looks simplistically for single or component causes with a biological basis, whereas an endpoint of complete health allows for a model of causation which accommodates a complex interaction of psychosocial and physical factors. Psychosocial factors include context, knowledge, attitudes, beliefs, personality, past experiences, peer values, and the social, legal and economic environment. All these factors affect the meaning or significance that is attached to symptoms. Causal models that rely on a more integrative approach, with stress and central nervous system responses as a final common pathway, may prove useful in explaining the effects of a multiplicity of environmental factors (Kipen and Fiedler 2002).

Hyams et al (1996) suggest that it will not be possible to explain war-related syndromes until there is a better understanding of health and illness in the general population. Population based studies suggest that more than one third of symptoms may be medically unexplained (Clauw et al 2003). Hyams proposes two basic questions:

1. What is the relation between chronic, non-specific symptoms and physiologic and psychological illness?
2. What factors – medical, environmental, psychological, or social- create a personal sense of ill health?

Many disease processes can be imagined as a continuum from complete health to ill health to disease. The division between what

is called health and what is called disease is often determined by a cut off point. Cut off points are usually set where symptoms become very functionally disabling and/or where treatment has been shown to be beneficial to the majority of people from this point onwards. This cut off point is not fixed- it changes according to the sensitivity of diagnostic tests, scientific understanding about the benefits of treatment and the availability of treatment options.

Common examples of this include treatment levels for hypertension, diabetes and hypercholesterolaemia. If the cut-off point is set too high, some people who would benefit from treatment will miss out. If the cut-off point is set too low, some people's health may actually be harmed because they will be labelled as sick and will receive treatment unnecessarily. Decisions about where symptoms, signs or tests are labelled "abnormal" need to keep this risk/benefit balance in mind and should be based on good evidence. At the clinical and social level, though, it is important to keep in mind that there is often a continuity between persons whose symptoms have been given disease status and those with unexplained symptoms.

Just because medically unexplained symptoms do not appear to fit the traditional medical disease paradigm, are hard to study and are not easily accommodated within the legislative restrictions of the RMA, it does not mean that they are not real and legitimate. Whether symptoms may or may not be due to a disease process, they can be very disabling functionally and greatly impair quality of life. Despite an absence of proven causes, treatment is still very important, although care must be taken to avoid well intentioned but harmful interventions.

There is little systematic evidence on which to base strong recommendations for interventions to prevent or mitigate post combat syndromes (Clauw et al 2003). There is some evidence that cognitive-behavioural interventions that prepare personnel for the realities of war offer some benefit (Clauw et al 2003). Social support appears to buffer the effect of stressful events. Critical incident debriefing does not appear to improve health outcomes and may do more harm than good. Constructive treatment after symptoms have developed involves management of symptoms and efforts to restore functioning, rather than focussing on exhaustive diagnostic testing. Outcomes are better if treatment is given early, before symptoms become chronic.

Conclusion

In summary, the objective strategies used to determine when symptoms without any identifiable pathological basis become a disease or syndrome include statistical clustering, response to treatment, expert consensus and symptom severity. The best approach relies on more than one method and should make clinical and pathophysiological sense. However, recognition of symptom clustering is also influenced by contemporary beliefs.

Studies to date do not rule out the possibility of distinct clinical diseases being eventually found to be responsible for at least some chronic unexplained symptoms. In relation to Gulf War related symptoms and other chronic symptom-defined conditions, it is difficult to know if they reflect physiological or psychological diseases with single or multiple causes, or a normal response to the physical and psychological stresses of war. The evidence we have to date is not very helpful in distinguishing between these possibilities.

A basic understanding of the prevalence of

symptoms in the general population is needed. Studies of military populations also have much potential to help answer the questions of health and illness, particularly if they are prospective in nature and collect accurate data on exposures. It is important to know the psychological and physical state of soldiers prior to deployment, in order to establish that there has been a change. Follow up immediately after the conflict and periodically thereafter will clearly establish the timing of any adverse health effects. Adequate preparation may help prevent post combat symptoms and early treatment of symptoms regardless of cause will minimise chronic effects.

Summary of Issues Raised by ESOs

Issues and responses collated from edited transcripts of the RMA Forum
March 2004

RMA Processes

Basis for Removing a Factor

ISSUE

Please clarify, when removing a SOP factor, the basis of sound medical-scientific evidence (SMSE) and how the new SMSE supports the removal of a particular factor?

RESPONSE

Professor Donald explained that the issue is that new studies emerge and those studies often contradict previous studies. They are sometimes better studies or bigger studies with more power than the ones that were previously in the literature. They sometimes cause the RMA to revise its opinion because of the quality of the studies or the size of the result, or all of those things. The whole body of evidence is taken into account when removing a factor.

Pearce Report Recommendations

ISSUE

What is the progress of the Pearce Report recommendations? In relation to recommendation 2, has the RMA considered the question of military experience as a desirable selection criterion for future appointments to the RMA?

RESPONSE

Professor Donald replied that the Minister of the day endorsed 18 of the 20 recommendations and the RMA has addressed all of those within its remit. The issue of how the RMA is constructed was outside the remit of the RMA. Mr Bill Maxwell (DVA) said that the government response had been to factor in the matter of military experience as a criterion but not to make it a prerequisite. However, there may be other means by which Defence experience could be brought into the process. There is already an established procedure where Departmental staff attend the informal part of the RMA meeting and comment upon the operationalisation of the draft SOPs. Some Defence Health people might be able to do something similar. Professor Donald agreed that this might be an appropriate approach, especially in light of the MRC Act and its applicability to current serving members. He undertook to take the matter up with the Commission.

ESO Response Time

ISSUE

Time allowed for ESO response time when asked to comment on RMA papers.

RESPONSE

Professor Donald said that the usual time given to response is about six to eight weeks but it depends on the RMA meeting schedule. The RMA is aware that there are sometimes delays by peak organisations in getting the papers out to individual ESOs. Viv Quinn (RSL) explained that the consultation process within their organisation can take longer than six weeks. Mrs Carole Friedrichs (RMA secretariat) responded that it was also necessary to recognise that a longer response time would delay the making of the instrument, which might also include changes that positively affect veterans. It was agreed to undertake further consultation with ESOs in relation to response time and electronic distribution.

RMA Protocols

ISSUE

What are the RMA Protocols for administration and management?

RESPONSE

Professor Donald answered that the RMA outlined its processes in this forum and the

previous Forum in 1988. These processes are documented in the proceedings of the 1998 forum.

Expediting Reviews of SOPs

ISSUE

What (early) options are available when a genuine claim is restricted by a SOP in its current format?

RESPONSE

Professor Donald said that at the moment the answer is that there are no quick options, although there are sometimes other factors in a SOP which the veteran could look at. Mr John O'Connor Whyte (Specialist Medical Review Council) made the point that there is only a three month window to appeal a decision in respect of a SOP to the SMRC, although he warned that the Council's processes also take some time. Professor Donald explained that even though there are over 50 investigations listed, but the RMA can prioritise some investigations if they bear on a number of claims. There was a suggestion from Dr Keith Horsley (DVA) that an amendment to the legislation such that a single factor could be reviewed might make the RMA's processes more efficient and responsive. Professor Donald agreed but said that there would need to be some caveats around that and there would need to be Government support for amending the legislation.

The Specialist Medical Review Council

ISSUE

If the SMRC decides that there is sufficient evidence to include a factor that the RMA has rejected, does the RMA take that at face value or do you have to review it again?

RESPONSE

Professor Donald replied that the SMRC can ask the RMA to do a review or they can instruct it to put a factor in. They have instructed the RMA to put a factor in only once, in relation to chronic lymphatic leukemia and electromagnetic fields. The RMA did as instructed. In relation to job strain and hypertension they asked the RMA to do a review. The RMA looked at it and decided that on the whole of the evidence available the proposition wasn't sustained. However, the SOP factors put in by the SMRC are no more permanent than the SOP factors put in by the RMA. All of the SOPs are subject to review and as the scientific literature changes, they may change.

MRC Act

ISSUE

The passing of the MRC Act means that the SOPs will be used to relate service to compensation claims for serving Defence Force members. How will this affect the relationship of the RMA with the Defence Force? How will the RMA consult with the Defence community?

RESPONSE

Professor Donald noted that the legislation is new and will require careful reading, but that the process of making SOPs will not change. The RMA has foreseen a need to make some new SOPs in relation to overuse injuries and has advertised investigations into a selection of overuse syndromes. There will also be a need to consider diseases that affect younger people because of extension of coverage to school cadets.

Members of the RMA are observers on the Medical Advisory Panel and so are kept informed of current discussions between Defence and DVA in relation to occupational health and safety issues. In the past the RMA has visited troops on deployment in Timor and Bouganville to gain an understanding of conditions of service and may do so again. The RMA is looking at developing other

mechanisms for consultation with the ADF.

Professor Andrew Wilson added that in addition to looking at specific conditions, there may also be specific exposures relevant to serving personnel that need to be thought about. The Centre for Military and Veterans' Health which is being launched in May is going to be an important resource for looking at these issues.

Professor Donald agreed but pointed out that health and mortality studies of groups of veterans often document exposures poorly. There are plans within ADF and DVA to overcome this problem by developing a prospective health surveillance program which will monitor exposures during deployment of small groups of soldiers.

Supporting documentation for requests

ISSUE

A request for a review of a SOP requires supporting information which may be difficult for a small organisation or individual to collect, especially when material on the internet is not peer reviewed. Section 196CA allows the Authority to refuse a request for review when there is insufficient new evidence. What is the quality and quantity of information required by the RMA in support of a request?

RESPONSE

Professor Donald explained that when the RMA first started it was important to get enough SOPs out there working so that the system would function. To that end, the Authority would sometimes just look at a particular factor. Subsequently it had legal advice that if a SOP is to be opened for investigation, it is necessary to look at the whole SOP, not just one factor. That meant that reviewing a SOP is a major task, sometimes taking many months. A mechanism was needed to be able to prioritise SOPs that had to be reviewed as against the ones where there was not a significant case for them to be reviewed.

When the RMA receives a request for review a medical officer will check the literature to see if there is anything new that would make a difference since the SOP was last made. Even if a minimal amount of information is supplied, staff of the secretariat will attempt to pursue it and identify relevant articles. The length of time since the SOP was last reveiwed is taken into consideration. Members of the RMA sometimes also know of new activities in the area under consideration. There is a process for deciding whether there is anything which would suggest to the Authority that it is reasonable to review the SOP, we don't just say "no" simply because of the lack of information provided. Section 196CA is a safety valve so that the RMA can priortise what really needs to be done.

Andrew Leiboff (medical research officer) added that the request must nominate a disease and a risk factor so that a search of the published evidence can be made. Internet searches are not dismissed as a source of information, but if the information is nothing but opinions then the quality of the evidence may be questionable.

Professor Andrew Wilson reinforced the point that it is not the internet per se that is the problem but the quality of the information that comes from it. The web is a major source for published peer reviewed literature and there are some fully peer reviewed journals that are only published on the web.

Documentation of Previous Studies

ISSUE

Why is it so time consuming to review earlier scientific studies when these would

presumably have been documented from previous investigations?

RESPONSE

Professor Donald agreed that there is a document available, that being a submission to the Authority of the critical appraisal of the literature, at the time the SOP was made previously. There are two issues with such documentation. One is that if a SOP is reviewed it is important to make sure that there were no mistakes. That requires having a significant look at that previous critical appraisal and maybe even re-reading some of the papers. The second thing is, if new papers have been published, then the question is what do they do to the balance of the evidence. In other words, how do they fit into the context of the balance of evidence in the previous study. Sometimes one good study will critically alter the balance of evidence and lead to a different conclusion.

Professor John Kaldor further explained that the previous submission does summarise the evidence, but it is a judgement, not a one dimensional summary. You don't come up with some score to which you can just add a further computation if a new paper comes along. You might, for example, have the situation of twenty studies that were done in the past but they all had major methodological flaws of different kinds and then one terrific study comes along that has got over that flaw. You have to have a look at the overall body of evidence in order to put the new study in context.

Guidelines for Critical Appraisal

ISSUE

Is there an international convention that defines the factors that are important in the analysis and appraisal of reports? Does that make it much easier to draw out the information?

RESPONSE

Professor Kaldor replied that there are a number of different sets of guidelines that have been put in place for doing a critical appraisal. The Cochrane collaboration, for example, is one very well known structure that recommends that reviews be done in a certain way, primarily in the therapeutics area. Various learned institutions or individuals have promulgated guidelines. You could not say there is one standard but there's a great deal in common among the different types of standards that are used. The sort of categories that the RMA uses are the ones in general use. Professor Kaldor explained that internally at the RMA there is an attempt to summarise information, not necessarily paper by paper, but in a way that combines the information with an awareness of those key categories.

Professor Donald added that most of the studies are done on "free-ranging human beings" who are pretty hard to round up. This limits the quality of evidence from epidemiological studies. You just cannot get a dose response sometimes because people, in doing the studies, have been unable to structure it in such a way that you could even calculate a dose response.

ESO Consultation to Inform Decision Making

ISSUE

Epidemiological studies vary in quality and it is sometimes difficult to find evidence. Previously the RMA had a lot of consultation and communication between ex-Service organisations and the Department of Veterans' Affairs so that the RMA could take into account a far wider view of the clinical evidence in relation to causality. Now there appears to be a greater emphasis on documentary evidence.

RESPONSE

Professor Donald responded that the RMA always has the option of exercising clinical judgement. He explained that probably nearly all of the straightforward decisions were made in those first three years and what is left is the matters which are less clear, matters which are in contention and matters in which the literature is sometimes very extensive. Professor Donald acknowledged that the issues have become more difficult and that it is time once again to have more face to face communication. The RMA intends to recommence holding meetings interstate.

Professor Kaldor further clarified the meaning of clinical judgement. Clinical judgment or "common sense" is distinct from or complementary to epidemiological data. He emphasised that those processes come in after the RMA has gone through a very comprehensive review of what is available. Clinical judgements are a mechanism of interpretation of the data and resolving ambiguities that cannot be resolved with the available data. They are not a substitute or an alternative pathway for that analysis.

Issues Relating To Particular Factors

Class of Veterans

ISSUE

Although you have stated that the legislation is not based on classes of veterans, there is a factor for 30 days service in Vietnam, so what is the difference?

RESPONSE

Professor Donald acknowledged that the Vietnam factor was a class of veteran factor but it came in about 1994/95 and the RMA has had advice that it cannot repeat that sort of factor. It was based on the fact that although there was some published literature, it was very difficult to untangle what the real exposures were. Not every soldier in Vietnam, for example, had the same exposure to Agent Orange. The 30 days was chosen because that was what was required to get the Vietnam Medal for active service. Similarly, for radiation the RMA has gone away from class of veteran factors to doses of radiation.

Professor Donald added that it is also important that the factors retain scientific credibility. The SOP system was introduced because the Auditor General advised parliament that the old system was inconsistent and lacking in credibility. The RMA must be able to point to a convincing link to the science. Furthermore, inclusion of a factor must be based on the entire body of evidence, not just on one published paper out of many.

DDT

ISSUE

DDT is not recognised in the SOPs yet there are studies which indicate damage to bird eggs.

RESPONSE

Dr Keith Horsley (DVA) agreed that DDT was banned because it was making eggshells too thin and the American Bald Eagle was becoming extinct. He noted however that DDT is in fact recognised in the SOPs because exposure to DDT is a factor in the SOP for pancreatic cancer. Professor Donald explained that the RMA has studied the effects of DDT extensively but there have only been two studies of significance, the one which allowed the RMA to include it in the SOP for cancer of the pancreas and another which showed that it protected African-American women from breast cancer.

Definition of METs

ISSUE

It is difficult for widows to substantiate the factor for "inability to undertake more than a mildly strenuous level of physical activity" because the definition uses METs as the unit of measurement.

RESPONSE

Professor Donald said that the RMA understands that it is often difficult for widows to remember details but this is a problem for the Department as it relates to the evidence. There is some guidance from the Department at two levels. The GARP documents provide some guidance on how to translate activity levels into METS. The Decision Support Unit also distributes explanatory bulletins.

Brigadier Bill Rolfe (VRB) explained that there is an evidentiary onus to put forward some material that relates in a positive way to the particular contention. The VRB takes into account a lack of records due to the passage of time but without some material it is difficult to make a case.

Lifting and Carrying Factors

ISSUE

Can you clarify the application of lifting and carrying factors in SOPs for cervical, thoracic and lumbar spondylosis?

RESPONSE

Professor Donald said that the load and the frequency of carrying or lifting are used to calculate the cumulative total. If heavy loads are lifted or carried more frequently, the total will be reached more quickly. Both picking up and putting down count as a single operation. The instrument for cervical spondylosis only has a carrying factor because the SMSE relates to carrying heavy loads on the head. Carrying implies an initial lift hence the same formula as for lifting can be used.

Dr Kym Hickey (RMA medical officer) added that it is just a matter of multiplying the weight of the load by how many times you lift it to get the cumulative loads.

Solar UV Formula

ISSUE

What are the results of recent RMA meetings concerning the Solar UV Formula?

RESPONSE

Professor Donald stated the background to this issue, that is, a potential problem with running the UV formula program on the Department's new computer system and a wish expressed by ex-Service organisations not to make any changes to the formula based factor. After much discussion over several meetings the RMA has decided to try to develop a new factor but retain the formula. The new factor will probably be a sort of screening factor based on the amount of time and the latitude where the veteran served. If the veteran does not succeed under the new factor then he or she can go to the formula for a more detailed examination. Mr Norm Clarke (Legacy) supported this proposal because it would take the guesswork out of trying to obtain a detailed lifetime history from war widows about their husband's clothing.

Stress and Stressors

Stress of Perceived Failure

ISSUE

Quite often a member of the defence force or veteran may experience stress from failure or perceived failure.

RESPONSE

Professor Beverley Raphael agreed with this statement and added that in combat situations your time sense is often distorted, and you think you had time to do things when in fact you didn't. In the Granville disaster people's sense of frustration about not being able to fulfil their functions and the stress of that became apparent. Those issues come up in the consideration of stressor exposures. The issue for the RMA is what does the scientific literature say and how does it delineate those stressors.

Response to Judges' Interpretations

ISSUE

When cases come to court, judges often provide their interpretation on the words in the SOP, for example in relation to intense fear, helplessness and horror. Does the RMA review those psychiatric conditions when that happens?

RESPONSE

Professor Raphael responded that the RMA does take note of issues that are brought up from individual cases. The RMA will look back and see what it based the wording on, and how that's reflected in the literature. One of the limitations is what the literature shows, even though the RMA tries to dissect out these things, sometimes the literature doesn't dissect them out at all.

Severe Stressor Definition

ISSUE

Some SOPs specify that a stressor be extreme or severe and there are many situations in which a veteran does not remember a severe stressor despite being in a combat situation for quite some time.

RESPONSE

Professor Raphael agreed that in the circumstances of combat there are a range of stressors, not all of which would meet the definition of a catastrophic stressor. The question that has come up for the RMA is does there have to be an actual or objective threat or is it sufficient for there to be a perception of it. That is a complex boundary. Nobody would argue that in combat there is actual threat of death. Less severe stressors may result in other conditions which are covered by the SOPs.

Lack of Evidence of Exposure to a Stressor

ISSUE

We see cases of veterans with a psychiatric disability but no incident or evidence of real stress, apart from service itself. The SOPs don't seem to apply to these cases. Are you looking at that area? Shouldn't the principle of beneficiality apply?

RESPONSE

Professor Raphael explained that it certainly could come up in what the RMA is looking at because there's an evolving literature in the whole aetiology of a range of psychiatric disorders. She pointed out that at least one in five of the Australian community has a diagnosable psychiatric disorder. The years of being a soldier or being in the services are the years in which these disorders come on, so there is also potentially a coincidental effect. There are a great many people in the ages of 18 to 40 who develop significant and disabling psychiatric illnesses who have never had exposure to combat. So that's what complicates understanding whether the service has contributed in this particular circumstance. While the RMA is open to looking at the issues, there has to be an identified causal chain.

Professor Donald added that the principle of beneficiality applies at a number of levels in

the system. In the evidentiary area where there is reverse standard of proof, then certainly you would expect that it would apply. At the reasonable hypothesis level, the evidence that is needed to put in a causal factor is in fact a very generous interpretation of the literature. It's not really a question of whether the generous nature of the legislation can be applied here. The problem for the RMA is that the issue is so complex that simple solutions that can be sustained are very difficult to find. Finding the evidence in the literature to sustain or underpin those simple solutions is very difficult because the literature is very complicated indeed.

Professor Raphael further added that the literature is becoming more sophisticated so it may become more obvious in future how to distinguish between service and other aspects of life. Also, it may be that a system of management might be more clearly linked to care than compensation.

Prolonged or Cumulative Stress

ISSUE

In respect of the severe stressor, the statement of principle for PTSD specifies an actual event, one single event, as opposed to someone who has been involved with prolonged stress or cumulative stress in a combat zone. For example, there is the veteran who has had the fear of being attacked or overrun for his whole period of service in Vietnam. There doesn't seem to be a window of opportunity for that veteran who may be suffering from PTSD.

RESPONSE

Professor Raphael replied that there is not the intent to exclude a veteran who has had exposure to that sort of stress but the fact is that in the literature a lower level of stress that is chronic may be more associated with anxiety and depressive disorders than with PTSD per se. So, sometimes the different definitions are reflective of that. Generally, if a person has been exposed to the sort of life threat continuously in combat, he would have had at least one event like that, so it shouldn't exclude him from being eligible for PTSD if that's the condition that he has. This is a matter for ongoing consideration by the RMA.

Stress from Natural Disasters

ISSUE

What is the literature in relation to stress from natural disasters such as Cyclone Tracy and the Brisbane floods and how can it be applied to military settings?

RESPONSE

Professor Raphael responded that the RMA does take the general disaster literature into account as well as military studies. Studies of disasters world-wide have shown impacts from the acute stressor exposure as well as from the chronic stressors of the aftermath.

Health Studies

Separating Out Multiple Deployments

ISSUE

There is an overlap between Korean War veterans and veterans of other conflicts; some Korean War veterans went on to serve in Vietnam and some had already served in the British atomic test program or World War II. How is this taken into account?

RESPONSE

Dr Keith Horsely replied that work is being done to separate these groups. There were about 30% of Korean War veterans who were World War II veterans and19% who were also Vietnam War veterans. An analysis

of the veterans who only went to Korea is planned. It will be difficult to construct a comparison group because nearly all the active army went to Korea. A comparison with older Australian men is being undertaken. Mr Bill Maxwell (DVA) added that the phenomenon of soldiers going on multiple deployments is also a feature of more recent deployments.

Dealing With Findings of Excess Symptoms

ISSUE

There are some diseases that may not have been identified from previous health studies. How can the system deal with the findings of excess symptoms being identified by these studies? Is it within the authority of the RMA to make recommendations to the Department?

RESPONSE

Professor Donald responded that there was no easy answer to that problem, which is also likely to unfold when the F111 health study is completed. Further investigation may be necessary to discover whether a new disease is being uncovered. The RMA has to work with the legislation. With health studies there is sometimes an unrealistic expectation that the RMA will be able to act upon the findings when in fact it will not produce an outcome that fits into the legislation.

Professor Donald added that the RMA does make recommendations to the Commission. The RMA has been advocating for prospective surveillance and ongoing systematic record keeping for nearly ten years. The RMA also has the opportunity to make suggestions or comments through the Medical Advisory Panel.

Mr Bill Maxwell (DVA) explained that the VEA does not require a person to lodge a claim for a diagnosed medical condition. It requires them to lodge a claim for the acceptance of incapacity, which can be described in terms of a range of symptoms. The department has to investigate the claim, establish the medical conditions present and then apply the relevant SOPs. If no label for those symptoms can be identified, the claim can be dealt with as a non-SOP condition. Dr Keith Horsley (DVA) added that it is DVA policy to provide treatment until such time as a label is applied to those symptoms.

Professor Wilson pointed out that retrospective health studies can help identify constellations of symptoms which might go to form a new syndrome. The advantage of prospective studies is that they provide the opportunity to study the exposures that actually contribute in some way to those symptoms or syndromes.

RMA Response to F111 Health Study

ISSUE

What action has the RMA taken in regards to the findings of the F111 Health Study and any other DVA/Defence Study?

RESPONSE

Professor Donald said that the RMA has been watching the F-111 study carefully. The Principle Medical Officer attends the meetings of the Steering Committee and the RMA gets the minutes of that meeting. The RMA has advertised an investigation into toxic encephalopathy which is specifically aimed at determining whether there is a disease under which some of the F111 deseal/reseal people would fit. Some of them may be covered by the existing psychiatric SOPs. However, there will potentially be people who were involved in the reseal/deseal process who do not fit into the categories that a SOP would cover.

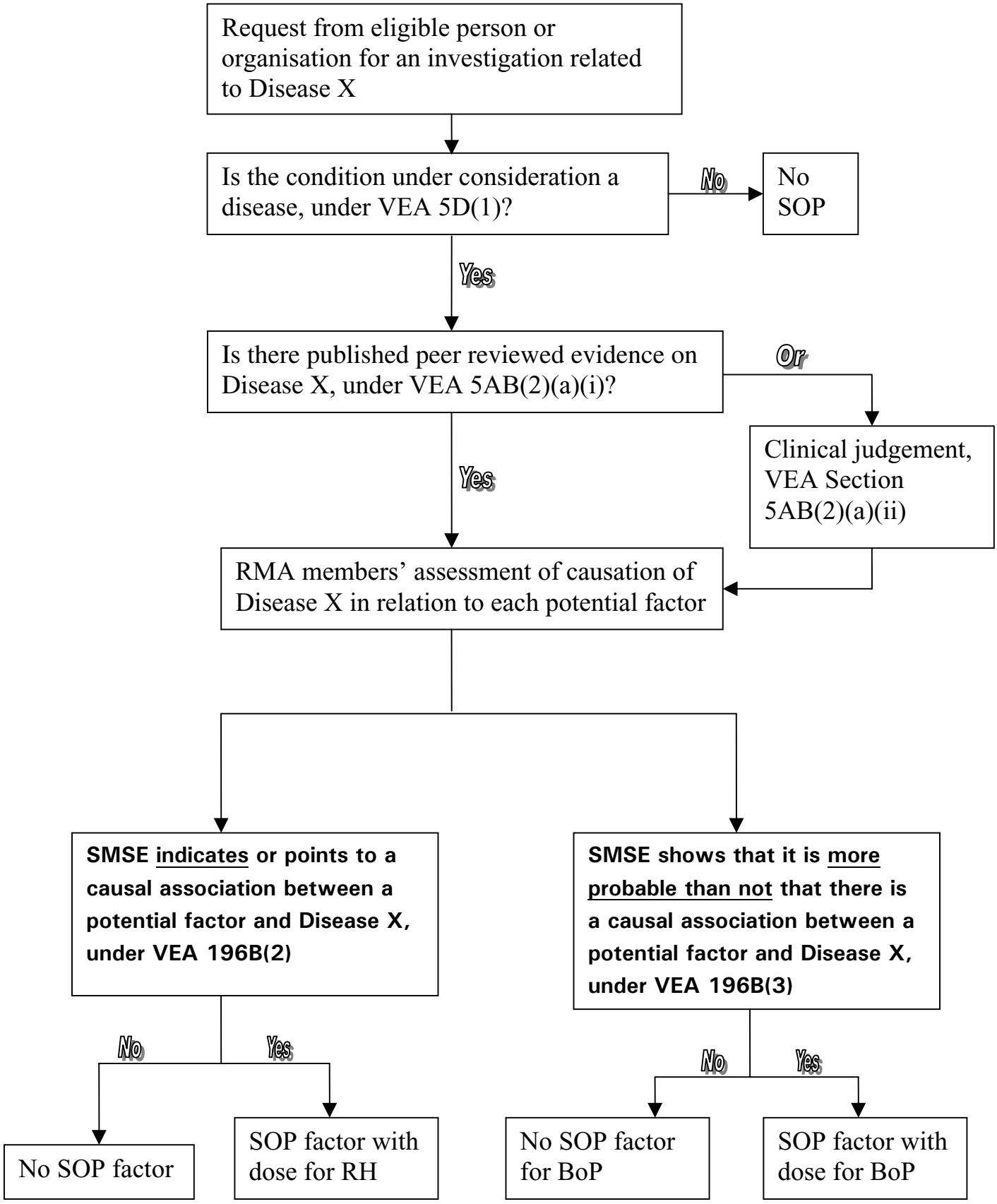
The RMA did obtain a copy of the chemical composition of the materials that were used

and were staggered by the list of chemicals. Dr Ian Gardner (Defence) pointed out that the study is not specifically about the use of chemicals, but also about deseal/reseal processes. Professor Donald further explained that it was recognised right up front that it would be impossible to identify the contribution of this huge range of chemicals, most of which had very poorly described toxicological principles. Therefore the study is really basically looking at the processes and asking the question, "Is there an association between working on these processes and adverse health outcomes?"

Mr Andrew Leiboff (medical research officer) added that the members of the RMA and Secretariat have been made aware of the chemicals which were used by this group and will routinely look for evidence of a causal link between those chemicals and the disease under investigation.

Appendix 1

Determination of SOPs Flowchart – 2004 Forum



Appendix 2

Background Terminology: Introduction To Some Epidemiological Terms

Dr Alex Bordujenko, RMA Secretariat

Epidemiology

This is the study of variations in disease frequency among population groups, and the factors that influence these variations. The principle objective of epidemiology has been to determine factors which may cause or contribute to disease processes in humans, so that preventive measures may be applied.

Epidemiologic observations have a long history, with much work developed through the study of acute epidemic diseases such as cholera and typhoid. The discipline has burgeoned over the latter half of the Twentieth century, with interest in the study of the cause, treatment and prevention of cancer, cardiovascular and other chronic disease, and of course the advent of computer storage and analysis systems.

Approaches for Epidemiological Study

Hennekens and Buring (1987) define epidemiology as "the study of the distribution and determinants of disease frequency in human populations." "Humans" distinguishes the approach from research using animal or other systems in experiments. "Populations" contrasts the practise of individual investigation as in clinical research. "Frequency" indicates the quantification of disease occurrence and the risk attributable to various potential causes. The term "distribution and determinants" points to the two major approaches of epidemiology:

1. examination of the distribution of disease frequency in populations (this can produce hypotheses about the causes of disease) known as descriptive studies; and
2. analytical studies which test these hypotheses by reviewing personal characteristics or exposures among individuals within the populations.

Descriptive studies use population based statistics on mortality, disease incidence, and survival. Other registries for example hospital based disease registries, may also be useful. Obviously the studies concern populations and not individuals and measures of any exposures are usually broad and may be subject to confounding or interfering factors. Selection of free living populations may introduce biases and confounding into the calculations. Examination of national and international trends, migrant studies and time trends has provided valuable insights into the causation of a number of chronic diseases for example breast, prostate and lung cancers.

Analytical studies have provided much useful information concerning the discovery and/or confirmation of a number of lifestyle and other environmental exposures as causes of chronic disease, including cancer. Examples of these include cigarette smoking, where, for smokers of 40 or more cigarettes per day there is a risk of lung cancer of more than twenty times that of a non-smoker. Another well documented example is occupational exposure to asbestos and the development of mesothelioma, where the relative risk is well over 100 fold that of the unexposed population. Analytical studies from several international sources in the last decade have also demonstrated that both the incidence and recurrence of neural tube defects can be greatly reduced by maternal folate supplementation in early pregnancy, even in the absence of maternal folate deficiency.

In chronic disease epidemiology, the types of analytical studies encountered are:

A. Cohort studies identify groups of individuals with and without a particular exposure, and follow them over time to examine disease incidence and/or mortality rates.

These may be current or past exposures. An association is suggested when rates of disease or death differ between the groups. These are able to directly measure incidence and mortality rates related to a particular exposure (especially with prospective design) but they require large numbers of exposed individuals particularly when considering uncommon diseases, before significant differences may be noted.

B. Case-control studies or case-referent studies identify people with a particular disease (case), and a group of people without the disease (controls), and then collect information about past exposures, for example by interview or questionnaire. They provide a method of studying rare diseases but may be subject to recall and other biases, and difficulty in measuring past exposures.

Data Presentation and Interpretation

The odds ratio (OR) is a measure of association used in case control studies to estimate the odds of exposure in cases to the odds of exposure in controls. This approximates, but is not synonymous with, the "relative risk" (RR) the measure of association used in cohort studies. The term relative risk (RR) is used to describe the comparison of the risk of a known exposed group versus a known unexposed group developing a specific condition. Thus if the relative risk is one the risk is the same for both groups and exposure is not seen to be associated with the development of the particular condition that is, there is no increase in the risk of a studied outcome with the exposure of interest. If the RR (or OR) is 1.5 then the risk for the studied outcome in the exposed versus the unexposed group is increased by 50%. An RR (or OR) of 2 implies a doubling of risk, and an RR (or OR) of less than one implies a reduction of risk. Problems in decision making occur when the described increase in risk is weak (under a two to three fold increase) and particularly when the relative risk is close to one, for example 1.1 (10% increase) or 1.3 (30% increase) rather than the 20 fold increases for heavy cigarette consumption and the incidence of lung cancer and the much grater increases seen with occupational asbestos exposure and the incidence of mesothelioma. Many epidemiologists are reluctant to accept as real, increases in risk of less than 100% (RR<=2) as likely to be causative unless the "Bradford Hill" types of criteria are stringently applied to the body of evidence pertinent to the putative association, and overall, a considered case can then be made to support causality.

Another term, the "confidence interval" (CI), is used to describe the range of relative risk (or odds ratio) rates within which the actual result lies, to within, for example, a 95% probability. Thus, if the confidence interval includes one then the result could have occurred due to chance and no true effect may exist. If the 95% confidence limits exclude one it does not exclude the possibility of a chance result, rather it indicates that chance would explain the observed (or a greater) risk estimate only one out of 20 times.

Selected Measures of Disease Frequency

As well as the relative risk and odds ratio a number of other measures of disease frequency need to be considered. A consideration of the basic concepts of these measures includes the formulae used to calculate such measures. In its simplest form

data from a two-by-two table from a case-control or cohort study with count denominators would appear as:

	Disease		
	Yes	No	Total
Exposure Yes	a	b	a+b
Exposure No	c	d	c+d
Total	a+c	b+d	a+b+c+d

a = the number of individuals who are exposed and have the disease

b = the number who are exposed and do not have the disease

c = the number who are not exposed and have the disease

d = the number who are not exposed and who do not have the disease

As stated above for cohort studies the term relative risk (RR) is used to describe the comparison of the risk of a known exposed group versus a known unexposed group developing a specific condition, that is the incidence of the disease in the exposed divided by the incidence in the unexposed Ie/Io or the cumulative incidence of the disease in the exposed divided by the cumulative incidence in the unexposed CIe/CIo.

The formula for calculating relative risk for cohort studies with count denominators is thus:

$$\frac{I_e}{I_o} = \frac{CI_e}{Ci_o} = \frac{a/(a+b)}{c/(c+d)}$$

(where a,b,c,d are derived from the 2x2 table outlined above).

For case control studies with count denominators the **odds ratio** is expressed as:

$$\frac{a/c}{b/d} = \frac{ad}{bc}$$

(where a,b,c,d are derived from the 2x2 table outlined above)

The odds ratio is said to provide a valid estimate of the relative risk for case-control studies where the cases are newly diagnosed, where prevalent cases are not included in the control group and where the selection of cases and controls is not based on exposure status.

Attributable risk is the measure which provides information about the absolute effect of the exposure and is the excess risk of disease in those exposed compared with those who are unexposed to a specific factor. This measure is defined as the difference between the incidence rates in the exposed and unexposed groups and may be calculated in cohort studies as

$$AR = CI_e - CI_o = a/(a+b) - c/(c+d)$$

(where a,b,c,d are derived from the 2x2 table outlined above)

The attributable risk percent (AR%), attributable rate percent attributable proportion or etiologic fraction is calculated as the attributable risk divided by the rate of disease among the exposed and is said to represent the proportion of disease in that group that could be prevented by absence of the exposure.

$$AR\% = AR/I_e \times 100 = (I_e - I_o) \times 100 = (1 - I_o/I_e) \times 100 = (1-1/RR) \times 100 =$$

$$(RR-1/RR) \times 100$$

Population Attributable Risk (PAR) is the measure used to estimate the excess rate of disease in the total study population of exposed and unexposed individuals that is attributable to the exposure. The PAR is calculated as the rate of disease in the population (incidence rate in total population = It) minus the rate in the unexposed group (Io):

$$PAR = I_t - I_o$$

or by multiplying the AR by the proportion

of exposed individuals in the population (Pe):

PAR = (AR) x (Pe)

Population Attributable Risk Percent (PAR%) is represented by:

$PAR\% = 100 \times (P_e) \times (RR-1)/1+(P_e) \times (RR-1)$

Epidemiologic Studies Need Careful Examination

(Refer to:- Darzins PJ, Smith BJ and Heller RF (1992). How to read a journal article. The Medical Journal of Australia, Vol 157 pp 389-394.)

The size of the population studied is important – the larger the sample size the greater the power (or ability) to detect a specified risk, the smaller the sample size the weaker the power. Negative results from small studies may not be conclusive as only large studies may confidently exclude or include low to moderate levels of risk.

When examining any study results, consideration of the possibility of a non-causal association is necessary. The observed association between exposure and disease may result from bias, confounding, chance, or cause-and-effect.

Bias is the term used for any systematic error in a study and may occur during study selection, information gathering or in reporting of the assessment of the exposure or outcome under investigation. Confounding bias is the possibility of the observed effect being due to other variables not adequately considered in study design or analysis of the results. Many types of study bias have been described including selection, information, recall, and interviewer bias. Confounding bias or confounding is due to variables which may themselves account for all or part of an apparent association between an exposure and a disease. They may also obscure an association. Chance is considered previously in the discussion of study power and Confidence Intervals.

Study Types

Study design has an effect on the quality of evidence which may be gained and a recognised 'hierarchy' of study types exist. In developing the following the "US Preventative Services Task Force: Guidelines for Quality of Evidence" (Fisher, 1989) have been considered. Given the specific needs of the RMA some modification has been undertaken. In this instance the level of evidence available is at best observational (cohort or case control studies). The following is broadly the division of available study designs and how these may be considered in the information gathering.

Analytic Studies:

1 Intervention Studies
- 1a Randomised Controlled Trial
- 1b Controlled Trial

2 Observational Studies
- 2a Cohort-Prospective
- 2b Cohort-Retrospective

3 Case Control Studies

Descriptive Studies:

4 Population (Correlational)

5 Individual
- 5a Cross Sectional Surveys
- 5b Case Series
- 5c Case Reports

Where the numbering 1-5 refers to the grade assigned to the quality of the evidence. Quality refers here to study design rather than individual study merit that is that the evidence from cohorts is graded as higher

than that from case control studies – this is the method used by the US Preventative Services Task Force.

While the RMA places emphasis on primary research published in the leading peer reviewed journals of either broad or discipline specific type; published, peer reviewed, reports on the epidemiology of disease such as those produced from time to time by the International Agency for Research into Cancer, the National Academy of Science, or the Surgeon Generals' Reports concerning to smoking related disease; are considered appropriate sources for examination. Published reports from sources such as the National Health and Medical Research Council and other expert committees are also be considered where contemporary, applicable material is available.

Consideration of Individual Studies

(Refer to:- Darzins PJ, Smith BJ and Heller RF (1992). How to read a journal article. The Medical Journal of Australia, Vol 157 pp 389-394.)

In the absence of interventional studies such as randomised controlled trials most reliance is placed on well designed and reported cohort and case control studies and Professor Heller provides a method of considering these. This forms a mental check list in consideration of materials.

The following questions may be specifically addressed.

1. What is the research question?
2. What is the study type?
3. What are the outcome factors and how are they measured?
4. What are the study factors and how are they measured?
5. What important confounders are considered?
6. What are the sampling frame and sampling method?
7. How many subjects reached follow-up?
8. Are statistical tests considered?
9. Are the results clinically/socially significant?
10. What conclusions did the authors reach about the study question?

After determining these features a decision on adequacy of methods and clarity of results is made considering:

bias – are the results biased in one direction. If so, what is the direction and magnitude of bias

confounding – are there any serious confounding or distorting influences? Has an attempt been made to deal with these and has this been adequate?

chance – is it likely the results occurred by chance? Consideration of the statistical content of the study.

It is recognized that for many putative factors evidence may only be available in descriptive studies. This is often the case for case reports or case series of disease associations or drug reactions.

Association and Causation

Association is the term used to describe the statistical dependence between two variables. In epidemiology it is the degree to which the rate of disease in persons with an exposure of interest is either higher or lower than the rate of disease among those without that exposure. Such an association does not mean, or even imply, that the observed relationship is one of cause and effect (Hennekens and Buring, 1987).

Making judgements about causality from epidemiologic data involves a logical

process which addresses two major areas:

1. Whether for any individual study, the observed association between an exposure and disease is valid. An assessment of validity requires a consideration of the likelihood of alternative explanations for the results and chance (the luck of the draw), bias (any systematic error in the study for example in subject selection, information gathering or reporting), or confounding (the observed effect being due to other variables not adequately considered in study design or analysis of the results); and
2. Whether the body of the evidence considered supports a judgement of causality. In this process standard epidemiological criteria are used (Hennekens and Buring, 1987).

Epidemiologic criteria used to assist in the assessment of causality

The RMA considers the individual studies with respect to the above and then, in considering the available evidence uses standard epidemiological criteria to make a judgement regarding causality with regard to the reasonable hypothesis and balance of probabilities standards of proof. The Bradford Hill criteria (Bradford-Hill, 1965), and more contemporary versions, are widely accepted in the interpretation of epidemiological studies for the purpose of assessing the possibility of a causal association.

Consideration of the body of evidence available for each contention against the current epidemiologic criteria will result in a judgement regarding causality. As Professor Holman (1997) notes, more than 30 different systems of causal verification have been described. In his technical appendix to the Pearce Report he outlines ten criteria for classification of evidence of causality, based on work by Mervyn Susser. The RMA has considered a number of such systems including those of Bradford Hill, Susser and those co-authored by Professor Holman in *"The Quantification of Drug Caused Morbidity and Mortality in Australia, 1995"* (English and Holman, 1995). The RMA recognises the underlying similarities which underpin these systems.

The exact description of these epidemiologic criteria varies between authors and the RMA recognises the need to consider both internal study validity (for individual studies) and factors important in the body of evidence (the applicable evidence available from epidemiological, clinical, toxicological and other research) in these criteria.

Sir Austin Bradford Hill, as well as other prominent statisticians and epidemiologists, including Mervyn Susser and Kenneth Rothman, have described how the subjective likelihood (or the correct judgement) of a causal relationship is increased when evidence relating to an association meets criteria devised to consider the available evidence. The Bradford Hill (Bradford-Hill, 1965) criteria are as follows:

1. Strength of Association
2. Consistency
3. Specificity
4. Temporality
5. Biological Gradient
6. Plausibility
7. Coherence
8. Experimental evidence
9. Analogy

The criteria used by the Expert Committee on Herbicide Exposure and Spina Bifida (1996) further refined the criteria to explicitly include consideration of bias and confounding in the criteria:

1. Statistical significance (that is the

possibility of chance being responsible for an apparent association; and study power)
2. Strength of association
3. Consistency of association between studies
4. Possibility of bias in measurement of exposure or outcome
5. Possibility of selection or confounding bias
6. Time sequence
7. Dose response
8. Biological plausibility (including aspects of theoretical coherence, biological coherence and factual coherence)

1. Statistical significance and power

If the criterion of statistical significance is satisfied then the evidence is supportive of an association. The failure of a test to reach statistical significance in the presence of adequate statistical power provides evidence against the association, however in the absence of adequate statistical power it may not necessarily detract from the association.

2. Strength of association

The greater the strength of association the more likely it is to be causal. Confounding is less likely to explain a strong association because the strength of the association between the confounding variable and the outcome must also be strong. While a strong association is supportive of causality, a weak association may not necessarily detract from the evidence of causality however adequate consideration of potential confounding or bias is essential.

3. Consistency of replication

Consistency of the evidence or the lack of evidence in the face of study diversity in time, place, circumstances and population, as well as research design, strongly supports or detracts from a causal hypothesis.

4. Possibility of bias in measurement of exposure or outcome

Consideration of any systematic error in the study in information gathering or in reporting of the assessment of the exposure or outcome under investigation. Absence of bias in the studies considered to show a positive association supports the existence of a putative association. The presence of bias detracts from the conclusions which may be drawn from the information.

5. Possibility of selection or confounding bias

Consideration of any systematic error in the study in subject selection; or the possibility of the observed effect being due to other variables not adequately considered in study design or analysis of the results. Absence of bias or confounding in the studies considered to show a positive association supports the existence of a putative association. The presence of bias or uncontrolled confounding detracts from the conclusions which may be drawn from the information.

6. Time sequence

The exposure must precede the disease or injury. This criterion is compatible with, but does not necessarily support causality. Reversal of the order of exposure and disease or injury is the most persuasive basis available for rejection of causality.

7. Dose response

A response which is in proportion to the level of exposure is strongly persuasive of a causal relation. However, its absence does not necessarily detract from the association.

8. Biological plausibility

(aspects of theoretical coherence, biological

coherence and factual coherence)

Theoretical coherence: Findings plausible in terms of pre-existing theory are supportive of the association. Conversely, findings that are implausible in terms of pre-existing theory detract from the evidence.

Factual coherence: Compatibility of a new result with pre-existing facts is supportive of the association. Incompatible pre-existing facts strongly detract from evidence of causality.

Biological coherence: Pre-existing knowledge which identifies a mechanism by which the chemical exposure may produce the disease or injury is supportive of case for the association being causal. Observations from species other than humans may also be used to support the potential mechanism of action. Incoherence between biological knowledge and study observations detracts from the case for a causal association.

As Rothman and Greenland (1997) eloquently acknowledge inductively oriented causal criteria are not sufficient within themselves and require sound scientific judgement to traverse the path for which the criteria are “the road map through complicated territory”.

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Appendix 3

Workshop Summary

A workshop was conducted at the forum for the purpose of giving delegates some direct experience of the processes by which the RMA works in deciding on which factors should be included in a Statement of Principles. The workshop was divided into two parts. For the first part, participants were divided into work groups of around eight people and provided with two studies each on which to go through a critical appraisal checklist (see box). Each group was allocated one of two topics relating to issues recently considered by the RMA: hepatitis C as a risk factor for diabetes, and inadequate intake of dietary fibre as a risk factor for colorectal cancer.

For the second part of the workshop, participants came back together for a discussion about whether the body of evidence was strong enough to support the inclusion of these risk factors in either the RH or BoP instruments. Participants were provided with a table summarising all the available peer-reviewed studies concerning those particular factors.

Professor Andrew Wilson led the discussion on hepatitis C and diabetes after Dr Ian Smith (RMA Secretariat) had gone through the answers to the critical appraisal questions for the two hepatitis C studies. All the groups felt that the material was sufficient only to include the factor in the RH instrument. This was in accordance with the decision of the RMA. Professor Wilson pointed out that in this case the exposure was easy to define, as it was simply a positive blood test. The issue of latency (time interval between exposure and outcome) was harder to resolve because of the lack of available data, particularly a lack certainty about a clear biological mechanism. Different mechanisms would involve different time frames. The most generous interpretation of the data in this case was to have no latency period.

CRITICAL APPRAISAL CHECKLIST

What is the study about?

- What is the study hypothesis (research question)?
- What is the study type?
- What is the outcome factor (disease of interest) and how is it measured?
- What are the risk factors and how are they measured?
- Where did the study subjects come from?

What are the main results?

- What is the size of the effect?
- Are the results statistically significant?
- What are the confidence intervals?

Can the results be explained by anything else apart from the risk factor under consideration?

- What are the important potential confounders in this association and were they taken into account?
- Is there any bias in the selection of study subjects or in the measurement of exposures or outcomes?
- Could the results be explained by chance?

What is the evidence for causation?

- What is the strength of the relationship?
- Is there a dose response effect?
- Is it clear that the exposure precedes the outcome?
- Are the results consistent with other evidence?
- Do the results make sense from our understanding of biology?

Conclusions

- What conclusions do the authors reach? Do you think that they are reasonable?

The final SOP factor (RH only) was:

"having hepatitis C virus infection before the clinical onset/clinical worsening of diabetes mellitus"

Professor John Kaldor led the discussion on dietary fibre and colorectal cancer after Andrew Leiboff (RMA Secretariat) had gone through the answers to the critical appraisal questions for the two dietary fibre studies. Professor Kaldor discussed two graphs showing a summary of the results and confidence intervals of all available case-control and cohort studies. Cohort studies are considered to be a stronger form of evidence. He pointed out that in the graph summarising the case-control studies most of the results were below the level of no effect, giving the overall impression that most studies suggest that dietary fibre protects against colorectal cancer. However, the graph summarising cohort studies showed that most of the results indicated no effect, apart from one recent large study.

In conclusion, there was enough indication to put a factor in the RH instrument, but insufficient indication to put a factor in the BoP instrument. Professor Kaldor explained that the RMA then had to decide upon the dose of fibre and the length of time in which fibre intake has to be reduced before cancer risk starts to increase. These decisions were based on the information in the available studies.

The final SOP factor (RH only) was:

"an inability to consume an average daily intake of 20 grams of fibre in food (or a total of 36 500 grams of fibre in food) over a continuous period of five years within the ten years immediately before the clinical onset of malignant neoplasm of the colorectum"

Professor Kaldor concluded that these two examples were good illustrations of some of the challenges faced by the RMA when making decisions about risk factors. In relation to hepatitis C and diabetes, the situation was one of having to come up with a decision based on very limited information of varying quality. In relation to dietary fibre and colorectal cancer, there was a lot more evidence available but the results were conflicting and there was an additional need to decide on dose. In either case, the decisions could change if new information from well conducted studies becomes available.

Appendix 4

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Appendix 5

Organisations Represented at the Forum

APPVA	Australian Peacekeepers & Peacemakers Veterans Association
ASASA	Australian Special Air Service Association
AVADSC	Australian Veterans & Defence Services Council
DoD	Department of Defence
DVA	Department of Veterans' Affairs
RDFWA	Regular Defence Force Welfare Association
RMA	Repatriation Medical Authority (the Authority)
RSL	Returned & Services League of Australia Limited
SMRC	Specialist Medical Review Council
TPI	Australian Federation of Totally & Permanently Incapacitated Ex-Servicemen and Women
VRB	Veterans' Review Board
VVAA	Vietnam Veterans Association of Australia
VVFA	Vietnam Veterans' Federation of Australia