Proceedings of the joint RMA, DVA & ESO Forum held in Canberra on 15 and 16 April 2008

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Contents

Papers presented at the Forum and not reproduced in this publication - recorded in enclosed DVDs

DVD 1

The operational context

ADF	Major General Michael Crane
DVA	Mr Mark Sullivan, AO
RSL	Major General Bill Crews, AO (Rtd)

What the "boffins" are doing: Military and veterans' research

CMVH – progress and future directions	Captain Sonya Bennett, RAN
Recent research findings and future research priorities in DVA	Dr Eileen Wilson
The challenges of conducting veteran health studies	Professor Malcolm Sim

DVD 2

What the "boffins" are doing: Military and veterans' research

Best practice mental health initiatives in the military	Colonel Peter Murphy
Long term mental health problems following trauma	Professor Mark Creamer

Disability in a post industrial society — Mr Barry Telford

Foreword

The RMA/DVA/ESO Forum was held in Canberra on the 15th and 16th April 2008, and was officially opened by the Minister for Veterans' Affairs, the Hon Alan Griffin. This was the Authority's third such Forum. There have been some similarities and some differences between each one, as many of our objectives for holding them are long-standing, although the context has changed somewhat over that time.

The first RMA/DVA/ESO Forum was held in 1998 as part of the implementation of the recommendations of the Pearce Review, an external review undertaken for the Minister of the then recently established Repatriation Medical Authority. The Review made a number of recommendations, including that the Authority consider holding a conference with medical-scientific experts having service experience. Accordingly, a main objective of the first Forum was to commence the process of elevating the ESO's knowledge and understanding of sound medical-scientific evidence (SMSE) and evidence-based medicine. Another important objective was to enhance the Authority's knowledge and understanding of the military experience.

A second RMA/DVA/ESO Forum was held in 2004, and, in addition to the above objectives, it provided an opportunity to review the Authority's achievements over the ten years since its establishment. The Forum canvassed some of the scientific and legal challenges faced by the Authority, including issues associated with defining syndromes and normal population abnormalities as diseases, problems with using health studies, the matter of what constitutes sound medical-scientific evidence and the question of standards of proof.

A number of direct and tangible benefits to the system have resulted from discussions and feedback from ESO representatives who attended previous Forums. These benefits include legislative amendments, improvements to the RMA website and changes to the consultation processes undertaken by the Authority when it proposes to remove one or more factors from a Statement of Principles (SoP). Less tangible, but still a very important outcome of the Forums (and the consultation process in general), has been, in my opinion, improved confidence in the system.

The positive benefits from previous Forums provided in large measure the impetus for the recent 2008 Forum. Our main theme on this occasion was the future of the Authority and the SoP regime as the basis of the Australian military compensation system. Having confidence in the credibility of the system is one of a number of key features which is critical to its future. In an effort to ensure that stakeholders understand all aspects of how the system works, our agenda covered a wide range of topics. We canvassed many of the day to day problems faced by the Authority in defining diseases and stressors, and highlighted some of the challenges that new technologies are raising for us, especially the genetic basis of cancer. Participants were involved in a workshop on critical appraisal and causal inference and I was impressed by the enthusiasm and understanding displayed by those involved. We invited speakers to explain the operational context and describe current research initiatives. Once again, we listened to your issues and did our best to answer your questions. Commissioner Bill Rolfe was kind enough to sum this all up as being part of our continuing efforts at "transparent excellence".

We hope that we have achieved our goal of a shared understanding of RMA issues and processes. Feedback has been extremely positive. This publication, together with the enclosed DVD, is a record of the proceedings. The printed document provides papers presented by Authority members and Secretariat staff, the Minister's opening address, a summary of the workshop and a summary of issues raised by ESOs. The DVD includes all other presentations, and gives a flavour of the event which, I hope you will agree, was as enjoyable as it was informative.

Professor Ken Donald
Chairperson
Repatriation Medical Authority

Opening Address to the Canberra Forum

The Hon Alan Griffin, MP
Minister for Veterans' Affairs

15 April 2008

[This document was prepared from the audio transcripts of the Forum and has been edited for clarity and continuity only]

I faced a couple of questions in thinking about what I might do today, and I thought, well, this is a fairly expert crowd. You've got some distinguished academics, experts in their field. You've also got some of the sharpest ESO reps in town here in the room, and that's important, because there's an element of the system which is adversarial, and there's certainly a need to make sure that all things are rigorously tested, so each of you play a very important role. Of course the problem with that in respect to my role is that I'm probably the only person in the room who actually isn't an expert in something. Correspondingly, then, my remarks will be brief.

There's no doubt, when you look at the Australian system, that medical evidence - looking at what really has happened and testing things out on a science basis - is a very important part of the system, and as part of that system the RMA plays an absolutely crucial role. We all know that the nature of service has implications that every day we're discovering more about and we're developing a better understanding, that even yesterday I remember having a meeting in my office with some people here today where we talked about the implications for service some fifty years ago.

As those matters develop, as science develops, the RMA plays an incredibly important role in terms of working out what all that means with respect to the veterans' community and those who the department and I have a responsibility for. All of that is crucial in terms of making sure we have a system which is robust, world-renowned, understood and respected generally within the wider community as being justified when we look at the question of service and the implications for that service in terms of the health of those who have served. And for those reasons it's a very important role.

But I mentioned the adversarial nature to it. That's probably putting a bit too high a point on it. The bottom line is these things do need to be tested. They need to be tested scientifically. They need to be tested – and they are tested, often on a legal basis. That's all part of making the system work and ensuring we don't rest on our laurels.

I think we're very lucky, with respect to the RMA, that we've got Ken Donald, and we've still got Ken Donald. In my time as a minister, and certainly as a shadow minister before that, I've met many of you over the last two or three years. Ken is one of those people who has always been a friendly face and a source of sound advice to me, even in a situation where I had absolutely no power to do anything at all, and I respect that because being able to develop relationships when you're on the way up can be very helpful for you when you're up there, and hopefully they'll be able to maintain them when they're on the way down.

But Ken certainly has always been someone who at things like RSL congresses, the travelling circus that we're about to start in another month or so – and I hear a bit of sniggering in the audience from Bill Crews. Yes, Bill, you will hear this speech again, and again, and again. But that is, again, an important part – the ESO meetings are an important part of that consultation. They're an important part of ensuring that we get an understanding of what's occurring amongst the rank and file of the veterans' community and it's an important place for us to impart our views. I know Ken takes it very seriously in terms of making sure he gets to a good range of those, to actually talk to people on the ground about what the issues mean with respect to them, because the problem you're dealing with matters of science is that you start off way above my head and you keep going higher, and I don't think I'm that stupid. So, it's got to be pretty difficult.

It's an important role and it's part of a system which is dynamic and flexible. It doesn't always get it right, but it gets it right more than most; and to all those here today I think this Forum is part of an important way to look at those issues and to make sure that we are always at the cutting edge.

Now, I thought, even though it's a very serious matter, I'd end up with a little bit of flippancy, and that's to try and just take the edge off it before we go into an hour and a half of Ken Donald. I actually have a test for those people which I'd like you to consider during the day. I've got a view that there's an SoP which is needed that hasn't actually come up yet. I've done some original research on it, and I've discovered, in the last week or two, starting off with the 90th anniversary of the Repatriation Commission the other day, that there's actually one component of the wider veterans' community which has an incredibly serious fatality and morbidity rate, that frankly there hasn't been an SoP done on, and I think it ought to be considered, and that is for Ministers for Veterans' Affairs.

I went through the last 10 ministers for Veterans' Affairs, and the situation is that, politically, all have died, bar one – John Faulkner. Every other one, either at the hands of a prime minister or an electorate, has, in fact, expired. This has been as good as it has got, and there's a range of issues there which I think are worthy of consideration. I mean, I know that exposure, and length of exposure, is often an important determinant with respect to impacts.

The one who actually has survived is the one who had the shortest tenure, and that was one year and one day. Those who have gone longer, have, in various stages, as I've said, expired completely in the context of the election, being De-Anne Kelly and Con Sciacca, although Con was revived subsequently, to an extent. Others have been, in a broader sense, killed by the death of a government, eg Bruce, and before that, Tony Messner.

Others who have survived in a window world, which we call "the back bench" and of which there were several around – Danna Vale, Bruce Scott – and others who were in the Senate – we're not quite sure whatever happened to them. But correspondingly, I've noted this in the last few days. It has given me a new sense of my mortality

of the seriousness of my task. It is maybe the only task I have. And in the context of looking at it with respect to the issue of SoPs, I had a look and I thought I'd just point you in a couple of directions where I think there may be some issues to look at.

I've certainly no doubt there are implications for the nervous system. Congenital anomalies – although I'm not sure I really want to be put into a control group which involves some of my colleagues who have served in this position before. And, beyond that, I'm not sure, but I can say, after meetings with some of you, that my digestive system is sorely tested.

But enough of that. Today is an important day. This is an important Forum and it provides you with an opportunity, as I've seen from the agenda, to consider some very important issues. It is a dynamic system. It's a system which is developing over time. There is a saying in politics that once you stop moving, you're dead. And in the circumstances of looking at the question of a dynamic system in the future, certainly the RMA and what it does, and you that are involved with it and in it, are a very, very important part of that system.

It's a great pleasure to be with you today at this occasion. I'm looking forward to catching up with you, as many as I can, at morning tea and tonight at dinner before I head off overseas. With representing the government at Villers-Bretonneux for next week and then on to Beersheba, there are certainly some important events coming up which I'll be very pleased to be at. I'll be back for May to start the circuit and to get around to every state and catch up with every one of you on home ground. Once again, thank you very much for having me today, and good luck with the Forum.

The RMA – now and into the future

Professor Ken Donald, AO
Chairperson
Repatriation Medical Authority

15 April 2008

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What I'm going to do is to talk to you for an unknown period of time, hopefully not an hour and a half, because we'll have time at the end for some questions, and the Minister has agreed that he will take questions, as well as myself. We'll try to leave some time before morning tea to ask some questions, as we will do at the end of every session.

I'm just going to go back a little bit over history, to provide some context. Some of the people here may be here for the first time and others may have memory problems, so I'll just go back over a bit of the past. Now, if you remember, the first Forum we had was in 1998 and we had been asked at that stage to review some of the recommendations of the Pearce Report.

When the RMA was first formed, the Minister for Veterans' Affairs was Con Sciacca, and Con gave an undertaking that at the end of the first year of the RMA operations, there would be a formal external review, and that was the Pearce/Holman Review. Part of that review did indicate that the system had become more equitable and more consistent, and decision-making was quicker and cheaper.

It also said that we should go ahead and do certain things. We should hold a medical scientific conference. We should start to outline documents about our powers and functioning processes, so that you people could understand how we operate. We should set up multi-disciplinary working parties to deal with some of these complex issues, and we should start a program of taking the ESOs with us in understanding how the evidence-based medical system would work, and we should also learn from you about the military experience, so that we could get a balance in the way in which SoPs were set out.

So that was the first Forum. We talked a lot about the standards of proof, and I'll revisit that briefly, today, because at that time there was a substantial amount of paranoia around in the veterans' community because of the change. I'll deal with that in a moment, because if you remember, the Auditor-General and the Baume Report had occurred in the early 1990s. The Auditor-General had complained that the system was unpredictable, inequitable, and had recommended, in fact, as part of his report and subsequently part of the Baume Report, that the standard of proof should go back to the civil standard. There was a feeling in the community that the RMA had been introduced by the government to change the standard of proof.

I remember in Melbourne when, at one of the early meetings, people were of the view that this was some sort of attempt to change the standard of proof. So, a lot of that first Forum was about discussions on what was the reasonable hypothesis that underpins this system, and we had a trip around the country for about six months, arguing and debating the standard of proof.

Another thing we did in that first Forum was to start the process of getting the ESOs able to do SoPs themselves, so that they could understand how we went about it. At that first meeting we provided, as we will again tomorrow, some papers on which we asked the ESOs to make a decision about what factors would go into a SoP, at the reasonable hypothesis level. It turned out that their standard was harsher than ours. So, it was interesting. The ESOs, in looking at the information, would have left out factors that we'd already put in. It was pretty clear that there needed to be a continuing program of understanding about how this causality mechanism works in the legislative context in which we find ourselves. We also had presentations about realities of service, and that will continue at this Forum.

The 2004 Forum was 10 years on from when the RMA was first formed, and we went back over the history of what happened, but you can see now that psychiatric conditions were starting to become a significant issue for debate, and they are still on the agenda for this Forum.

One of the other problems we started with at that Forum was this question about "When is a disease a disease?" given that nowadays, many parameters are being measured by chemists and laboratories. Even things like high blood pressure are not clear cut. When is elevated blood pressure actually a disease? Those sorts of questions started to arise, because an elevated blood pressure is only a risk factor for a disease, not a disease in its own right.

Questions such as "When did it become a disease?" Does it become a disease when your doctor tells you you've got it? Does it become a disease when you have to be treated? I can remember telling you that the standard that's set for hypertension is 140 over 90, systolic over diastolic; but, of course, blood vessels are already damaged at 100 over 60. So, at 120 over 70, there's more damage to blood vessels. At 140 over 90, it's called a disease.

If, in fact, we diagnosed hypertension at 120 over 70, and treated it, there would be many lives saved in the western world per year; but we couldn't afford to do it. So, the question of "What's a disease?" has an economic base sometimes, as well as a medical parameter. Therefore that issue about "What's a normal population?" began to emerge and the question "When is obesity a disease?" started to emerge. We went on, also, to look at critical appraisal and causal inference, because that underpins everything we do.

Health studies were on the agenda then, and they still are today. What are the expectations of health studies? Health studies by themselves have had very little impact on SoPs. With a couple of exceptions, I can't think of a factor that has gone into a SoP because of health studies. That's because the factors that go into SoPs come from the widest possible literature about disease causation, so that factors that stood out in health studies were already being considered or were already in existing SoPs.

What health studies actually do is go to the issue of whether a group of soldiers has been exposed or not, but this has very little impact on questions of causation. One exception is the SHOAMP study that caused us to develop the solvent-related chronic encephalopathy SoP. That's one of the few health studies that really has made any difference at all, to any SoP, which might be a surprise to you because the veteran community has a bit of a thing about health studies.

I've been on a bit of a campaign saying, "Be careful about health studies", because they do have the capacity to make people who are well, sick. Therefore I'm not a great fan of health studies. As a public health physician, I see serious dangers in health studies in the way in which they can redefine a quite well group of people as sick. And, of course, if we're looking for factors in SoPs, we don't just go to health studies. There are thousands of publications out there about the same diseases which deal with the causes. The causes are almost always in the SoPs before the health studies are published. However, the health studies do give you evidence to say you were exposed, which goes to the question of something that the RMA is not involved with, of course, the question of whether the relevant events occurred on service or not.

The issues around health studies were discussed at the 2004 Forum. We also started to talk about protective effects. Beverley Raphael and I are of the view that most people who suffer traumatic stressors suffer a growth phenomenon and become better people as a result. I guess we have a view that there is too much emphasis on the negative effects of stressors, and not enough emphasis on the fact that stressors are a growth phenomenon and they actually are good for some people. In fact, they are probably good for most people. It's not something the popular press likes to push too hard.

Another problem that was discussed at the 2004 Forum was the problem with syndromes. "When does a syndrome become a disease? " We still don't recognise Gulf War Syndrome as a disease, for reasons that we will, again, reiterate during this Forum. Lastly, we dealt with your questions – sometimes well, sometimes not well.

Some things have happened as a result of the Forums. Some legislative amendments had their genesis in the Forums, for example the single-factor focussed review. We improved the website as a result of your complaints about it, and we've gone on to a better consultation period. Improved confidence in the system has come out of the previous two Forums, and that is what I think we're really on about. Unless the system is transparent, unless you understand it, and unless you know how we do things, we will not retain that confidence. So, we have got to be able to take you along with us to keep the confidence in the system.

I guess my measure of the confidence in the system is that over 14 years, I've never once been unduly pressured by a Minister to put in or take out a factor. I've never once been unduly pressured by the Commission to put in or take out a factor. I've been criticised and appraised by the veteran community, but I've had only one occasion in which I have formed the view that that criticism and appraisal was personal abuse – one in 14 years – which I think is an indication that the system is healthy. So, we are not under undue pressure from government. We are not under undue pressure from the Commission, and our relationship with the victims, if you like, of our SoPs, is such that only once in 14 years have I felt that a veteran was playing the man and not the ball, despite the fact that we don't agree on everything.

So, I think that's the sign of a very healthy system, in which everybody is playing their part appropriately. I think out of these Forums, that sort of level of confidence is one of the major outcomes. Just to remind you, at this Forum we're revisiting a bit of the history. I'll go on to deal with what I think the future might be. We'll have an update on the operational context of the things that are happening to our defence personnel. We now have a much more vigorous and expansive research group who will be presenting to us some of their findings.

We're still going to talk about defining diseases. That's still a problem for us. We're still going to talk about stress and stressors which are an issue for us. Barry's going to talk about disability in our post-industrial society which is really, from the summary papers I've read, quite challenging. The idea is that if you are looking at people's well-being: compensation isn't the only part of getting healthy individuals. I think that there is an issue there has not yet been properly addressed by our society in general, and in that I include us and I include the Commission, and I include the government and the parliament.

We're going to take you again through critical appraisal and causal inference, so that we can make sure that we are still talking about the same process and that the standards of proof haven't shifted, and we'll deal with your questions again.

Now, we've set ourselves some tasks for this Forum. We will improve your understanding of our processes. We'll share some understandings about future challenges in the current issues. We might even start to think about some solutions, and we will develop a document that we will circulate.

There are some emerging issues that the RMA will have to start to take into account over the next 10 years. Laboratories are measuring more and more substances that may influence disease and risks. So, in other words, your circulating proteins and your genetic makeup are being unravelled, and the predictors of which diseases you might get are much clearer now than they were. The same risk factors will have different effects on different individuals, and it's now becoming increasingly possible to say which people are going to get lung cancer from smoking, and which people will not get

lung cancer from smoking, based on their genetics and based on the enzyme systems that flow from that.

Now, this has been known in animals for a long time. I remember when I was a boy doing cancer research, there were certain carcinogens that simply didn't work in guinea pigs but would work in mice and rats and things, because those animals don't have the enzyme that creates the real carcinogen from the "raw material" in the environment. So, increasingly, we're going to be faced with the situation of knowing which people are susceptible and which ones are not susceptible to certain exposures. How that will influence the system, I don't know, but it will become a significant part of medical practice and treatment.

Warfare is changing in style. There's going to be increasing use of biologically active materials and particularly nanoparticles. The science of nanoparticles is going to influence warfare and influence everyday life, and it's going to become a significant issue around exposures in humans.

We're going to have increasing amounts of knowledge and better software to analyse it. We are just about overwhelmed by knowledge now. The medical literature increases by many hundreds of pages a day, that means hundreds of pages a day of new information that has to be handled. A whole lot of new drugs and on-line treatments are going to come into existence. So, there are some issues out there which are going to impact on this system over the next 10 or 15 years. Some of those will be dealt with in more detail during the Forum.

Let's now very quickly put the system in context. Remember the Repatriation Act started in 1920 and the principle of beneficial legislation was established, both by the legislation and the second reading speeches at that time, and it remains intact to this day. Every government since 1920 has, at some stage of its tenure, made a formal commitment to the beneficiality of the legislation.

The RMA came into existence in 1994, at the same time as SMRC. The RMA came into existence because the Auditor-General pointed out that taxpayers' money couldn't be justifiably spent on the existing system. If we don't preserve this system's credibility for the next 10 or 20 years, if we allow inconsistencies to come in, if we allow silly decisions to be put in place, then the Auditor-General will have to react again. In 1992 the then Auditor-General made the recommendation that the Commission include some way of strong central decision-making - that was eventually the RMA. A recommendation of the subsequent Baume report was that we go back to the civil standard of proof.

Con Sciacca was the Minister and he, in his second reading speech, made some comments about the way in which this change would happen. He was careful to point out that reasonable hypothesis is retained – he made a formal commitment to that in his second reading speech. Just as a matter of interest, in that second reading speech, Con said that the success rate for claims in 1977 had been about 30 per cent. The success rate for claims at the time he introduced the legislation was above 70%. I'm not sure how far above 70%, but that's what he said in the Parliament, and we have looked at the success rate for claims for the last 12 months, to find that they are still above 70%. It is actually 72% for the primary level, and this is before the VRB gets a chance to add some extras.

So, my argument to you would be that Con Sciacca's undertaking in 1994, that the standard of proof would not change, has been met. This is only one indicator, but I think it's a fairly powerful one, that the standard of proof remains intact. There are things that could have influenced that, other than just the standard of proof, but as a broad measure, I think we can be confident, and perhaps you can be confident, that the reasonable hypothesis standard of proof was preserved during this change.

Remember the Bushell/Byrnes cases where the High Court argued about the reasonable hypothesis standard of proof at great length. You'll all remember that preceded the RMA, and I've listed some of the statements by the judges on the High Court about how they defined "reasonable hypothesis" in legal terms – just to remind you:

A hypothesis must possess some degree of acceptability or credibility – it must not be obviously fanciful, impossible, incredible, or not tenable, or too remote or too tenuous.

Good with words, lawyers. I think, clearly, the words that come through for me are that the evidence must point to the hypothesis being real, and not merely leave open the question. In scientific terms, an hypothesis is any proposition. "The moon is made of green cheese" is an hypothesis, but to be a reasonable hypothesis, it must not be merely left open, there must be something pointing to it being true, and whatever it is that's pointing to it being true, must be based on all of the evidence available.

Justice Toohey says "consistent with the known facts". I've always interpreted that to mean "all of the known facts", so we take all of the literature into account in making a decision about whether there is a reasonable hypothesis for including a factor in a SoP or not.

The statement that's missing is the one that always tickled my fancy. One of the judges indicated that a reasonable hypothesis was about the same as backing a 20 to 1 shot at the races (one of the judges must have owned racehorses). When Pearce and Holman looked at our propositions for reasonable hypothesis, and where they could analyse the data and do calculations, D'Arcy Holman (who, as you know, is a very clever epidemiologist and statistician), came up with the view that where he could calculate it, we were putting in factors when there was about a 10% chance that it was true – sometimes down to 5%.

Remember that in ordinary science, 5% is a sort of cut-off point. Before scientists will accept something is likely to be true, and not due to chance, they want it to be 95%. I say it's the 5% uncertainty that means science will never get there. In our case, we use the inverse standard of that. In other words, an increase in risk of somewhere between 5 and 10% is where we trigger a reasonable hypothesis, which is not far away from the judge's 20 to 1 shot. So, all of these words, in our context, translate into a measurable number – around about 10%, or a relative risk of 1.1.

We pay very great attention to making sure that at our meetings we have a lawyer present the whole time. Martin is here today, actually, probably writing down what I'm saying and testing it against the Act. Many times during our two-day meetings, we refer matters to Martin by asking, "Are we acting lawfully?" There are two things that will bring the RMA unstuck – firstly, if it doesn't understand its own legislation and act lawfully in all of its decision-making; and, secondly, if it loses its consistency in decision-making. We keep both of those issues permanently on our agenda. "Are we making decisions consistently?" John Kaldor is our conscience in that. He brings it up at every meeting. He and I get into quite serious arguments about it at times.

This question of whether the RMA can make decisions at the same standard of proof on a regular basis, and make those decisions within the legislative framework that it has been given, is absolutely the crucial centrepiece of the RMA retaining its credibility with the scientific community on the one hand, the general population on the other, and the veterans on another. If it loses credibility in either the scientific community, the general community or the veterans' community, somebody like the Auditor-General is going to start taking an interest, because it's a lot of money – 10 or 11 billion dollars. So, if that credibility is lost, then there are potential issues.

Pearce and Holman did find that we were dealing with this matter in a legislative way, or a legal fashion, and that we needed to go on doing so. Incidentally, just to remind you, serving members are now covered by the SoPs, as a result of the 2004 introduction of the Military Rehabilitation and Compensation Act.

One of the things that we don't do, and sometimes we get letters and requests from people wanting us to go into this arena, is deal with the question of the relationship to service of the facts of an individual case. We put down all of the causes of disease that we can find from the literature, but we are silent about whether any particular group of soldiers, or whether any individual soldier, is exposed to those causes. That's an evidentiary matter which is decided separately from the SoPs, but there is still confusion about it from time to time. A couple of the questions that have been put to us for this Forum from ESOs, are in fact about that issue, not about the SoPs.

For example, one of the classics is radiation. We set a dose of radiation, but we frequently get letters saying, "Why don't you include this circumstance here, as being a factor in a SoP?" Well, the answer is, we don't know what radiation exposure occurred at that point. We do know from the literature what dose of the radiation will cause a particular cancer, but we don't know what dose every soldier got in a particular circumstance. That's an evidentiary matter that has to be calculated separately.

Our legislation prevents us from going there because we cannot include classes of veterans as factors. In other words, our legislation restricts us to including causes of disease as factors, not classes of veterans. That's a centrepiece of the legislation which we can't breach. That is different from Canada – I think our Canadian colleagues in the room would find that is different. So, the issue about what exposures an individual soldier received are quite separate from our factors. Our factors are only about the doses of whatever exposure it is that would cause disease in the average citizen at the two standards of proof in the legislation.

We also aren't allowed to do research. I think the Cabinet was pretty wary of letting five academics loose with money to do their own research. Perhaps it was just a matter of stopping some academics being a little bit frivolous with the money, although there were probably more serious reasons for it, such as not wanting us to be unduly influenced by our own research findings.

Again, we're going to go through this business of causation with you at this Forum, because it's so central to the issue and it's so central to maintaining the standard of proof that underpins the system. It's a rigorous process.

One of the anomalies, or one of the idiosyncrasies of this system is that the more studies there are about a particular issue, the less likely a factor is to go in, because if there's only one study, and it comes out positive, we've got that as the only basis on which we can function, so we tend to put the factor in. On the other hand, if there are 20 studies and 10 of them are positive and 10 of them are negative, we don't put the factor in because it's pretty clear that chance is now at work. So, those issues about which there's been more research done can pose more of a problem for us, and I'll show you a couple of examples in a moment, just to illustrate that.

Sometimes include factors based on case reports only. Now, most epidemiologists would choke on that because that's anecdotal, it's not evidence. The legislation, I remind you, binds us to use epidemiological evidence where it is available, and to make a decision which is based on all of the facts that it provides to us. However, where we don't have epidemiological evidence, there's a second piece in the legislation that

says we can use our clinical judgment at the same level of judgment we would use to diagnose and treat a patient, to make a decision.

That means that if there is no epidemiological evidence, we can do what we do as doctors all the time and that's have an informed guess. We assess the available information and use our past experience to guess, "I think you've got flu" and we'll treat you for flu. So, we can use that clinical level of judgment when we've nothing else, and therefore when we get case reports, we can make a judgment. We can say, "Well, there is a single case report about this", and there's a relationship in that patient with that exposure. That's not evidence, that's just an anecdote. But then we can ask, "Well, is that likely to be true in our clinical judgment? Is that something that's got the ring of truth about it?" and we can put it in, if that's the case.

The parliament put that provision there to ensure the beneficiality of the system, so that we have a second tier to which we can go, to include factors that wouldn't otherwise be there. Therefore the structure of the system is really very critical. The way in which the legislation directs or allows us to put factors in is highly critical, and any change to it, any fiddling with it, would have unknown consequences if we weren't careful.

Figure 1: Studies of asbestos exposure and relative risk of mesothelioma (Bourdes et al 2000)

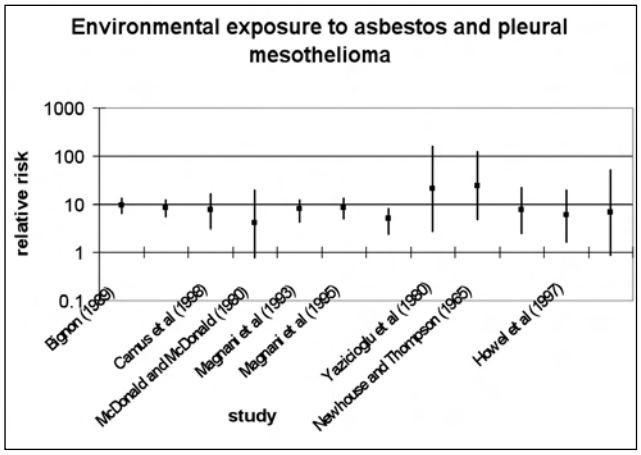
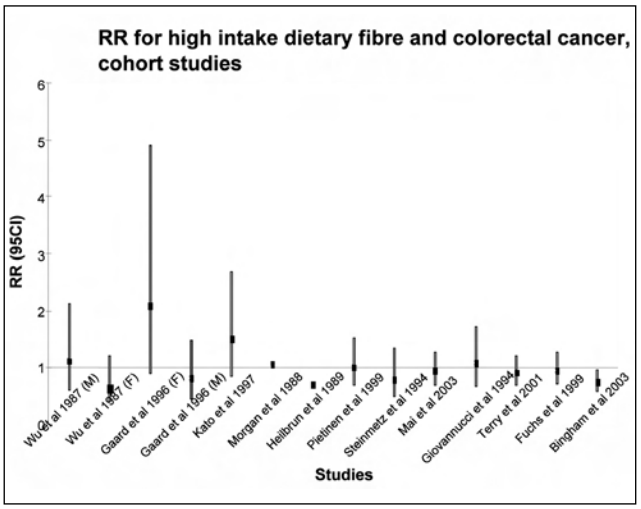


Figure 1 shows you a number of studies on asbestos and the risk of pleural mesothelioma. The Y axis shows relative risk on an exponential scale – the 1 is the null line, 10 is a 10-fold increase, and 100 is a 100-fold increase in risk. You'll notice that every study, every single study we've got available, says asbestos causes mesothelioma. Most of them show a 10-fold increase. That is rock solid epidemiology, and that's the extreme - you rarely, rarely get such a situation. Only once is the confidence interval below the null value. This is a case in which the epidemiology is absolutely clear-cut.

Figure 2: Cohort studies of dietary fibre and colorectal cancer



Now, here is another graph (Figure 2) which explains or illustrates what I said before, about what happens when you get a lot of studies. This is about dietary fibre and colorectal cancer, and if you remember dietary fibre has been taken out as a factor and returned as a factor - it is in RH only at the moment. Now, I will explain to you why this happened. A relative risk of one means no increase in risk. Anything below one decreases the risk, and anything above one increases the risk. Now, look at the studies – one up, one down, one up, one down, one up, one on the line, down, on the line, up, down, down, down – why have we got it in? I've just convinced myself we probably should take it out again.

Quite seriously, that's what epidemiology does to you a lot of the time, and, quite frankly, if it is in the reasonable hypothesis at the moment, you got lucky. That's chance at work. The problem is, at the point in history when you only have three studies, there are two smaller studies above the line but one larger study way below the line, and it seems as if it might be real. Then more studies come along and suddenly it's not quite so real. The other problem with this is some of those studies are awful and they don't take proper account of chance and confounding. One of the things this job has taught me is that there's an awful lot of poor epidemiology out there. It's beyond my comprehension how some of the studies that are published ever got through the so-called "peer review" system. This is the sort of situation that gives us nightmares. If the next time a new study about fibre and colorectal cancer comes up with a relative risk above the line, we might take it out. I don't know, but it just illustrates to you how difficult the epidemiology can turn out to be.

So, what are the things that really trigger us to put a factor in? Basically, the body of evidence. We look at the level of the evidence. We look at the quality of the evidence. We look to see whether we get a dose response, and take into account latency periods. We pay attention to the legislation all the time. We keep our eye on the standard of proof all the time. We take notice of court decisions, some of which have been quite unkind

to us. Some of the judges have said quite interesting things about us.

We keep the second reading speech in mind. We consistently try to calibrate ourselves to make sure that we are making decisions at the same standard, at the same level. We talk about that a lot. We understand that the words we put down have to go out and work in the field. At our meetings we have people from both the Defence Forces and from the department who are going to operationalise the SoPs. They are not present when we go into our formal session to agree to the SoPs, we do that by ourselves. However, when we're making up our mind about what to do, we take advice from operational staff from Veterans' Affairs and from Defence about the wording that captures, one, what's really happening; and, two, what can be operationalised in the field without unnecessary complications.

We now have a lot of people doing health studies, and a lot of information beginning to emerge from those systematic studies. As I pointed out before, those health studies are more about which troops – which soldiers, sailors or airmen - were exposed to which agents or events, and what diseases they have, but they have very little impact on factors in SoPs, because most of the factors are in there on the basis of the medical literature that continues to expand at an enormous rate.

Sometimes veterans come to us and say, "Well, you don't take into account the military experience enough" or, "What about the military experience?" In fact, nearly all of the factors are basically there because of the civilian experience, which is much more investigated, has much more literature about it, and provides evidence for many more factors than would otherwise occur. If we confined ourselves only to the military literature, more than half the factors would just disappear, because there'd be no evidence for them. So, most of the factors, virtually all of them, are there because of the civilian literature.

A couple of fellows have said to me recently, as I'm getting older, "What's going to happen when you go from the RMA?" Well, the RMA will simply go on doing its thing. There's now a body of evidence. There's now case law, if you like to call it that. There are a lot of SoPs that set a standard, and I don't think very much would change. I do think we, that is the RMA and you, need to have written down (which will happen in the report from this Forum) the things that will maintain the SoP system into the future, the things that will maintain its credibility and satisfy the Auditor-General, making sure the taxpayers continue to be prepared to put money into it, and making sure that you feel that you are getting a fair go.

I think the first thing is adherence to the law. The RMA must continue to have a lawyer at all of its meetings. We get our independent legal advice from the Australian Government Solicitor's Office and we pay for it. We don't depend upon the department, for example. We get independent legal advice at our meetings and we use it regularly as Martin will testify - he walks away from a meeting with a plethora of issues to think about. We really have to make sure that the legislation is constantly in front of us; we have to work on the consistency of the standards of proof. The RMA has to be able to talk to you about how it sets the reasonable hypothesis - it has to be able to say how it's trying to be consistent - so that we don't, on the one hand, wobble down into that 5% area, where we're just talking about chance or we don't get up to a standard which would unfairly exclude people who are supposed to be covered by beneficial legislation.

The quality of the evidence and the levels of probability are fundamental. As I said before, there is a lot of poor evidence out there. Then there is this question of the level of probability. A relative risk of 1.1 is a 10% increase in risk. It's about what we think the reasonable hypothesis means. We make that as a public statement, so that if another RMA were to come along and say, "We are making a 1.3 relative risk our standard," you would have another ground for debate. Is 1.1 the correct standard? That is what we have settled on, that is what we think fits the High Court judge's words of the Bushell/Byrnes era. Now, 1.1 relative risk makes most epidemiologists raise their eyebrows. That is a very generous point to trigger a causal relationship. We try to make sure that we give weight to the best studies; that will keep us from becoming random, because we are operating at such a low level of probability. The critical assessment and regular review of all the SoPs is important. All SoPs are under constant review and our list at any one time has about 85 SoPs under formal review, but we get letters about many of them on a regular basis.

The SoPs are living instruments and they are never finished, so that's another issue. They will all have to change. This consultation and other consultations we have are absolutely fundamental to the maintenance of the system, as is full and frank debate - and I expect a bit of that in a couple of minutes. If we pay attention to those half dozen or so critical issues, that will start to set a forward agenda to make sure that the Auditor-General or somebody else doesn't come along and say, "The system is no longer credible". That is all I wanted to say in introduction, to set the scene. I think we now have some time for questions.

1

The RMA now and into the future

Professor Ken Donald, AO
2008 RMA/DVA/ESO Forum

2

1998 Forum objectives

- Address recommendations 4,9 & 10 from the Pearce Report
  - hold a medical-scientific conference
  - commence development of a Repatriation Medical Authority (RMA) document outlining its powers, functions and processes
  - establish a multidisciplinary working party
- Commence the process of elevating the ESO's knowledge and understanding of sound medical-scientific evidence (SMSE) and evidence based medicine.
- Enhance the RMA's knowledge and understanding of the "military experience".

3

1998 Forum agenda

- Day 1
  - The RMA's understanding of the powers and functions it exercises under the VEA.
  - How to evaluate a medical scientific paper (talk plus workshop)
  - Causal inference (talks plus workshop)
- Day 2
  - Realities of service: presentations to inform the RMA Members on life in the service.
  - Workshop factors

4

2004 Forum agenda

- Day 1
  - The RMA Ten Years On- what the RMA has achieved and its evolving role
  - Psychiatric conditions- including 'stress and stressors'
  - 'Normal' population abnormalities versus risk factors
  - Critical Appraisal & Causal Inference (talk and workshops)
- Day 2
  - Presentations by DVA- MRC Bill and Health Studies
  - Presentations by ADF- Centre for Military & Veterans' Health and ADF Initiatives
  - The expectations from 'Health Studies'
  - Protective effects of exposures
  - 'Syndromes' and 'Causes'
  - ESO questions

5

Changes resulting from previous RMA Forums

- Legislative amendments
  - 196CA
  - single factor (focussed) review
- Improvements to RMA website
  - alphabetical index and common names index
- Process changes
  - 2 month consultation period and electronic provision of documentation where removal of a factor is being proposed
- Improved levels of confidence in the system

6

2008 Forum agenda

- Day 1
  - The RMA now and into the future
  - The operational context (ADF, DVA, RSL)
  - Military and Veterans' research (CMVH, DVA, Centre EOH, ADF, ACPMH)
  - Defining diseases
  - Stress and stressors
- Day 2
  - Disability in a post-industrial society
  - Critical appraisal and causal inference (talk and workshop)
  - ESO questions*

*and throughout forum

7

2008 Forum outcomes

- The level of knowledge and understanding of the processes of SoP development is enhanced
- A shared understanding of current issues and future challenges is developed
- Possible solutions to problems are canvassed
- A forum publication is developed

8

Emerging developments

- identification of biomarkers
  - measurable changes in body substances which may influence disease risk
  - includes biomarkers of susceptibility, exposure and effect
    - (eg variation in genes which metabolise organophosphates, urinary metabolites of benzene or naphthalene and jet fuels, chromosomal aberrations and cancer risk)
- changes in styles of warfare
  - chemical/biological/radiological warfare
  - remote operations (eg use of forward robots)
- better software for collecting and analysing data
- potential new exposures
  - eg nanoparticles, heavy metal-tungsten alloys
- new drugs, availability of online treatment
- increased access to increasing volume of information

9

Origins of the repatriation system

- Repatriation Act 1920
  - principle of beneficial legislation established
- Veterans' Entitlements Act 1986
- Powers and functions of the RMA 1994
  - powers and functions of the SMRC established simultaneously

10

Auditor General's Report 1992-3 (Baume Report)

- "Inconsistencies in decision-making have been significant, readily identifiable and a feature of the system for many years"
- Recommended that the Commission include strong and accessible central aetiological/decision-making support to branches
- Civil standard

11

Second reading speech Legislation amendment bill 1994

- "a medical hypothesis linking particular kinds of injury, disease or death with war service, that does not have a sound medical-scientific base, will no longer be sufficient to constitute a 'reasonable hypothesis'."
- "The changes are intended to ensure that the credibility of the repatriation system is maintained and that medical opinions supported by **little** or no medical-scientific evidence do not prevail over the carefully developed mass of medical-scientific opinion."
- Reasonable hypothesis retained

12

Success rate of claims

- Pre 1977, around 30%*
- 1994, above 70%*
- 2006/7, 72% for primary level SoP claims where incapacity found

*Minister's second reading speech for amendment to VEA Act 1994

13

Conflicting medical opinions

- Bushell v. Repatriation Commission [1992] HCA (anxiety and hypertension)
- Byrnes v. Repatriation Commission [1993] HCA (injury and cervical/thoracic spondylosis)

14

Reasonable hypothesis

- **Brennan J.**
  - "To be reasonable, a hypothesis must possess some degree of acceptability or credibility - it must not be obviously fanciful, impossible, incredible or not tenable or too remote or too tenuous. (para 8).
  - "For a reasonable hypothesis to be 'raised' by material before the Board, we think it must find some support in that material - that is, the material must point to, and not merely leave open, a hypothesis as a reasonable hypothesis." (para 8).
  - "The exercise is not one of balancing or weighing the respective merits of a range of professional opinions. Rather, it is a case of determining whether the particular theory has a rational foundation." (para 9).
- **Toohey J.**
  - "A reasonable hypothesis requires more than a possibility, not fanciful or unreal, consistent with the known facts. It is an hypothesis pointed to by the facts… " (para 31)

Bushell v. Repatriation Commission [1992] HCA

15

The RMA must act within the law

16

Pearce-Holman review 1997

- the system is more equitable, more efficient and less adversarial than before
  - claims are processed faster at less cost and a greater proportion succeed at the primary level
  - ability to claim not dependent on ability to find a supportive medical practitioner
  - consistency hard to determine but less variability in acceptance rates b/w states
  - principle of beneficiality maintained
- the RMA must adhere to a standard of proof that is within the bounds accepted by the medical-scientific community

17

Legislation which refers to SoPs

- 1994 amendment to VEA
  - establishes the RMA and provides its functions and powers (S.196)
  - the Specialist Medical Review Council established simultaneously
    - empowered to review the contents of a SoP or a decision by the RMA not to determine a SoP
- Military Rehabilitation and Compensation Act 2004
  - compensation for current serving members for injuries/diseases incurred from 1 July 2004

18

What the RMA does not do

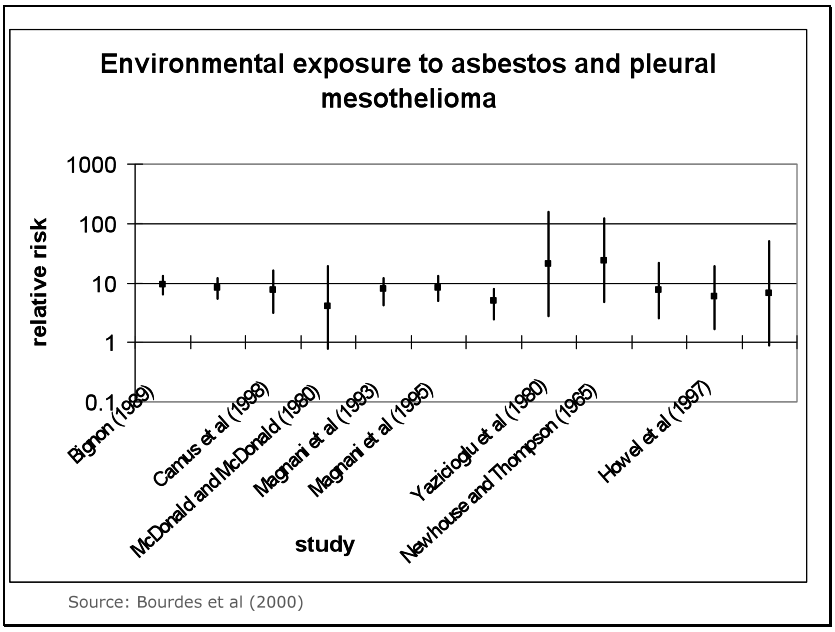
- The RMA does not determine the service related facts of individual claims
  - Department of Veterans' Affairs officers must match the facts of an individual claim with an existing SoP
- The RMA may not carry out its own research

19

RMA assessment of causation

- Assessment of causation is a rigorous process, governed by epidemiological evidence and objective criteria
- There is assessment of the quality of the study as well as the results
- The whole body of information is considered (systematic review)
- Because of the beneficial nature of the legislation, the RMA can make judgements about causality, particularly at the reasonable hypothesis level, on the basis of weaker evidence and at lower levels of probability (RR) than might be accepted in other contexts

20



Source: Bourdes et al (2000)

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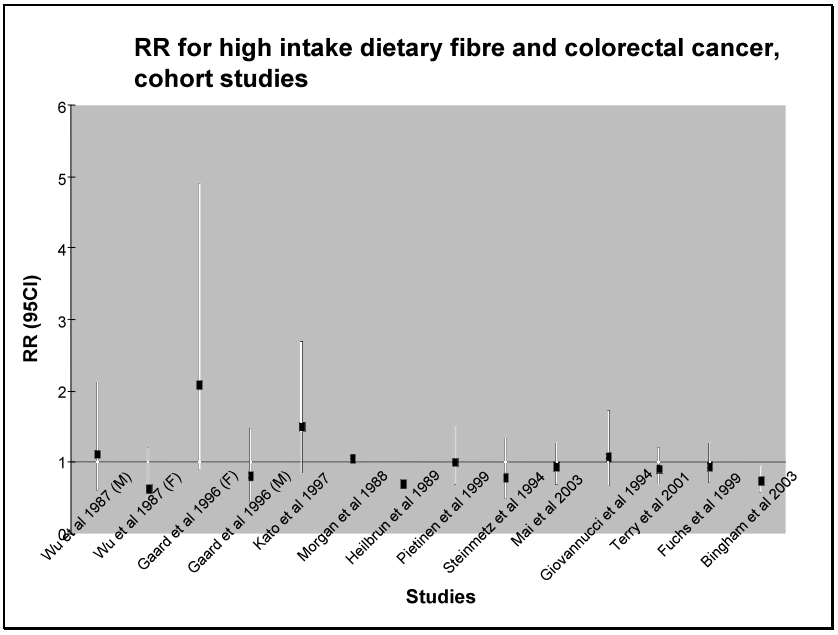


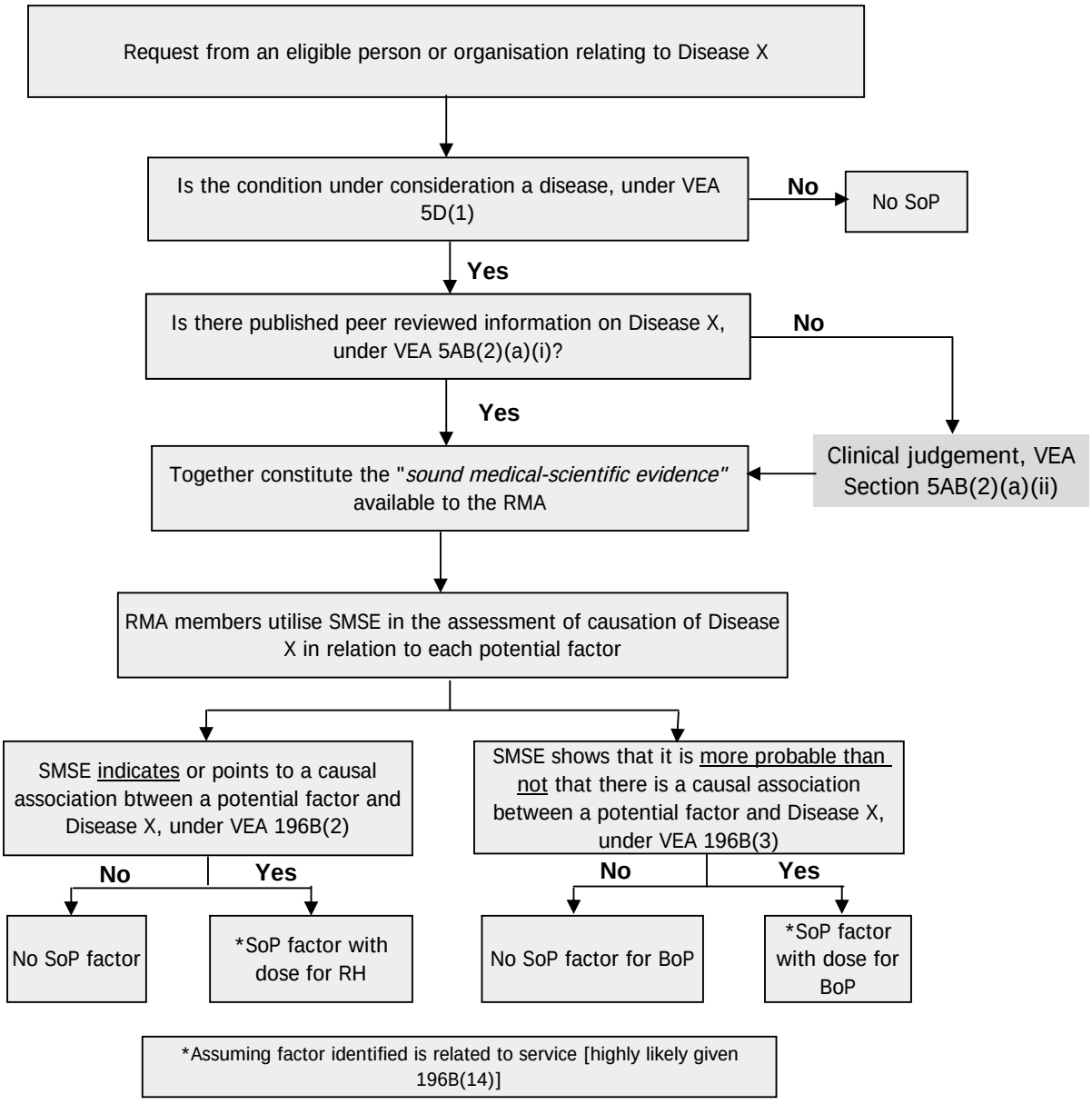
22

Considerations when developing factors

- Body of evidence
  - level of evidence, dose, latency
- Legislation
  - disease definition, standard of proof
- Court decisions and second reading speech
- Consistency with factors in other SoPs and "calibration" of the standard of proof
- Operational issues
  - wording is clear and is applicable to the circumstances experienced by veterans and serving members

23

Determination of Statements of Principles



24

Health studies

- Centre for Military and Veterans' Health
- Australian Centre for Posttraumatic Mental Health
- Monash Centre for Occupational and Environmental Health
- AIHW
- Defence
- DVA
- Other universities or research organisations (eg TUNRA)

25

Future of the SoP system

- Adherence to the law
- Consistency of standards of proof
- Expertise in judging quality of evidence and levels of probability
- Adherence to high standards of scientific research
- Critical assessment and regular review of processes and SoPs
- Consultation with stakeholders
- Full and frank debate within the processes of the RMA

Defining Disease

Dr Justine Ward
Principal Medical Officer
Repatriation Medical Authority

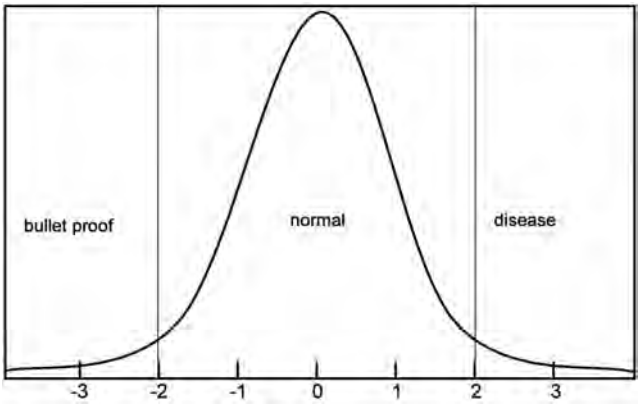
15 April 2008

[This document was prepared from the audio transcripts of the Forum and has been edited for clarity and continuity only]

This afternoon I'd like to explain to you some of the issues that the RMA faces when making a definition for SoP purposes. Firstly, the purpose of a SoP definition is to define what the SoP is or isn't about. This is so that you as users can determine which SoP you should apply. If there's no SoP available, you can make a so-called "non-SoP" claim. We also provide ICD codes with the definition where it is helpful. ICD codes are helpful when they clarify what the SoP is about, but if the ICD codes don't match the word definition, and could cause confusion, the RMA will leave them out. The definition of disease that we have to work with within the VEA is very general and in some ways not particularly helpful, but it does explicitly exclude aggravation and it also excludes temporary abnormalities.

I've categorised the types of issues I'm going to talk about and I'll briefly discuss each of these in turn Firstly, we come to the issue of cut off points which this diagram illustrates (Figure 1)**.** Within a given population, when you measure a biological parameter such as blood pressure, the range of values will often be distributed in this pattern, which is known as a normal distribution.

Figure 1: Normal distribution



You can see that most of the values are close to the mean or the average value, and there's a spread of values above and below the mean. Taking blood pressure as an example, the cut-off point on the right would be at the level of 140 on 90, that is the level at which there is a clinically significant increase in risk. The increase in risk is chiefly that of cardiac events or stroke. Those people around the mean would have a blood pressure of about 120 on 80, and their risk would be average. Those people at the lower end would have a blood pressure at which they could barely stand up, and they would be at the lowest risk.

The cut-off point which is chosen as the point which defines disease may be dependent on a number of factors, including the point at which people become symptomatic, the point at which they develop pathology, the point at which they respond to treatment with improved outcomes, or a combination of these. 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 may actually be harmed because they will be labelled as sick and treated unnecessarily. Therefore, decisions about where symptom signs or test are labelled abnormal need to keep this risk-benefit balance in mind and should be based on good evidence. Some examples of current Statements of Principles which are defined by cut-off points are hypertension, osteoporosis, diabetes, morbid obesity and depressive disorder.

Table 1: Some diseases defined by cut-off points

Disease	Definition
Hypertension	BP ≥ 140/90, or treatment for hypertension
Osteoporosis	BMD ≥ 2.5 SD below the mean for young adults, or radiological evidence of fracture combined with reduced bone density
Diabetes	Fasting glucose ≥7 mmol/l on two occasions, non-fasting glucose ≥ 11.1 mmol/l on two occasions or glucose level ≥ 11.1 on glucose tolerance test
Morbid obesity	BMI ≥ 40, or BMI ≥ 35 and having treatment
Depressive disorder	DSM-IV-TR definition used to define cut-off point as prominent and persistent depression

You'll see that a number of these definitions include qualitative factors as well as the numerical cut-off point, such as the need for treatment. Obesity and osteopaenia are not there because they're two risk factors which the RMA investigated and subsequently declared were not diseases within the meaning of the VEA. Briefly, the RMA's reasoning was that obesity by itself is not symptomatic, although morbid obesity often is. Furthermore, obesity is a risk factor which is shared by a large and ever increasing proportion of the population, in the order of around 20% nowadays. Osteopaenia is also asymptomatic and of itself is not a risk factor for fracture, although it may become so in combination with other risk factors.

Many physical and mental illnesses, in fact, are actually part of the spectrum, and the distinction between health and disease is not always clear-cut. Diagnostic criteria such as those provided in DSM-IV are formulated to guide clinicians in making this distinction. For complex conditions, the RMA sometimes adopts currently recognised diagnostic criteria in its definitions.

Another dilemma when making definitions is whether or not we should make SoPs for asymptomatic conditions. The examples of hiatus hernia, infectious diseases and ischaemic heart disease illustrate different aspects of that problem. There is a SoP for hiatus hernia because it's clearly not a normal anatomical variation, even though it often doesn't cause associated symptoms such as reflux.

Many infectious diseases, particularly viral infections, can be acquired without causing any symptoms or only a mild illness which is not clearly recognisable. Hepatitis A infection is a good example of this. The person will develop antibodies which may happen to be

measured many years later incidentally. Their presence demonstrates that the person was exposed to the virus at some stage in the past and has developed immunity. The person is not ill and has no long lasting problems as a result of having had the infection. Furthermore, the timing of the infection is impossible to ascertain and could not, therefore, be able to be related to service.

Ischaemic heart disease, the third example I have provided, is often due to atherosclerosis and its associated processes. Most of us in the Western world will start developing atherosclerosis from early adolescence. It's a gradual process and remains asymptomatic unless it manifests, usually in later life, as angina, peripheral vascular disease, stroke or other ischaemic disease, depending on which arteries are affected. In the case of ischaemic heart disease, insufficient blood flow to the heart will cause pain on exertion, or even at rest. There are various diagnostic tests that can demonstrate whether blood flow to the heart is insufficient.

The next category of issues with disease definitions is the problem of circularity. Some conditions (for example PTSD, solvent-related chronic encephalopathy and asbestosis) are defined by a set of symptoms in relation to a specific exposure. In these cases, some circularity is inevitable, but where possible the RMA tries to avoid this. The factors within the SoPs will spell out the degree and type of exposure shown by the sound medical-scientific evidence to be necessary to cause disease. So, for example, in the asbestosis SoPs, the factors require inhaling respirable asbestos fibres for at least 1000 hours in an enclosed space, or 3000 hours in an open environment.

The next category is ill-defined syndromes. You've heard people mention Gulf War syndrome, and currently, although much good research has been conducted on service men and women by the various countries which participated in the Gulf War, there is still no definitive solution to the question of Gulf War illness. Part of the reason lies in the delay in collecting relevant information and the incompleteness of data concerning specific exposures. Simon Wessely, a prominent researcher in the area of Gulf War illness, suggests that the window of opportunity for investigating health problems relating to this deployment has probably passed, but it is to be hoped that better and more timely collection of data will provide more useful information in future conflicts. You've heard this afternoon how Malcolm Sim and his team, and the Centre for Military and Veterans' Health are collecting data and designing studies which will help to meet those needs.

The last category I wish to discuss is the issue of coverage, and that can be looked at in two ways; coverage of the SoP regime as a whole and coverage of an individual SoP. It was Parliament's intention that the SoP regime should cover as broad a range as possible of conditions which are likely to be claimed by veterans or serving personnel. Currently over 93% of primary VEA claims are covered by SoPs, and for many years the authority has determined an average of 5 to 10 SoPs per year for new conditions, either in response to requests or where it has itself identified a gap. Thus, the extent of coverage of the SoP regime is gradually being extended.

What I want to focus on here is the extent of coverage of an individual SoP, which poses another type of definitional issue for the RMA. For any given condition, there may be a range of ways of defining it, from the highest, most overarching category, to the narrowest possible interpretation. The options are canvassed and discussed by the Authority, and the final position taken will depend on a number of factors which are unique to that particular condition, such as relevant pathological processes, the range of potential causes, the capacity to be clear about what is included or excluded and the nature of the epidemiological evidence.

In general, epidemiological studies of relationships between an exposure and a specific, narrowly defined outcome provide more compelling evidence about causation than studies which use broad categories as outcomes. Different conditions with different pathological processes are sometimes inappropriately or artificially lumped together, and this often happens, to give an example, in studies of leukaemia. This is why we have separate SoPs for each different type of leukaemia - the nature of the evidence is peculiar to each particular type of leukaemia.

The RMA went the other way when it was asked to make SoPs about macular branch vein occlusion (the macula is a spot on the back of the retina which is very important for vision). After investigation, the RMA determined SoPs for the far broader condition of retinal vascular occlusive disease. One reason why the RMA made that decision is that retinal vascular occlusive disease is a condition which is claimed reasonably frequently. In addition, the aetiological literature does not commonly separate out central retinal vein occlusion from branch vein occlusion. Moreover, there is considerable overlap between the causes of retinal arterial disease and the causes of retinal venous disease. So, the RMA considered that SoPs covering a wider range of conditions would be sensible in this instance.

At this point, I've covered all the issues I want to cover. You can see that defining a disease is not always as straightforward as it might seem. Thank you all for your attention.

1

Defining Diseases

2008 RMA/DVA/ESO Forum

Dr Justine Ward, RMA Principal Medical Officer

2

Purpose of SoP definitions

- To define what the SoP is about (or not about)
  - diagnosis of the condition is made by a medical practitioner
- The word definition takes precedence over ICD codes
  - if ICD codes do not match the word definition they may be omitted

3

Section 5(D)

Disease means

(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;

but does not include:

(c) the aggravation of such an ailment, disorder, defect or morbid condition; or

(d) a temporary departure from:

(i) the normal physiological state; or

(ii) the accepted ranges of normal physiological or biochemical measures;

that results from normal physiological stress (for example the effects of exercise on blood pressure) or the temporary effect of extraneous agents (for example, alcohol on blood cholesterol levels)

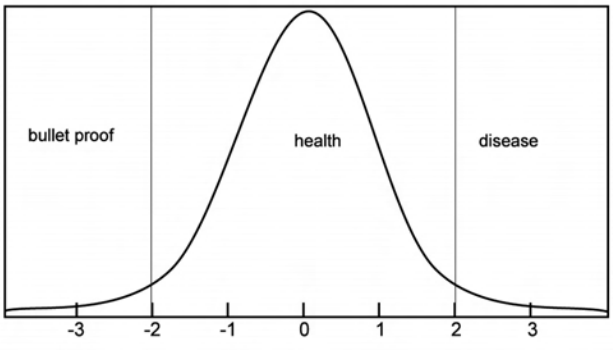
4

Types of issues with definitions

- Normal range/cut off points
- Symptomatic vs asymptomatic
- Circular definitions- diseases defined by both symptoms and the cause, the cause is listed as a factor
- Ill defined syndromes or medically unexplained physical symptoms which do not meet the definition of disease
- Extent of coverage

5

Cut-off points



6

Some diseases defined by cut-off points

- **Hypertension**: BP ≥ 140/90, or treatment for hypertension
- Osteoporosis: BMD ≥ 2.5 SD below the mean for young adults, or radiological evidence of fracture combined with reduced bone density
- Diabetes: fasting glucose ≥7 mmol/l on two occasions, non-fasting glucose ≥ 11.1 mmol/l on two occasions or glucose level ≥ 11.1 on glucose tolerance test
- Morbid obesity: BMI ≥ 40, or BMI ≥ 35 and having treatment
- Depressive disorder: DSM-IV-TR definition used to define cut-off point as prominent and persistent depression

7

Symptomatic vs asymptomatic

- **Hiatus hernia**: an acquired anatomical abnormality but often asymptomatic
- **Hepatitis A**: excludes immunological evidence of past subclinical infections
- **IHD**: a cardiac disability characterised by insufficient blood flow to the muscle tissue of the heart due to atherosclerosis, thrombosis or vasospasm of the coronary arteries

8

Circularity

- **PTSD**: exposure to the traumatic event and the symptoms resulting from that exposure both form part of the definition; the factors relate to exposure to a specified type of traumatic event
- **Solvent related chronic encephalopathy**: exposure to the solvent and the symptoms of brain pathology both form part of the definition; the factors relate to exposure to inhalants or volatile substances
- **Asbestosis**: a lung disease caused by deposition of asbestos in the lung; the factors relate to asbestos exposure

9

Ill-defined syndromes

- The RMA has declared that multiple chemical sensitivities and Gulf War syndrome are not diseases within the meaning of section 5(D)
  - no unique, consistent pattern of symptoms
  - no proven causative exposure
  - no consistent pathology
  - no reliable clinical or laboratory test

10

Extent of coverage

- Broad vs narrow
  - leukaemia versus specific SoPs for each leukaemia separately
  - retinal vascular occlusive disease versus macular branch vein occlusion

Genetic Disease and Cancer

Professor Robyn Ward
Member
Repatriation Medical Authority

15 April 2008

[This document was prepared from the audio transcripts of the Forum and has been edited for clarity and continuity only]

We are constantly being told to try to keep things simple. Unfortunately I'm going to have to say that things are getting very complicated, even things that we took for granted, like defining diseases, which has been, for all intents and purposes, a relatively simple task. It's becoming increasingly difficult to define diseases using the known paradigms in which we've worked in the past.

I want to really talk a little bit about the new ways we're starting to think about disease, and to do that I think it's important to just take a look at where we've come from. A long, long time ago primitive man defined disease as evil spirits, and perhaps that still has a lot of merit even today. I'm sure there'll be people who would agree with that sort of definition, even in modern times. The Greeks had a view of disease that related to humors. The Chinese view of disease relates to a flow of energy, and I guess that's manifested today in the underlying methodology that goes behind acupuncture and why people think that acupuncture works or doesn't work as the case may be.

Chiropractors talk about disease in terms of blockages of nervous impulses. When they rip your back to pieces on their stretchers, what they're telling you they're doing is not causing you enormous amounts of pain, but they're releasing a whole lot of nervous impulses that are going to make you feel a whole lot better in a couple of weeks when you can stand up again.

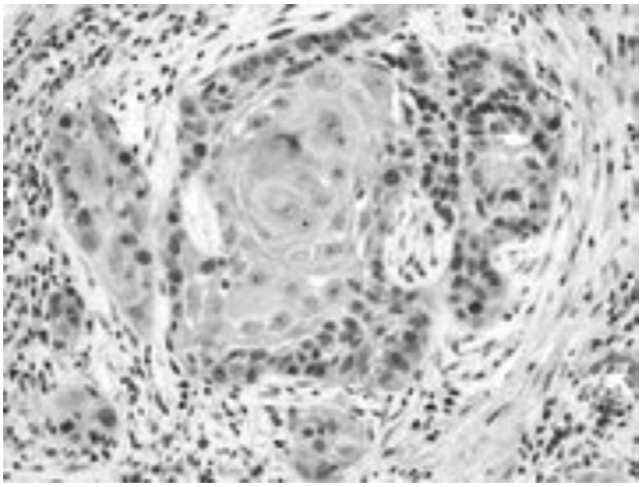
Our Western concept of disease until very recently has largely figured around the concept of pathological processes. That is to say that it's related to how our own body responds to insults from outside. Overlayed upon that we have now this whole new world, which is a genetic definition of disease.

To elaborate a little bit on the older or the traditional Western style definition of disease - a long while ago the pathologists really led the way in this area. They said the body really only has a few ways of responding to any insult, and it doesn't matter whether you're invaded by tuberculosis or hit by a car or the blood supply to your heart gets cut off. They characterised things in terms of a couple of different sorts of responses. One was inflammation, where things get red and swollen, for example if you receive a severe hit to your leg.

After injury, the body heals by responding in a certain demonstrable pathological way to that process. It doesn't matter whether you're healing after a surgical operation or you're healing after a run-in with a bike or a train. Cancer is another sort of response of the tissue to what is really a cell going berserk within your own body. A lot of the manifestations of cancer are related to the tissue's response to that funny cell.

Infarction is another term that many of you will be familiar with. This describes the response of a tissue to a lack of a blood supply. Doctors, being not very imaginative people, really define all diseases in terms of those pathological processes. They basically define a disease by the site in which it occurs and one of those processes, for example, breast cancer, colon cancer, lung cancer, appendicitis - inflammation of the appendix, cholecystitis - inflammation of the gall bladder, etc. Doctors to date haven't had very imaginative ways of describing the diseases they're talking about. They essentially still use that nomenclature that was described in the 1800s.

Figure 1: Squamous cell carcinoma

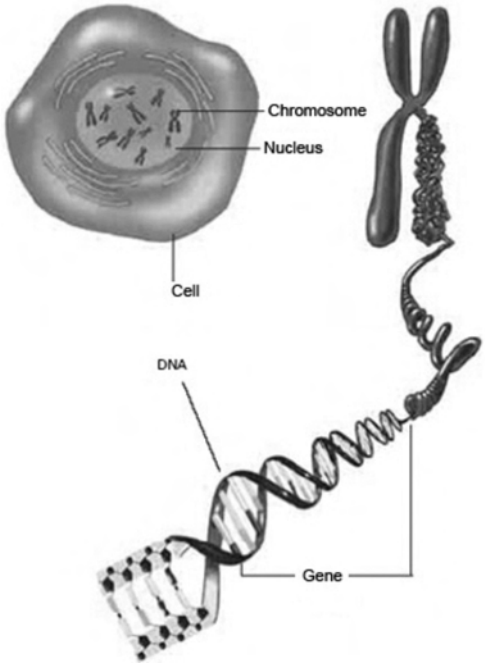


This is a slide of squamous cell carcinoma and a pathologist like Professor Donald can easily determine this. To anyone else in the room it probably means very little. So that's the traditional view of disease.

Now I want to move on and describe a little bit about the genetic view of a disease. I want to try to describe to you how that genetic view tells us a lot about where we've come from and how some very new discoveries are now allowing us, maybe, to replace the epidemiological view of disease and may, in the next 10 or 20 years, see that sort of view of disease almost made redundant.

Our body is made up of many, many cells. Each cell is about a hundredth of a millimetre, and within each cell in our body is a nucleus, and within the nucleus are chromosomes – 23 pairs of chromosomes. We get one set of chromosomes from our mother and one set of chromosomes from our father. There are three billion bases in those chromosomes and these bases are signified by letters of the alphabet. So there's three billion letters inside every cell of our body, and your alphabet is different to my alphabet. Everyone has a different make-up of those billion different bases.

Figure 2: The genetic code

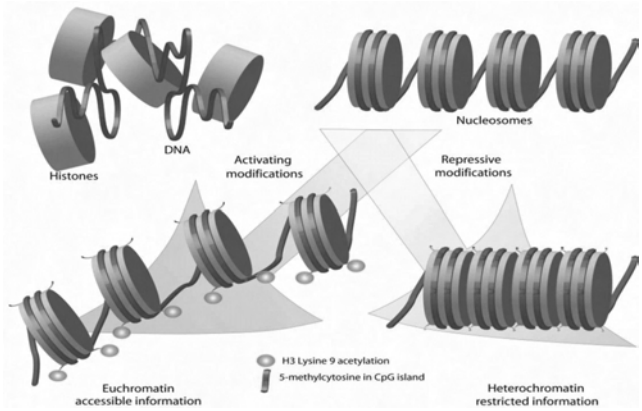


Each of those bases are all lined up in a sequence into these chromosomes and each chromosome uncoiled is about 8.5 centimetres. So you can imagine you've got 8.5 centimetres of just one chromosome, and that has to get into something which is about a thousandth of a millimetre in size in every cell of our body. The body has a very ingenious way of doing that, and I'll tell you about that in a minute. About five or six years ago the human genome project was finished, and in that project two very big groups, one from the United Kingdom and another from the United States, worked around the clock for years and years to actually unravel the entire human genome. They went through and looked at every one of those three billion bases and worked out the orders in which they should go.

You have probably seen the photos on the TV shows where there were just rooms and rooms and rooms full of these very fantastic pieces of equipment, and people working around the clock to decipher the human genome. Bear that in mind when we come back to something I'll tell you in a minute. The Human Genome Project, despite sorting through those 3 billion bases, actually identified only about 25,000 different genes that determine the difference between each of us.

Now, how do we get the 8.5 centimetre bit of chromosome inside a minute cell? What happens is that DNA is wound around a spool. People knew about this spool that the DNA was wound around in the 1880s. They thought that the only purpose of that spool was actually to get the DNA packed up so tight that it would fit inside a cell making it really just a packaging function of the DNA.

Figure 3: Getting the DNA into the cell



What's happened very recently is that people have found now that these little things around which the DNA is wound are actually a different sort of code inside our cells. It's not the code that's given to us from our mother and father, but it's actually the code that might tell us what we've been exposed to throughout our life. So, what that means is that in the past the only way we knew you drank a lot of alcohol was to ask you. We said, "How many grams of alcohol did you drink and for how long did you drink it? When did you drink it? Were you young or were you old, when you took that alcohol in?"

What has now been realised is that a lot of those exposures, and the footprint of those exposures, are coded within that spool around which our DNA is wound. So there may be a time, not too distant, where we could actually look at that piece of information from person to person and say, "Your mother drank a lot of alcohol when you were in utero, and then you didn't drink much later on, and then you took up cigarette smoking and then you did something else and then you did something else". So it will no longer matter what you tell your doctor, we may be actually able to find out what really happened to you.

The other thing that it will be able to tell us is what actually happened to the substance inside our own bodies. Oftentimes when you drink a lot of alcohol, it will have a detrimental effect on your body. For the next person it may not, because your liver is very good at getting rid of all the nasty parts of the alcohol. So, what it will also do is provide you with a direct impact statement as to what that toxin actually did to your own body and why it did something to your body and not something to the next person's body.

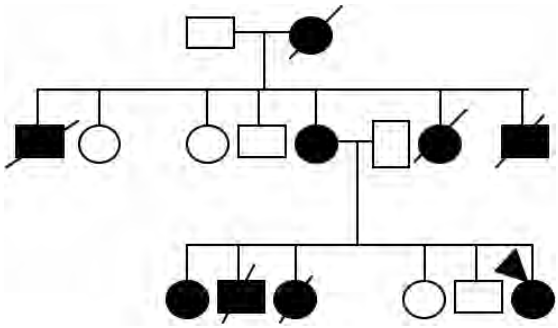
Remember I told you that in the early part of this decade the whole human genome was cloned, and they spent years and years doing that with big pieces of equipment. In that very short period of time it's now become possible for me to take a blood sample from all the people in the front row and within a morning actually know what your genome contains. Essentially it's become very simple to do using gene chip technology what took many, many man hours and very big pieces of equipment a very long time to do.

A gene chip consists of a lot of coloured dots on something the size of a postage stamp. We can read a huge amount of information from all those different coloured dots, for example we can tell that a certain blood sample came from a female and she had breast cancer. We can know a lot about why she got the cancer and we know her age. We can do that from person to person to person to see what genetic differences there are between this person and the next person, who would have a different looking profile.

Gene chips are now widely available. They're still not routinely used in regular day to day medicine, but they're getting closer and closer to that. They're routinely used in research laboratories and in the next few years we will see them used routinely in clinical practice as well as in research settings. The cost of the equipment needed to do this has dropped dramatically. It used to be about $10,000 to get a few chips and now it's about $200. The price is dropping and dropping so that sort of information will be increasingly accessible to ordinary laboratories.

I want to talk a little bit now about how genetics already impacts on things. We know that some people will almost inevitably get cancer, no matter what they do in their life. These people are born with very strong predisposition genes, which make it almost inevitable that they will get cancer. What I'm showing you in this figure is what's called the pedigree of a family I look after. The squares are males, the circles are females, and every black dot indicates that that person has got cancer. These people, even if they lived inside a bubble without any exposure to carcinogens at all, would almost all get cancer because they carry a very bad gene. Although families of this type were known back in the 1800s, we didn't know why they were all getting cancer. It's possible in very simple ways to actually look at those families, to take a blood sample, and know that this person or this person is likely or unlikely to get these sorts of cancers.

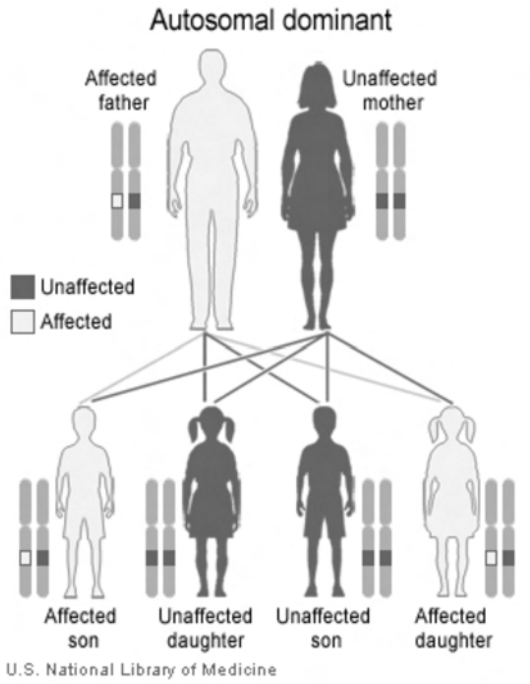
Figure 4: Family pedigree of colorectal cancer



So unravelling the mystery around these sorts of families is becoming increasingly possible. I'm sure people will be familiar with families with many different members who have got cancer at a young age. Showing you how this works is a slightly different thing. Looking at Figure 5 below, we have an affected father and an unaffected mother. As I said, they each have pairs of chromosomes.

The father has a bad gene and the mother has two good genes, but the father has passed the bad gene on to one of his daughters and one of his sons. What this means is that these people have started life with one sort of protective gene and one bad gene, and through life they almost inevitably end up getting cancer. These people typically have very, very severe manifestations of disease.

Figure 5: Autosomal dominant inheritance



One example of those sorts of family cancer syndromes where we know the genetic basis of the disease is familial adenomatous polyposis. The bowel is supposed to be nice and smooth but the diseased bowel has literally thousands of polyps through it. This is an hereditary sort of cancer related to a bad gene in which any sort of exposure doesn't make any difference, the person still ends up with cancer. Similarly a person with a different sort of condition called xeroderma pigmentosa will inevitably get skin cancers, no matter what happens during life. We know the genetic basis of these sorts of diseases.

Having said all this, the conditions I was just talking about are very rare. Less than 5% of cancers are related to that sort of condition. But increasingly we're now starting to understand that not just rare conditions, but also very common conditions are now explicable on the basis of a genetic change that you're born with or that happens to you through life.

I want to tell you something that was actually in the news only a couple of weeks ago. It was a discovery by three different groups in the world, all famous researchers, who discovered the same thing at the same time, and published these three identical findings in very important research journals. What they did was try to explain, and they pretty much did explain, a link between lung cancer and being addicted to cigarette smoking. They linked behaviour to actually getting a disease.

They set out with the statement "Smoking causes cancer". I don't think anyone would dispute that. Lung cancer is the commonest cause of cancer death. There's about a million people who get lung cancer per annum, and most of those people die, but the paradox is that not everyone who smokes actually gets cancer. We all know people who have lived till they're 90 and smoked like chimneys, but they never got cancer. It doesn't seem reasonable. Some people can quit smoking and other people find it impossible, no matter what is done, and some people who have never smoked at all get lung cancer. So the question is, how are those things linked?

The researchers found a lung cancer gene on one of the chromosomes. Amazingly, this same gene is the gene that responds to nicotine as well. The finding was that people who smoke and can't stop smoking are the ones that are also getting lung cancer. They found that 50% of the population carry one copy of this bad gene, but about 10% of the population carry two copies of the bad gene. These studies found that if you have one bad gene, the risk of lung cancer increases by about 30%. If you have two bad genes, the risk of lung cancer increases by about 80%. If you've one bad gene, you average one more cigarette per day than the control group. They discovered that by comparing gene profiles of people who had lung cancer and people who were healthy, and people who were smokers and people who weren't. If you have two bad genes, you average two more cigarettes a day, and the people with two bad genes were the people who couldn't abstain from cigarettes on a long-term basis. The other finding was that people who had never smoked, but had bad genes, also got lung cancer.

What I'm trying to illustrate by all this is that the diseases we get are also linked to the behaviours we undertake. What has been discovered is what has been assumed for a long time and that is the addiction to nicotine. I think these two things are inextricably linked. What we'll see in the future is this changing paradigm by which disease and behaviour are linked, and then a little bit further down the line we might see those same sorts of chips, which are just now starting to come into common day use in research laboratories, used to actually unravel what you've really been exposed to, not what you say you've been exposed to. That may be something people may not want to know about.

I was thinking about a lung cancer SoP in 2050. We may have a whole history of exposures, such as cigarettes, asbestos and radon. We know all these things are related to lung cancer, but there may be a balance now between all the different genes that you have that predispose you to disease or predispose you to behaviours, and the effects of protective genes. The sum totality of that now has to be figured into the exposure equation, and then we have to come up with something that says this disease is related to these particular factors. I think this will be far more challenging than what we're trying to do today. Thank you very much.

1

Genetic disease and Cancer

A GLIMPSE OF THE FUTURE

2

Concepts of disease

- Primitive man – "evil spirits"
- Greek view – humors
- Traditional Chinese view – flow of energy; acupuncture
- Chiropractors – blockage of nervous impulses
- Western concept – pathological process – response of tissue to injury
- Genetic paradigm

3

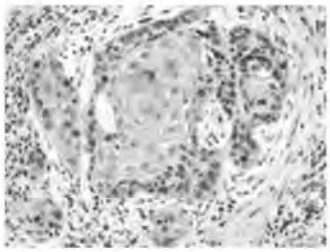
Western view

- Pathological process
  - Inflammation
  - Healing
  - Cancer
  - Infarction
- Pattern of reaction of tissue to injury
- Only recognised by microscopic examination of diseased tissue

Disease = pathological process in specific tissue

4

Diagnosis of cancer



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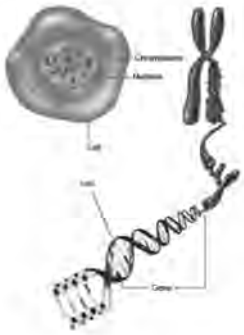
The genetic code



- 3 billion bases organised as 23 chromosome pairs
- Each chromosome uncoiled measures between 1.7 and 8.5 cm
- Human genome project identified 25,000 genes

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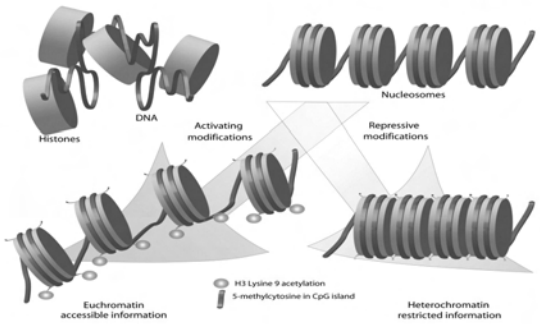
Getting the DNA into a cell



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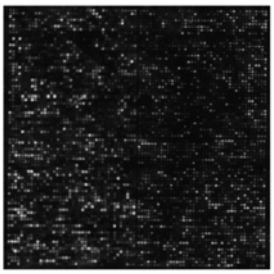
Microarrays, gene chips, DNA chips



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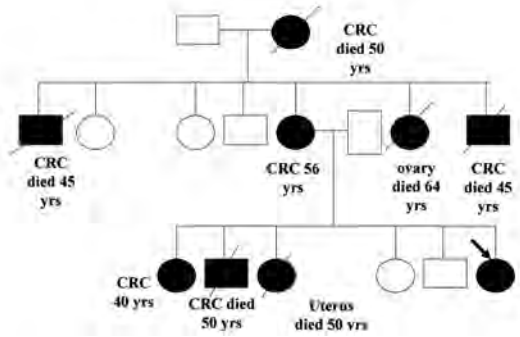
In some people cancer is almost inevitable – exposures make no difference



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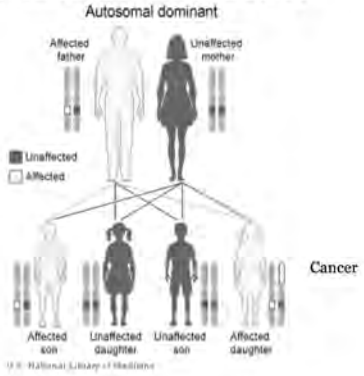
Dominant inheritance – one bad gene gives cancer a head start



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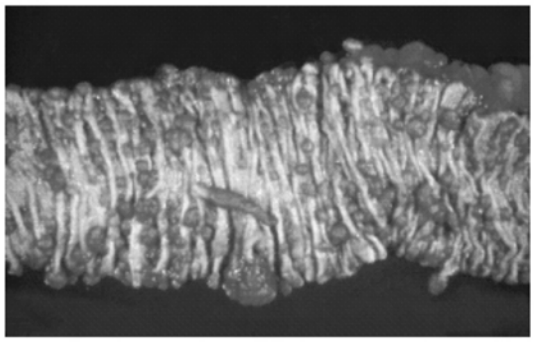
Thousands of bowel polyps



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Xeroderma pigmentosa – skin can't repair damage from UV radiation

12

Lung cancer & nicotine dependence

- Smoking causes cancer
- Not everyone who smokes gets cancer
- Lung cancer is the commonest cause of cancer death
- Some people can quit smoking for others its impossible
- >1x10⁶ people get lung cancer/annum
- Some people who have never smoked get lung cancer

13

The mystery explained – in part

- Lung cancer gene on chromosome 15
- Gene responds to nicotine
- 50% of the population carry one copy of the gene variant
- 10% of the population carry 2 copies of the bad gene

14

What happens if you have the bad genes

- One bad gene – risk of lung cancer increased by 30%
- Two bad genes – risk of lung cancer increased by 80%
- One bad gene – you average 1 more cigs/day
- Two bad genes – you average 2 more cigs/day
- Never smokers with the bad genes got lung cancer

15

RMA in 2050 - Lung cancer SOP

Stress and Stressors

Professor Beverley Raphael, AO
Member
Repatriation Medical Authority

15 April 2008

[This document was prepared from the audio transcripts of the Forum and has been edited for clarity and continuity only]

I'm going to talk about stress but I'm also going to talk about the challenge of defining stress and stressors. Stress is a very broad concept, and a word that is used indiscriminately. Even in an exciting place like the RMA, we've fought hard to have some definition of this concept, because the word "stress" is often assumed to be an operational definition we can use. The RMA considers that it is useful to make the distinction between stressors and stress. Stressors are exposures, that is, events or ongoing circumstances. Stress is the reaction - the psychological and physiological reactions - to such exposures. Stress is part of life and it is part of our developmental process as we deal with challenges throughout our lifespan. These are critical issues to our development and without them we'd probably be "blobs". Stress is necessary for the development of personal growth. The individual reaction to stressors is affected by a number of factors, including genetic influences, learning, environments, social and cultural aspects of what might be defined as a stressor or stress and perceptions of stressors. If we have the perception that we're going to die, even if nobody else does, that is a very stressful experience for us.

Personal characteristics may influence stress. Resilience is an important characteristic, and one which people are increasingly focussing on when they are looking at the concept of possible protective factors in the face of a range of exposures - biological, psychological and social. Positive social and environmental factors, learning and training, and the levels of control, skills, mastery and experience that individuals possess, may contribute to resilience.

Combat is a high risk exposure, and this is reflected in the high rates of lifetime and 12-month prevalence of PTSD. This is traditionally the stress-related disorder that everybody thinks about. Being exposed to a major stressor doesn't result only in PTSD, but PTSD has been the research link through which researchers have generally examined exposure to a stressor, so there are far more studies about PTSD than almost anything else.

Military service has many positive benefits that have been highlighted in various studies and I'm going to touch on some of these today. We have endeavoured to consolidate the previous stressor factors included in SOPs, bearing in mind the complexity and inadequacy of the definition of stressor exposures in much of the literature. Experiencing a severe stressor, such as the threat of death, or another type of very severe psychosocial stressor, fits with one of the criteria for PTSD. After extensively researching literature that seeks to identify the types of experiences that people have had that they considered to be stressor exposures, we have tried to be clearer in identifying new stressor factors by making more consistent categories.

We can talk about combat quite easily, because if you go to war and you're trained, it's expected that warfare will involve you in life-threatening circumstances of one kind or another. It's to do with defeating the enemy, but various types of deployment mean that troops confront some of these stressors in different ways. The timeframes may vary enormously between the different SoPs and that relates, in most instances, to the availability of the scientific literature. Stressor factors, if they're significant, are usually involved in both the onset and the worsening of a condition, and may contribute to its maintenance. What we've done is chosen to categorise the stressors to exemplify the types of events which qualify as stressors at a given level of severity. For example, a category 1A stressor is defined by one of the following severe traumatic events: experiencing a life-threatening event, being subject to serious physical attack, rape, sexual assault, being threatened with a weapon, being held hostage or being kidnapped. It therefore includes combat, and does not exclude any emotional response to such events. It does take into account how people might perceive a stressor and it doesn't exclude the fact that you might be distressed by it, and think you're going to die. The "category 1A" stressor factor is in the SoPs for PTSD, drug dependence and drug abuse, alcohol dependence and alcohol abuse, depressive disorder, bipolar disorder, acute stress disorder, anxiety disorder, ischaemic heart disease and cerebrovascular accident.

A "category 1B stressor" means one of the following severe traumatic events:

being an eye witness to a person being killed or critically injured; viewing corpses or critically injured casualties; being an eye witness (actually observing an incident first hand and able to give direct evidence of it) to atrocities; killing or maiming another person and being an eye witness to or participating in, the clearance of critically injured casualties. The RMA takes seriously what a person in the defence forces or a veteran may have been exposed to. Most of the major disorders are reflected by experience of this type of stressor.

"Category 2" stressors are more vaguely defined in the literature. I would have to pay tribute to the RMA researchers for trawling through a morass of literature, where consistent definition of the exposures has been extremely limited in most studies. These are much more diffuse and generic stressors. Nevertheless, they are in the scientific literature and are much more likely to be the category of stressor which leads to depressive disorder, bipolar disorder or anxiety disorder.

In addition to the categories of stressors, there are quite specific stressors which the science shows to be relevant. These include bereavement, which is expressed in the SoPs as "experiencing the death of a significant other". A significant other is defined as a person with whom there is a close family bond or a close personal relationship and who is important or influential in one's life. The SoPs for drug dependence and drug abuse, alcohol dependence and alcohol abuse, depressive disorder, anxiety disorder and ischaemic heart disease have this factor. Experiencing the traumatic death of a significant other is a factor

in the SoPs for acute stress disorder and PTSD. A large Danish population study has shown that experiencing the death from suicide of a close family member is a specific stressor and this is a factor in the SoP for bipolar disorder. Having a significant other who experiences a category 1A stressor is another specific type of stressor and is associated with the anxiety spectrum disorders and depressive disorders.

Other specific stressors that have been identified include having a medical illness or injury which is life threatening or which results in serious physical or cognitive disability and having chronic pain of at least three months' duration. Both of these stressors have been causally associated with depressive disorder and anxiety disorder. A number of SoPs have a factor for having a clinically significant psychiatric disorder. In other words, the experience of having a psychiatric disorder is a stressor in its own right.

To conclude, the definition of stressors is a minefield of complexity. We recognise the impacts that such exposures might have and we've provided a glimpse of how they might be viewed and linked in the scientific literature. It would be fair to say that, although there are vast numbers of studies which are focussed on PTSD, there is only a limited number which describe the ways in which stressor exposures have been defined, classified and compared.

1

Stress and stressors

Professor Beverley Raphael

2008 RMA/DVA/ESO Forum

2

"Stress" is a broad concept, a word in the English language. Even in the scientific literature it is often poorly defined and variably measured.

3

The RMA considers that it is useful to make the following distinction:

STRESSORS or EXPOSURES

ie events or ongoing circumstances

STRESS:

The REACTION, PSYCHOLOGICAL & PHYSIOLOGICAL

4

Stress & Its Effects

- Stress is part of life
- Stress is challenge
- Stress is necessary for development & personal growth

5

Stress & Individual Reactivity

- Genetic influences
- Learning
- Environments
- Social & cultural aspects
- Perceptions of stressors

6

Resilience & Personal Strengths

- Personal characteristics; biological (including genes); psychological & social
- Positive social & environmental factors
- Learning & training
- Control, skills, mastery & experience

7

Not All Stressor Exposures Lead to Problems or Illness

Combat Exposure is a higher risk BUT not everyone is affected

- **Lifetime Prevalence Rates PTSD**
  - 17.1% Vietnam Veterans (Australian Vietnam Veterans' Health Study; O'Toole et al., 1996)
  - 7.8% General Community e.g. rape, abuse, assault – US data (National Comorbidity Survey; Kessler et al., 1995)
- **12-month Prevalence Rates PTSD**
  - 5.1% Gulf War Veteran (Australian Gulf War Study; Ikin et al., 2004)
  - 1.3% General Community eg rape, abuse, assault (Australian National Survey of Mental Health and Well-Being, Andrews et al., 1997)

8

Not All Stressor Exposures Lead to Problems or Illness (2)

Military Service also has Positive Benefits

eg Aldwin et al (1994)

- Positive & Negative Effects Increased with Greater Combat Exposure
- Positive Effects included:-
  - Learning Cooperation & Team work
  - Broadening of perspective
  - Coping Skills
  - Independence & Self Discipline

9

Previous stressor factors

- **experiencing a severe stressor"** means, the person experienced, witnessed or was confronted with, an event or events that involved actual or threat of death or serious injury, or a threat to the person's or other people's physical integrity, which event or events might evoke intense fear, helplessness or horror.
  - In the setting of service in the Defence Forces, or other service where the Veterans' Entitlements Act applies, events that qualify as sever stressor include:
  - Threat of serious injury or death; or
  - Engagement with the enemy; or
  - Witnessing casualties or participation in or observation of casualty clearance, atrocities or abusive violence;

10

Previous stressor factors (2)

- **"severe psychosocial stressor"** means an identifiable occurrence that evokes feelings of substantial distress in an individual, for example, being shot at, death or serious injury in a close friend or relative, assault (including sexual assault), severe illness or injury, experiencing a loss such as divorce or separation, loss of employment, major financial problems or legal problems.

11

New stressor factors

- Clearer, more consistent categories and more detail concerning the types of events which qualify as stressors
  - as well as combat-related stressors, serving members are exposed to stressors which are similar to those experienced by the general population
- Time frames for a given category may differ between SoPs according to the evidence for that particular condition
- Stressor factors usually in both onset and worsening

12

Category 1A stressor

- **"a category 1A stressor"** means one or more of the following severe traumatic events:
  - experiencing a life-threatening event;
  - being subject to a serious physical attack or assault including rape and sexual molestation; or
  - being threatened with a weapon, being held captive, being kidnapped, or being tortured;
    - includes combat
    - does not exclude an emotional response to events

13

SoPs with a category 1A stressor

- PTSD
- Drug dependence and drug abuse
- Alcohol dependence and alcohol abuse
- Depressive disorder
- Bipolar disorder
- Acute stress disorder
- Anxiety disorder
- Ischaemic heart disease
- Cerebrovascular accident (RH)

14

Category 1B stressor

- **"a category 1B stressor"** means one of the following severe traumatic events:
  - being an eyewitness to a person being killed or critically injured;
  - viewing corpses or critically injured casualties as an eyewitness;
  - being an eyewitness to atrocities inflicted on another person or persons;
  - killing or maiming a person; or
  - being an eyewitness to or participating in, the clearance of critically injured casualties;

  "an eyewitness" means a person who observes an incident first hand and can give direct evidence of it. This excludes a person exposed only to media coverage of the incident;

15

SoPs with a category 1B stressor

- PTSD
- Drug dependence and drug abuse
- Alcohol dependence and alcohol abuse
- Depressive disorder
- Bipolar disorder
- Acute stress disorder
- Anxiety disorder
- Ischaemic heart disease

16

Category 2 stressor

- **"a category 2 stressor"** means one or more of the following negative life events, the effects of which are chronic in nature and cause the person to feel on-going distress, concern or worry:
  - being socially isolated and unable to maintain friendships or family relationships, due to physical location, language barriers, disability, or medical or psychiatric illness;
  - experiencing a problem with a long-term relationship including: the break-up of a close personal relationship, the need for marital or relationship counselling, marital separation, or divorce;
  - having concerns in the work or school environment including: on-going disharmony with fellow work or school colleagues, perceived lack of social support within the work or school environment, perceived lack of control over tasks performed and stressful work loads, or experiencing bullying in the workplace or school environment;

17

Category 2 stressor

- experiencing serious legal issues including: being detained or held in custody, on-going involvement with the police concerning violations of the law, or court appearances associated with personal legal problems;
- having severe financial hardship including: loss of employment, long periods of unemployment, foreclosure on a property, or bankruptcy;
- having a family member or significant other experience a major deterioration in their health; or
- being a full-time caregiver to a family member or significant other with a severe physical, mental or developmental disability;

18

SoPs with a category 2 stressor

- Depressive disorder
- Bipolar disorder
- Anxiety disorder

19

Specific stressors (1)

- experiencing the death of a significant other
  - **"a significant other"** means a person who has a close family bond or a close personal relationship and is important or influential in one's life;
- SoPs with this factor
  - drug dependence and drug abuse, alcohol dependence and alcohol abuse, depressive disorder, bipolar disorder, anxiety disorder, ischaemic heart disease

20

Specific stressors (2)

- experiencing the traumatic death of a significant other
- SoPs with this factor
  - acute stress disorder, PTSD

21

Specific stressors (3)

- experiencing the death from suicide of a close family member
  - **"a close family member"** means a parent, child or sibling with whom the person has a close relationship;
- SoPs with this factor
  - bipolar disorder

22

Specific stressors (4)

- having a significant other who experiences a category 1A stressor
- SoPs with this factor
  - acute stress disorder, PTSD, depressive disorder, anxiety disorder

23

Specific stressors (5)

- having a medical illness or injury which is life-threatening or which results in serious physical or cognitive disability
- SoPs with this factor
  - depressive disorder, anxiety disorder

24

Specific stressors (7)

- having a clinically significant psychiatric condition
  - **"clinically significant"** means sufficient to warrant ongoing management, which may involve regular visits (for example, at least monthly), to a psychiatrist, counsellor or general practitioner
- SoPs with this factor
  - drug dependence and drug abuse, alcohol dependence and alcohol abuse, depressive disorder, anxiety disorder, bipolar disorder (anxiety spectrum disorder), ischaemic heart disease (depressive disorder)

Critical Appraisal and Causal Inference

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Member
Repatriation Medical Authority

16 April 2008

[This document was prepared from the audio transcripts of the Forum and has been edited for clarity and continuity only]

I would like to discuss how we read a scientific paper, focussing on the issues that go through the minds of the RMA members, working together with the researchers, in order to come to conclusions about a paper. We're not expecting to give you detailed technical knowledge, but rather a sense of what type of thinking goes on.

There's no SoP without a disease so before commencing a SoP, we have to be sure there's a disease. That's a really important part of our discussion. Is this a real disease? Is there evidence that it actually is a disease, and what is the disease? Before we can go into the literature to find out what its causes are, we need to be very sure of this. Once we decide there is a disease, we research the published literature to find out whether there is anything known about its causes. The scientific publications are really the raw material of the RMA. We say we don't do research, but this actually is a form of research. It's not primary research, it's secondary research, but going to the published literature is very much driven by research processes. Questions that often arise are, "What is relevant?" "What is the applicable literature?" The literature is expanding at a phenomenal rate, but at the same time, so are parallel sources of information, particularly through the internet. We therefore have quite strict definitions of what is a relevant publication for the purpose of constructing a SoP.

First of all, the literature has to be what's called "peer reviewed". There are many different ways of peer reviewing things, and many different levels of journals in which things are peer reviewed. It generally means that someone has written up the study and sent it off to a journal which has what's called a peer review process, which means they send it around to people who are supposed to be knowledgeable in the field and send back comments. The article is then revised based on the comments and it's accepted or rejected on the basis of the editor's decision. Peer review therefore depends on sensible editors and on good people to do the reviewing. It's by no means a foolproof process, but it's a minimum hurdle that has to be jumped by papers to receive our consideration.

Secondly, a relevant publication has to have what we call original data on a topic or it has to be a review of original data. It can't be some sort of rumination or contemplation of the issue, some thought provoking new hypothesis or inference from mathematical jottings or modelling. It has to be new empirical data about what happened to human beings, or a review of such empirical data, still satisfying that criteria of being peer reviewed. It has to be about people - we don't review data on animals or things that happen in test tubes, we review data about something that happened to at least one person. There has to be either one person newly reported or a summary of somebody else's experience of reporting on that one person. Furthermore, if it's purely a description of the disease, it doesn't enter into our considerations concerning causality. It has to provide something new about possible factors that might cause the disease. These are the relevant factors that have to come into play before a publication can be processed for a SoP.

I alluded to consideration of at least one potential factor. What is meant by a factor? All of us have an intuitive idea of what we mean by a factor, but the definition has to be formalised. First of all, a factor must be something that potentially can be an exposure resulting through service. The RMA has had some very convoluted discussions about whether something could possibly happen in service. Generally we err on the side of "yes it could happen through service" even if it's never actually been known to happen through service. We do allow this criterion to stretch pretty far.

Secondly, a potential factor is something that increases the likelihood of the person developing the disease or the likelihood of the disease worsening. This is the point where we depart from normal speak into technical speak. Why? Because of the word 'likelihood'. What is a person's 'likelihood?' This is a very mysterious concept, because you can measure someone's blood pressure, you can measure their temperature, you can test if their bones are in the right alignment but you can't measure their likelihood. You can't go to one person and say "What's your likelihood?". It's not a measurable entity in a single person.

Likelihood is an entity that's only measurable in groups of people and populations - it's a statistical concept. The likelihood is a probability that's measured by looking at groups of people - fifty people, a hundred people, a thousand people - the more the better. Likelihood is a tricky concept because we measure it in groups of people but we apply it to single person. Once you apply it to a single person, you still don't know whether that individual person is going to be affected by that likelihood, but we conceptualise it that way. That's a key difference between the approach of clinical medicine which works on individuals, and public health or epidemiological practice which relies on groups.

If something increases the likelihood of a person developing the disease, it is a cause, and therefore qualifies to be a factor. Consider these examples. The first set are things that you might think are really obvious causes of a disease or an injury. For example, somebody falls and then develops a bruise. You don't have to do an epidemiological study to prove the person got the bruise from the fall. Or, if you spend the day in the sun and then at the end of the day you are sunburnt. What caused the sunburn? No epidemiological study required. Or you might carry a pack all day, and then at the end of the day you have a sore back. If you didn't have a sore back at the start of the day and you have one at the end, there's a very, very high likelihood you got that sore back from carrying that pack. There are, however, some other possibilities. You might have got the bruise because you had been bashed the night before and you stumbled and whacked your arm against the door frame. Or in the case of the sunburn, it might

not actually be sunburn, it might be a reaction from some medication you've taken. Or you might have a sore back because you slept in a bad position. It's not an epidemiological study that's going to separate those causes from each other so even in those situations, the causal inference is not perfect, but it's pretty strong. The reason that it's so strong is because the injury or illness that you get happens very soon after your exposure. There's no lag time, it's an immediate reaction and there's little reason to suspect that anything else caused it. Generally speaking, those other explanations I gave are pretty remote.

Needless to say, we don't spend much time at the RMA on examples like these. Instead, we focus on examples such as being exposed to a chemical and 25 years later developing a rare form of cancer. Did that chemical cause the cancer? Or, after undertaking repetitive, physically stressful activity over 15 to 20 years, arthritis develops in various joints. Is that because of that long term low level or repeated physical activity or would arthritis have developed anyway with ageing? If you're exposed to a stressor and then 15 years later you develop depression, is that cause and effect? Establishing causality for those sorts of relationships is a very different undertaking from the first set of examples I gave. The first reason is that the timeframes are much longer, so you cannot observe a direct sequence of events. Secondly, even though I came up with those other fictitious reasons why you could have developed a bruise or a red face or a sore back, those reasons are pretty remote. The diseases in the second set of examples - cancer, arthritis, mental illness - can be caused by many things other than the potential one you're trying to assess as the cause: they are what we call multi-factorial. So it's the long timeframes and the multi-factorial causes of these kinds of diseases that make it difficult to assess causation.

When we endeavour to define a factor for the purpose of an RMA Statement of Principles, what do we do? Firstly, we assess the published literature using the process of "critical appraisal". This process is very well defined and allows us to decide whether there's evidence that the factor is associated with an increase in the likelihood or probability of disease. Once this assessment has taken place, we examine whether the association is a causal one.

These are two separate and very different activities. I really want to emphasise that because a lot of the questions we get about RMA processes are because people don't see the distinction between the critical appraisal process and the causal inference process. Critical appraisal is a systematic, well defined, stepwise process that is taught at all good universities and we're trying to teach you a little bit about it this morning. We're going to help you go through the paces of critical appraisal on two example papers. Critical appraisal is the common language for reading published epidemiology. When epidemiologists get together to discuss papers, they speak critical appraisal language. Casual inference is a different kettle of fish altogether. Various esteemed organisations, some very influential epidemiologists, public health leaders, philosophers and lawyers have tried to write down principles for causal inference. There's a massive body of literature about causal inference, but it is much, much harder to define, codify, or implement compared to critical appraisal. Causation is a philosophical concept - it depends on the context and your overall perspective as to how you go about causal inference.

For example, there's a very famous set of postulates in medicine that was set up by a German scientist in the 19th century by the name of Koch, who was the first person to discover some very important infectious diseases. Koch's postulates, as they were called, were the first attempt to really codify how you do causality in medicine. Those postulates have since been shown to be utterly irrelevant and meaningless in a whole range of other causal situations in medicine for reasons I won't go into, but they were the landmark of their time. One hundred years later, epidemiologists in the UK, Richard Doll and Austin Bradford Hill set up what are called the Bradford Hill criteria for causal inference and they served their purpose of looking at causes of cancer and chronic diseases, but again they have weaknesses and limitations. They've been endlessly critiqued and debated and there's still no single rigorous methodology for doing causal inference.

With critical appraisal the latitude for debate is much more limited. We look at papers and we generally agree on what they say, or at worst disagree on fine points. The critical appraisals then get put into the discussion of causal inference, and the key question arises, "Is this a factor?", "Yes or no?" This process relies very much on our collective expertise and experience and also our team debating styles and engagement. We test ideas against each other and we work within the framework of the beneficial nature of the legislation, to come up with what we think is a consistent and reasonable set of outcomes.

That's the preamble to what you'll be doing this morning. What I'm going to do now is go through three chunks of work that make up critical appraisal, and we are calling them, unsurprisingly, critical appraisal one, critical appraisal two, and critical appraisal three. They correspond directly to the three groups of questions that are going to be applied to each paper (Table 1).

Table 1: Critical appraisal questions

Group 1: 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 (exposures) and how are they measured?
Where did the study subjects come from?
Group 2: What are the main results?
What is the size of the effect?
Are the results statistically significant?
What are the confidence intervals?
Group 3: 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?

First of all, critical appraisal one. What is the study about? This defines what a study actually did, not what it found, but how the basic bones of the study were set up. We need to know what the study hypothesis or research question was. We need to know what the outcomes or diseases it was investigating were, what factors it looked at, who were the study subjects, and what the study type was. I'll come back to each of these points in a second, but these are the key elements of describing a study. As I said, this doesn't tell you anything about its results or how valid it is, it is just what they tried to do in the study.

Now to the study outcomes or diseases. It is obviously essential to know what disease is being studied. Some studies look at one disease and some studies look at multiple diseases. When you are doing your critical appraisal, you need to look at the paper and say, "Okay, we are studying arthritis. But how did they define arthritis? Did they define arthritis on the basis of people saying that they had stiff joints? Or did they define arthritis on the basis of doing scans? What do we really mean by arthritis?" This is very important because papers purport to study a disease, but when we look closely, they didn't even define whether the people in the study had the disease by well-agreed criteria. You really have to be sure you know how they're defining the disease in the paper.

Once you know how they defined the disease itself, it is important to know how they recruited people who had the disease into the study. Did they do it by going through hospital records, did they do it by ringing people up on a telephone survey and saying, "Have you got this disease and do you want to be in a study?" Did they do it by linking to, say, cancer registry records? How did they find out that people in the study had the disease? What was the mechanism of getting hold of people with the disease?

The third aspect is looking for any problems with the definition and procedures for measurement. In other words, is there anything, to use that word from yesterday, "dodgy" about the way they did things? You can often find things that are dodgy, especially, for example, if you are looking at a study of people who had a disease on the basis that they say they've got the disease. That can be quite a weak basis, but you'll find many studies in the published literature that are based on people's self report of disease.

Another problem is if they got people into the study by asking them to sign up through the internet or getting them to connect to the research centre by telephoning or emailing in. The reason that would be a little bit unsatisfactory is because it wouldn't be a representative sample, as it is made up of those who referred themselves in. On the other hand, if they did a study that was based on a total population survey, and they picked out every single person in the population with the disease and studied them, that would be the other extreme. In between those two extremes, there are many, many different ways to get people with the disease into the study.

Similar issues apply to the study factors. Many studies look at multiple factors. In fact, most studies look at multiple factors. Again, the question arises, how is the study factor defined? What do we mean by being exposed to asbestos? Does that mean that the person worked in an industry where asbestos was widely used or does it mean that a person actually did a specific activity? Or that a person worked in an environment where there was a lot of visible dust from asbestos production or application activities? What is the definition of being exposed to the factor?

Every factor gives rise to a range of questions about the measurement of the exposure. How did they measure not just whether people were exposed but how much they were exposed and when they were exposed? Many studies rely on people's recollection which says, for example, "Okay, I was working in shipbuilding, and I started in this year and at that particular time period there was a lot of asbestos involved in the construction, but then at a certain year they stopped it, so that's how I figured out what my years of exposure to asbestos were." When you look at a paper, you ask if there were any problems with the way they defined the exposure. Was this done in a rigorous and defensible manner? If there are weaknesses, it is generally not because

researchers are trying to take short cuts; it may be because there's no other way, and you have to rely on measures that are not ideal. Even though Professor Ward tells us that we'll be able to just scan your DNA and read everything about past exposures, I think we are a few years away from that, and while we get there we are going to rely a lot on self report.

The next point about describing a study is to find out what kind of study they did. There are many different ways to figure out whether a factor caused a disease using different epidemiological designs. The classiest one is called the randomised trial, which is the ideal but it's almost never done. The reason it's almost never done is because their purpose is usually for testing new medicines, when you're trying to see if something works to reduce the effects of a disease. You can't randomly assign people to something that might increase the chances they'll get a disease. You can't assign one group of people to be exposed to asbestos and one group not to be, that doesn't happen. It has happened inadvertently, however - there are trials of drugs that have been randomly assigned to cause benefit but have ended up causing bad side effects. In the field that I work in primarily, infectious diseases and HIV research, there have been trials where they've tried to look at HIV prevention agents that have ended up causing people to have a higher chance of catching HIV.

The next best option is what's called a cohort study, and there are different kinds of cohort studies. In a cohort study you recruit people or get lists of people who are defined in various ways, whether it's because they were exposed to a particular factor or because they are accessible in some other way, and you track them into the future. Sometimes you find people using records from the past and tracking them up to the present day. The main point about a cohort study is you try to get information about what people were exposed to before they developed any health problems. That's the reason why this is quite a strong methodological approach.

Case-control studies are a sort of a short cut where you go straight to the people with the disease. You don't try and recruit a cohort of people who haven't got the disease, you go straight to a bunch of people with the disease and compare them to the people who haven't got the disease. A case-control study does have some serious limitations and I won't go into them in great detail, but they are largely to do with the fact that you're dealing with a bunch of people who already have the disease and comparing them to those who haven't. There's already a difference in how they're going to think about their past and tell you about their exposures, which may be very different from those who are well, simply because of their experience of having a disease. Another design is the cross-sectional study, but again, I won't go into detail, apart from telling you that they have serious limitations. Next in the hierarchy there are correlation studies. An example of this type of study is looking at the patterns of hepatitis B on the world map, compared to the patterns of liver cancer. They're called correlation studies because you look at populations to see whether factors distribute in a way that's similar to the disease in question. They're very rough and ready, but they can be powerful for generating hypotheses and setting your train of thinking going. We would never use a correlation study to come up with a factor in a Statement of Principles - there are too many weaknesses in the methodology.

The weakest of all study types is case reports. Case reports prove that the disease and the factor may coexist in a person - that's about all they can prove - but they certainly can't take you to the next step. However, for certain reasons to do with the way we work in the RMA and unlike much of epidemiology, we do actually allow case reports to play a role in our inference for deciding if something can be a factor or not. It's one particular example of the beneficial aspect of the legislation, not only allowing us to go to lower probabilities or lower doses when we determine causality, but actually to take a much weaker paradigm than is normally used in public health inference about causation.

The second group of questions are about the main results - what did this study actually find? A study may have several factors and several diseases, so you're going to have to consider each factor and each disease, and each factor-disease combination. The basic measure, the most commonly reported measure of the effect of a factor in causing a disease, is called the relative risk. The relative risk is the key measure, and I'll come back to its meaning shortly.

Another thing you look at is statistical significance, which is shown by the P value or the P. You look for a very small one, and in this context the smaller the better. Often we're doing very big studies, but the idea is to get a very small P value, which means a very, very small probability that the results you're looking at are caused by chance. If it's got lots of zeros, if it's 0.001 for example, then that's very small. There's a sort of a convention that says if it's less than 0.05, that's small enough to be considered statistically significant, but the smaller the better. Another thing you look at is confidence intervals, which provide an alternative way of assessing statistical significance, as well as other information about the relative risk.

Finally, having considered the relative risk, the P value and the confidence intervals, we then try and look within this study to see whether the relative risk seems to change according to different aspects of exposure. For example, studies often break up the study population into groups according to levels of exposure, or the time that has elapsed since people were exposed or even according to personal characteristics. So, we might conclude that the effect of exposure is greater at higher dose levels, or diminishes with time since exposure stopped, or is increased in older people compared to younger people.

Figure 1: Relative risk

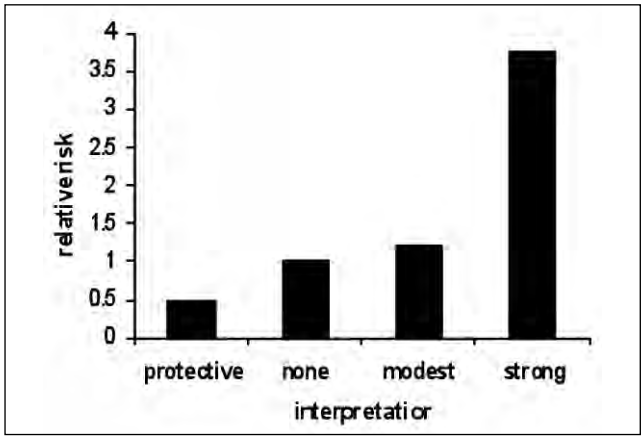


Figure 1 shows different kinds of relative risk. The relative risk can range from zero to anything, but it's always a positive number. If the relative risk is one, that means there's no effect. The factor does not influence the occurrence of the disease. A relative risk of one simply means that the people who've got the factor have the same amount of disease as the people who haven't got the factor. If the relative risk is less than one, for example a relative risk of 0.5, that means that the people exposed to the factor actually had less disease, and the factor is said to be protective. A relative risk of 0.5 means that people who've been exposed to the factor had half the risk compared to those that didn't have the factor.

One example of a protective effect is regular exercise and the effect of reducing the chance of developing heart disease. In some of our Statements of Principles we have a factor for inability to exercise at more than a certain level. In other words, if you couldn't exercise you are missing out on the potential benefit of that protective factor, and you would increase your risk of heart disease. In this way we create a factor that is a cause of disease in an SoP, ie not exercising, out of an exposure that is actually beneficial.

A modest or moderate effect is where the relative risk is getting up to about 1.5. That means that if you are exposed to the factor, your risk of disease is increased by around 50%. That's the sort of increase in risk that might often result in a factor being put into a Statement of Principles. The risk is clearly elevated, and although it is a modest increase by comparison with some other disease-causing agents, it still could qualify as a factor. On the other hand, an exposure for which the relative risk increases three or fourfold is a very strong risk factor. We don't find that many exposures that increase disease risk by that much. There are some around but most things we find in epidemiology increase the chance of disease by 1.5 to 2.5.

There are nevertheless some very famous examples of strong risk factors, cigarette smoking being the most well known in terms of its lung cancer relationship. The relative risk for lung cancer of smoking one pack a day for a long time is about 20. Another very strong risk factor is exposure to asbestos, which gives rise to a relative risk of getting mesothelioma that is of the order of several hundredfold. There are some other very dramatic relative risks in epidemiology, but most are in the more modest range.

The third group of questions that we consider in critically appraising published studies involves looking at the findings and asking whether any association observed between the study factors and the disease could have an alternative explanation. The three major things we look at are confounding, bias and chance.

We will go through each of those in turn, starting with confounding. As an example, let us say we are conducting a study of the relationship between exposure to a chemical from working in a chemical production facility and the development of some form of cancer. However, maybe there were some other factors in that environment or the lives of the employees that were also a potential cause of cancer. The obvious example is always cigarette smoking as an alternative cause of cancer. You have to ask, "In doing the study did people adequately take account of the alternative possibilities?" There are many ways you could do that, and there's no time in a lecture like this to go through those methods, but in reviewing a paper using critical appraisal, you'd be looking for evidence that the authors actually looked thoroughly at other potential risk factors. Some diseases, such as Parkinson's disease or various types of lymphoma have very few known causes and so there's not much of a chance that there could be confounding by factors that we are aware of. Other diseases like heart disease have a whole slew of different causes that we know about and you have to really look closely to make sure the researchers have taken care of all those different possible confounding relationships.

If you are looking at the relationship between alcohol and hypertension, you need to consider what else causes hypertension? Were those other factors looked at in the study and did the study authors try to exclude them as possible causes of the hypertension in these study participants? In assessing studies for confounding, there are two issues that arise. First of all did the researchers actually consider such factors, and secondly, if they did consider confounders, how did they measure them and try and take account of them?

The second problem that can arise in studies is "bias". Bias is a cousin of confounding but it's slightly different. There are different ways you can get bias. For example, suppose you were studying people who had a disease, but the way you recruited them was very strongly associated with a factor that was a being studied as a cause of the disease. Perhaps you were trying to figure out whether working in a particular occupation had been a cause of the disease, but the people with disease in the study were recruited from an occupational health and safety registry held for that occupation. There could then be an over-representation of people from the occupation in the study population. Recruitment of study

subjects should ideally be undertaken in a way that's not dependent on the factors being studied as potential causes of the disease under investigation.

Secondly, the mechanism within a study for diagnosing the disease of interest should be independent of whether the person is exposed to any factor that is being studied as a cause of the disease. That might sound obvious, but consider this example. A person who has been extensively exposed to the sun might get very regular checks for skin cancer, whereas a person who has been less exposed might be checked less frequently. Now, we know that sun causes skin cancer, but you would want to be sure that the people in the study who hadn't been exposed to the sun had checks as regularly as the people who had, because you might just be detecting more cases by looking more often in the exposed group, and the result would be that the strength of the association between sun and skin cancer would be exaggerated, or "biased".

Likewise when it is the other way around - you need to make sure that the study isn't somehow better able to detect the factor of interest more often in people with the disease compared to those without. For example, in a case-control study of a rare disease, a person with the disease may be asked, "Can you remember ever having been exposed to a particular chemical?" Perhaps the chemical has nothing to do with the disease, but a person with the disease has been extensively reflecting on what may have caused it, and recalls a history of exposure to the chemical, whereas a person who does not have the disease may not have been going through the same ruminative processes

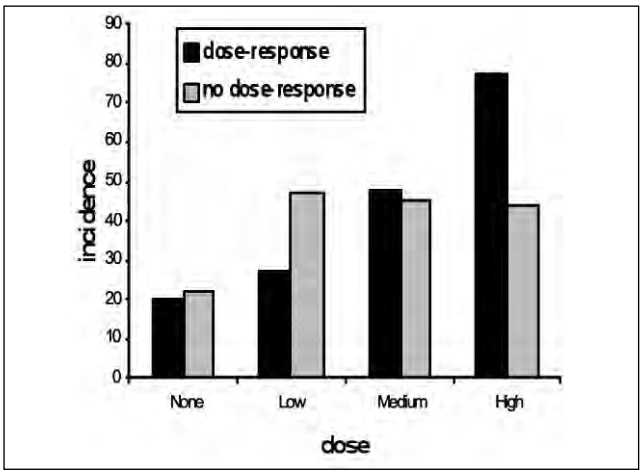
The third alternative explanation is "chance". This is where the P value becomes important. If it is very small, then you can say that chance is probably not a factor. If the P value is above 0.05, then you'd be worried that the association between the risk factor and the diseases might just be due to chance.

When we have clear idea from the process of critical appraisal about the quality of the studies that have been conducted concerning the relationship between a specific factor and a disease, as well as their main findings, we can examine the question of causality. As I noted earlier, it is much harder to define formal processes for assessing causality than it is to standardise critical appraisal.

A very important element of causal inference is the strength of the relationship (Figure 1). If you had relative risks of 4 or 5 or 6, they are much stronger indications of causation than relative risks of 1.5 or 1.7, even if there is the same degree of statistical significance. We seriously consider all relative risks that are statistically significantly different from 1.0, but when we are trying to decide about causality, the magnitude of the risk is very important.

A dose-response relationship is also very valuable. If the risk of disease goes up with increasing exposure to the factor, the case for causation becomes more convincing. Figure 2 shows an example of a dose-response effect. With the black bars, the disease incidence increases steadily according to the level of exposure, whereas with the grey bars it goes up from no exposure to low exposure, but then levels off or goes down at higher levels of exposure. The grey bars do not exclude the possibility of causation, as the pattern may be due to mismeasurement of the factor, but it certainly doesn't provide compelling evidence in support of a factor.

Figure 2: Dose-response effect



Another crucial component of causality is evidence from the study that the disease developed after participants were exposed to the factor in question. This again sounds obvious, but a case-control study is comparing exposure history in people who have the disease already with history in people who haven't got the disease. If there is no basis in the primary evidence from the study as to whether participants developed the disease after being exposed to the risk factor or before being exposed to the risk factor, it is difficult to confidently assert a causal relationship.

To suggest that an exposure is causally related to a disease, you'd also like the evidence to be consistent. You'd like the evidence from epidemiological studies to be consistent with other studies and the biological evidence more generally: It should make sense biologically. Although this step is not crucial, it can be very uncomfortable for us intellectually to attribute causation to a factor if we can't think of any possible mechanism by which its relationship to disease is supposed to be operating.

I'll wrap up here after what has been a very brief sprint through the topic of critical appraisal and causal inference.

1

Inside the mind of the RMA: Epidemiologist reveals all!

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2

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16 April 2008

3

The creation of a SoP

1. In the beginning, there is a disease
2. Do we know anything about its causes?
3. Scientific publications…

the raw material of the RMA

4

What is a relevant publication?

- "peer-reviewed"
- "original data" or review of original data
- Describes at least one person with the disease
- Considers at least one potential "factor"

5

What is a potential factor?

- Something that a person can be exposed to through service…
- That increases the likelihood of the person developing the disease (or worsening…)
- A cause of the disease

6

Examples 1

- Fall → bruise?
- Sun → sunburn?
- Carry pack → sore back?

7

Examples 2

- Exposure to chemical → cancer?
- Physical activity → arthritis?
- Stressor → mental illness?

8

Defining a factor

- Assess the published literature
  - **Critical appraisal**
- Decide whether there is enough evidence to state that the factor "increases the likelihood" of disease
  - **Causal inference**

9

Two **very different** activities

- Critical appraisal
  - Well defined, stepwise process that is taught to at all good universities
  - The common language for reading epidemiology
- Causal inference

10

Critical Appraisal 1: What is the study about?

- **Hypothesis (research question)**
- Outcomes (diseases)
- Factor(s)
- Study subjects
- Study type

11

The study outcomes (diseases)

- How is it defined?
- How did the study identify/recruit people with and without the disease?
- Are there any definitional or measurement problems?

12

The study factor (s)

- How is it defined?
- How did the study measure **whether** (and **when**, and **how much**) people were exposed to the factor?
- Are there any definitional or measurement problems?

13

Study types for identifying factors

- **Randomised trial**: **ideal**, *rarely* **done**
- **Cohort study**: *strong*, **rarely** *done*
- **Case-contro**l: *serious limitations*
- **Cross-section:** *very serious limitations*
- **Correlation:** *only for generating hypotheses*
- **Case reports**

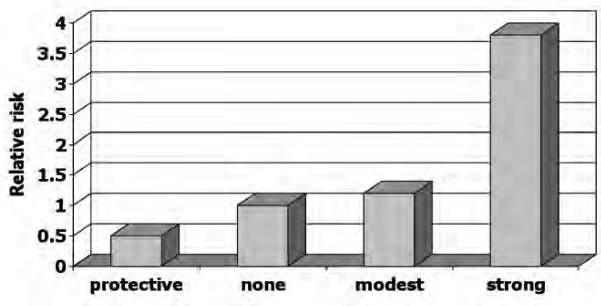
14

Critical Appraisal 2: Main results

- The size of the effect: **relative risk**
- Statistical significance: **small p**
- Confidence intervals…
- Effect of
  - Exposure level
  - time
  - personal characteristics

15

Different levels of effect



16

Critical Appraisal 3: Alternative explanations

- Confounding by other factor(s)
- Bias in selection or measurement
- Chance

17

Confounding

- Are there other factors that are known or suspected to cause the disease?
- Were they measured, and taken into account in the study design or analysis?

18

Bias

- In recruiting study subjects
- In assessing whether a person had the disease (should be independent of the factor)
- In assessing exposure (should be independent of the disease)

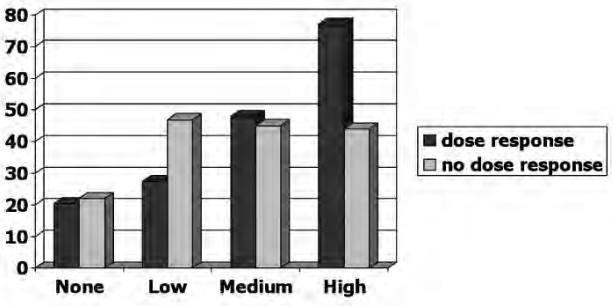
19

Critical appraisal 4: Evidence for causation

- Strength of the relationship (size of the relative risk)
- Dose response relationship?
- Exposure-disease sequence?
- Consistency with other evidence?
- Biological plausibility?

20

Disease incidence compared to dose



Summary of Issues Raised by ESOs

Issues and responses collated from edited transcripts of the RMA Forum 16 April 2008

Military issues

ISSUE
Military health studies and military exposures

You stated that most of the investigations were done on the general public and that the military studies rarely have much impact. Yet our experiences from the military point of view are that the exposures can be for an excessive period of time. For example, the general public only take doxycycline for a month or two but military people take it for 12 months to two years, which might have a different effect. How can an allowance be made for that situation?

RESPONSE (Professor Donald)

Where there are data available from military studies, they are taken into account. So if the studies that have been done for doxycycline included military studies with long term exposure, that would become part of our deliberations. My point is that there are not many military studies available and 99.9% of the epidemiology about the causation of disease that is available comes from civilian studies. Probably less than 0.1% comes from military studies, so it's just a mass effect. Where military studies are available, we clearly use them the same as we use everything else. So it's not that we don't use them, it's just there are so few of them available.

About the specific question of doxycycline and it's long term effects - there are people in malarious areas who take doxycycline long term and there are people with acne who take it for a life time or a very long time. So there are studies of long term exposure in non-military population that we can look at. The nub of the question is that we don't ignore military studies, but there are not many of them available.

In relation to doxycycline or any other hazard, unless there is evidence from studies that they are causally related to diseases, even at this very low level of requirement of proof, then we can't put a factor in. The RMA can't do a study of the long-term effect of doxycyline because the parliament said we're not allowed to do our own research and I think the parliament was right in that. I don't think you would want the RMA commissioning its own research. We've got enough to do without going down that path and that would distract us from the real task. There is now quite a strong research community based around a whole lot of material that is looking at veterans, so I would go to CMVH, or to Malcolm Sim or somebody, with a proposition about doxycycline, but the RMA is not the body who will do those sorts of investigations. Your lobbying really needs to be to the research community, rather than to the RMA, but if somebody else does the studies, we would use them in deciding about factors.

ISSUE
Lack of documentation of exposures during service

Serving personnel have exposure to various hazards, but there is no system of acknowledgement going to the RMA from Defence.

RESPONSE (Professor Donald)

The question of what exposures defence personnel have during deployment has always been a problem and it remains a problem, but more and more records are being kept and monitoring of personnel in combat is being done. Certainly we're aware that the Americans are monitoring individual soldiers much more closely than they were and I think our forces are beginning to do the same. So the question of knowing what exposures people have received, I think, is improving.

Making and using SoPs

ISSUE
Classes of veterans

You said there were no classes of veterans mentioned in this Statement of Principles, but what about having been a prisoner of war or having been in Vietnam?

RESPONSE (Professor Donald)

That comes up from time to time and my advice is always, "Don't go there." Quite frankly I wonder if both of those factors are legal. They went in for particular reasons. They are there as surrogates for exposure that was difficult to quantify. The only justification I would be able to use if I was taken to court on them, is that they are capable of being defined as surrogates for real or specific exposures. "Class of Veteran" factors that were not surrogates for real and specific exposures would be clearly illegal in my opinion.

ISSUE
Sound medical-scientific evidence and case reports

You were discussing a single case presentation on which you would make a causation decision on your own clinical judgement. Who will you accept those cases from? Are these published cases only or can I write in and say, "I've got a customer with an xyz problem"?

RESPONSE (Professor Donald)

We use cases that are in published literature. Part of the definition of sound medical-scientific evidence does require a peer review process and we've always interpreted that as peer review for publication in a reasonable journal.

ISSUE
Health studies

(Professor Kaldor)

I wanted to make a comment about what Ken said about there being a lot of "dodgy" epidemiology out there. There certainly is, as in any field. Epidemiology can be done very expensively, and it can be done very cheaply. Some of the most astonishing findings have come from relatively cheap work. For example, people have investigated certain questions by looking at maps and seeing where diseases occur and seeing that risk factors occur in those same places and saying to themselves "Hang on, maybe something is going on there." That is a very cheap way to do research. An example of this is some of the earlier studies that looked at Hepatitis B as a cause of liver cancer. They looked at the maps of liver cancer and looked at maps of where Hepatitis B was and said, "Something is going on here." That wasn't proof, at a very basic level, but it certainly started a lot of people thinking. Another recent example is the map of where HIV is occurring in Africa, compared with the different places that practice male circumcision. The maps showed that the places that practice male circumcision had much less HIV, and it took about 15 years before trials actually proved that male circumcision did reduce the chance of getting HIV.

So what I'm saying is you can do very cheap and effective studies, or reasonably interesting studies, that you would really call methodologically quite limited, but that can nevertheless be very valuable. When you write those papers up, you write the conclusion and you say, "Well, this is what we have seen from the study, but there are a lot of questions around it," because of what we call methodological limitations. You highlight all the qualifications and the caveats around the study, but it still can get published and it can still be very valuable in informing the debate, even if it is not a definitive study. There is distinction between people doing things with very limited amounts of research resources and trying to come up with some interesting conclusions and just generally doing something dodgy. As long as you say what is wrong with the study and say what its limitations and interpretation are, then it is legitimate and we end up using those sort of studies more and more. I just want to make that distinction between what is fundamentally dodgy and what is the best that can be done within certain resources and certain settings.

(Professor Donald)

I'd better make an explanation about the value of health studies to the RMA. In our system, if you take cancer X, and there are 20 known causes of cancer X from the world literature, they will all already be in the SoP. If you do a study of a group of veterans, it is unlikely that there'll be any exposure in there that's different to the 20 that are already in the SoP, it's just that those veterans will have been exposed to some of the already known causes. It's unlikely, from the RMA's point of view, that these studies of veterans will throw up new causes of disease because you don't discover new causes of disease on a very regular basis, the literature has been pored over so much. My concern is that the veterans often come in with the view that a health study will do something about them getting compensation. It is unlikely to because it won't find a new cause for cancer, or for their cancer. What a health study does do is allow the Defence Force the possibility of avoiding a future exposure. In other words if it's used in policy and prevention, it's got a value. It also goes to the question of service-related exposure to known causes.

ISSUE
Standard of proof for reasonable hypothesis

How do you actually quantify a reasonable hypothesis statistically, because the scientific literature presumes a probability of 1 in 20, whereas the legal test is 51%.

RESPONSE (Professor Donald)

On the same body of evidence, you can make decisions at different levels of proof. For example, if a public health physician is going to close down a local corner pie shop a lower standard of proof will apply than if he is going to make a decision that every refrigerator in Canberra has to be turned off for a month. We make decisions all the time which are at different levels of proof on the same database. Scientists have chosen 95%. After you get used to it, you calibrate yourself and you can make decisions that are around about the 10% level. The question of balance of probabilities has been debated in all sorts of parliaments, all over the world . In fact, the human mind will accept something as more likely than not to be true well before 51%. Most people think something is true at around about 30% likely to be true. The human mind isn't a very statistically valid instrument - you have got to calibrate it, you've got to consciously get it to set a level. I presume soldiers do the same thing in assessing risk. To something that looks very risky, they might say, "No, that is not really risky at all, I'll calibrate myself to this. This is risky, that isn't." If you ask the average citizen out there, "Do you think that's risky?", they'll say, "You bet it is." It is just the way human minds work.

ISSUE
Standard of proof for reasonable hypothesis - further clarification

You kept mentioning 10% as being the cut-off level, and I assume that that means that if there is less than one chance in ten that this will lead to that, you ignore it. But the High Court said one in 20 was the go. Why aren't you operating on 5%?

RESPONSE (Professor Donald)

The issue here is that 5% and below is basically static. Statistically, that's chance. We just have human brains,

like everybody else, but we calibrate ourselves to go down as low as we can go, without calling a factor on the basis of chance. That is the mindset. Now, as it turns out, we make that decision somewhere between 5 and 10%, but the human mind is not a sufficiently precise instrument to tell the difference between 6%, 7%, 8% – it is just not on and so what we do is we push ourselves down to the level as close as we can get before we think chance is kicking in. When you start putting numbers on that like 5 and 10, it makes it sound as if that is something that the human brain can do precisely, but it can't. It is not as if we sit down and say, "Yes, we're going to cut off at 10." We sit down and we say, "We're going to push this until we're down to chance and then pull back a little bit."

ISSUE
Differences between RH and BoP SoPs

Why do some SoPs have different causation factors to the corresponding BOP SoPs, that is, why are some factors removed from the BOP SoP instead of just varying the dose within the factor?

RESPONSE (Professor Donald)

That is a reflection on the different standards of proof. The reasonable hypothesis requires us to be of the view that the facts indicate a causal relationship. The word "indicate" is in the legislation. If you translate that back to the language of the High Court, it basically says it can't be a hypothesis that is just left open, it must be a hypothesis in which the facts lead towards a conclusion or an indication that the hypothesis is positive. For the balance of probability SoP, it clearly says that we have to be of the view that it is more probable than not, in the words of the legislation, that the relationship is a causative one. Some things that are just possibilities but indicate that there might be a relationship at a low level of proof go in at the RH level, but we might ask if the evidence is sufficient for it to go in the BoP SoP? Is it more likely than not to be true? If it doesn't make that test, it drops out of the BOP SoP.

The commonest way we make the difference between the RH and BOP SoP is by varying the dose. That happens when it is clear that a factor is in, because if it's more probable than not then it will be in the BOP SoP and it will automatically be in the RH SoP. We then push the dose down in the RH SoP to close to the absolute minimum we can imagine would be possible, but we leave the dose in the BOP SoP as relevant to more probable than not to cause the disease.

ISSUE
Worsening factors are the same as onset factors

Why are the factors for the worsening of a condition the same as for onset, especially in regards to osteoarthrosis and lumbar spondylosis? If a person already had a weak spine, then why would it be necessary for the same amount of lifting over the same period of time to make it worse? If you have osteoarthritis of the knees, your doctor will tell you to stop running.

RESPONSE (Professor Donald)

My take on that is that there's usually no real extensive literature on worsening and we think it's a reasonable hypothesis that the things that cause the disease will make it worse. Very frequently we don't have hard evidence to support that, but in the beneficial legislation it's reasonable for us to make an assumption.

Everybody in the room has got a different strength of spine but we set one lifting dose for everybody because we tend to take the doses down so low that you can't go much lower. Some of the lifting weights that are required are the sorts of things that happen in the average kitchen around Australia every day of the week, so that the doses have been pushed down to a level where there's not really any rationale to go any further down. When you're down at the very limits of something that might be reasonable, but probably is really far below what's the real cause, you can't usually halve that again. You finish up with statistical chance and static and you bring the system into total disrepute.

It's not necessarily the case that to do something to an injury will make that injury worse. The analogy I like to give here is if you take a group of rowers who put on the same pair of pants each morning to go rowing and they row for three hours a day - the pants will wear out and get a hole in them, but their skin will get thicker. In other words, we are not inanimate objects and so we have repair mechanisms that respond to stresses, and bones in particular respond to use. Bones are structured, and so is cartilage, in such a way that they respond to usage. In fact, bones strengthen because when bones are used and move, the crystalline structures in the bones set up little potentials on the outside and little electric currents flow that actually cause deposits of extra bone. So, using a bone will maintain its strength, and using cartilage, as long as it's got a good blood supply, will stimulate its repair. It's not a simple relationship - use is often good for you and Beverley will say stress is good for you. We've got to get away from this idea that exercise is bad for you or that responding to normal day-to-day stresses of living is bad for you, it's not. You could put mice in a box and take away all their stress and they would die. So, exercise and managing stress are a very important part of staying healthy.

ISSUE
Interpretation of SoPs

Why can't you give a statement of the intent of a SoP? Why are the SoPs unimpeachable?

RESPONSE (Professor Donald)

We are not in the business of giving legal advice. Once the SoP leaves us and goes through parliament, it become the law, endorsed by the parliament. The way it is then interpreted is like any other law. In other words, the interpretation of what that SoP really means now is the court's, or the VRB's or somebody else's, not ours. We have occasionally changed a SoP because we have seen that the operational staff in the department, or on occasion the courts, have put an interpretation on a factor that was not what we intended. When we put a SoP out there we get legal advice and we get operational advice and we try to pick the set of words that capture what we intend. Once that has been through parliament, then we are not the people who interpret what that means, the courts are, because it is now a law and we are not a court. If we did provide an interpretation we would be exceeding our mandate from the parliament, we would be setting ourselves up instead of the courts.

ISSUE
Use of SoPs by other jurisdictions

Are you ever approached by other jurisdictions to provide advice and do you know of any other attempts to apply a similar model, for example, in workers' compensation settings?

RESPONSE (Professor Donald)

I am not aware of any other legislation that requires this process in compensation, but I am aware that other groups do use our SoPs, as a sort of a benchmark. SoPs are on the internet and we know some of our Canadian colleagues use them when they're sorting out whether a claim is likely to be reasonable. Obviously that relates to veterans. We know that some people and various compensation groups use them unofficially, to help in their decision making. There is no other jurisdiction or setting that I know of in which SoPs are formally used under legislation, but they get used unofficially in a number of contexts.

Technological issues

ISSUE
Biomarkers

Can people be tested for biomarkers so that they can be prevented from being exposed in the first place? It is an issue for Defence because there is a duty of care.

RESPONSE (Professor Donald)

The laboratory technology to do a lot of that testing is now available and is rapidly becoming more available. With the development of more molecular techniques and nano technology, prying into your susceptibilities is going to become a routine laboratory procedure. The real issue is around the social and ethical questions about how that is used. The technologies are here, you could now set up a system to test soldiers before you recruit them and you could rate them on their susceptibility to certain environmental agents before you deploy them. But the question is, "What advantage would that be?" It has the potential to do harm as well as good and it is another debate that is going to happen in the next ten years. It is an ethical issue, but any employer has a duty of care, though, not just Defence.

ISSUE
Repairing damaged genes

Are we at the stage that we can repair a damaged gene?

RESPONSE (Professor Ward)

We're not at the stage of repairing damaged genes, so we recommend that if someone is carrying a disease predisposition gene, that they undergo more intensive screening, and in some cases we even do preventative things, like removing someone's bowel.

In regard to that spooling thing that the DNA wraps around, those things that happen to that spool are actually reversible with drugs, unlike your gene which you can't change. There are drugs that actually undo what's written down on the spool. Those drugs have just started to be invented, so it may be possible to undo the things that you've been exposed to through life.

ISSUE
Implications of detecting genetic protective or vulnerability factors

That proposed 2050 SoP is pretty frightening in that it seems to me to be carrying sound scientific medical evidence to the point where it starts to dehumanise the veteran. I'm thinking of a situation where a veteran had circumstances of service identical to another veteran, but because you took his genes out and labelled them, you then granted one claim and didn't grant the other. That would be difficult to explain to people who are affected by service, the vulnerable, sick and so on. It strikes me that this is a pretty big step.

RESPONSE (Professor Ward)

I wasn't proposing we implement it tomorrow, and what I've deliberately ignored is all the ethical and social issues around this. What I'm flagging here is that this sort of thing is happening in day-to-day medicine. Science is moving on, but what hasn't caught up yet is all the ethical and other social debates that need to happen about how this information should be used. It's a good time to have that debate before it is actually foisted upon us. There's been a

lot of emphasis on developing the technology and making the discoveries and not the same level of engagement in terms of understanding the ethical and social implications of using this technology. It might be technically possible to do it but it may not be something society wants us to do. So I think it's an important thing to start thinking about now, not in 2050.

(Professor Donald)

This technology is going to continue to be developed, and it will become pocket technology, so you'll be able to get it on your mobile phone and that sort of thing. We thought we would do this presentation so that at least you were aware of where the science is going. Now, how far the law, the justice system or the compensation system might or might now follow it is another matter. There has to be a community debate; it's not the privileged position of just the scientists to deal with these matters.

ISSUE
Translocations

In New Zealand we just had a report on the operational personnel who were irradiated in the British nuclear bomb tests, and it was shown that there has been translocation in some parts of those genes. How does that affect the sort of system you've got there and where is it going to lead them? Could they pass that on to their offspring?

RESPONSE (Professor Ward)

It depends which cells the translocations have been identified in. Translocations are a very gross change where bits of one chromosome fall off and go and stick to the another one, and then because the other one's got a bit of, say chromosome 9, it falls off and goes and sits back on the first one, so they swap over. What you do find sometimes is people do get transient, rather than long term persistent translocations in genes. A lot of those translocations are in fact self-limiting, that is, they happen and then they disappear. Translocations are usually serious changes if they're happening consistently in all cells in a body. That's one step on from what I'm talking about in relation to gene chips.

Translocations are most commonly identified in diseases like leukaemias. The starting point is a stem cell that acquires a translocation. If it happens in a stem cell then every other cell that emanates from the stem cell will have that translocation. You get leukaemia if it's happening in your blood cells. In other cases, translocations can happen in cells that are way, way down the line and they're destined to die anyway. Translocations that happen in those cells don't really have any consequence for you because they're only a small group of cells in your body and they will eventually die out. It's the translocations that happen in the stem cells that can give you a disease because they can give rise to lots of other cells. The consequences really depend on where these translocations occurred.

You don't pass on translocations to your children; they're things that you acquire in life. Translocations can happen in utero to a foetus, but they are then not present in the mother, for example, in Down syndrome.

ISSUE
Genetic research in Defence

If you were going to advise Defence or DVA about developing a research agenda around how to use genetic vulnerability, what would you be suggesting? If we don't know anything then we can't get criticised for putting people at risk, but the other side of this is that in 20 years time there might be some court case that holds the ADF liable for not having used the available information. For an Army psychiatrist the most telling issue is the serotonin transporter gene which shows that you can predict peoples' vulnerability to stress. Should we just completely ignore that or should we try and develop a research agenda around it? And if so, how would you advise Defence about these issues?

RESPONSE (Professor Ward)

Being an academic, I think it is important to develop research agendas. Most of the studies that are happening in this area are huge, collaborative studies, they're not done in silos any more. I think it's important to push some of that Defence research into the mainstream because the people that you're dealing with will have had exposures that perhaps may not have been much greater than what you see in the general population. What you identify in those people may be very useful information, not just for the Defence Forces but also for the general population. It's also important in terms of getting enough power in these sorts of studies to bring it into the bigger agenda of people who are looking at associations between exposures and the genetic profile in hundreds of thousands of people.

Stressor factors and psychiatric SoPs

ISSUE
Subjective versus objective stressors

Participating, seeing or witnessing a stressor event is a strong element throughout the stressor factors, and that seems objective. I noticed that there were other stressor factors for the death of a very close relative, like a parent who you were very close to and/or the suicide of a sibling, a parent and all that, and that can be subjective. If I am in Afghanistan serving and my mother commits suicide, that's subjective, not objective - I'm not there but it is happening.

RESPONSE (Professor Raphael)

Yes, that would come under the category of traumatic bereavement. It would still be covered because you perceived it as traumatic.

ISSUE
Diagnosis of psychiatric conditions

Should diagnoses of psychiatric conditions be made by solicitors or legal people? Can the SoPs for psychiatric conditions be made so the diagnosis can't be interfered with by legal people? Could it be put into the SoP that the condition be diagnosed by a qualified medical practitioner?

RESPONSE

(Professor Raphael)

Professor McFarlane and I have been to court and the lawyers have informed us that we have not diagnosed the case properly, but we've all had that debate in the courtroom, and I think most of us here who have worked clinically with people who have experienced PTSD, have been very familiar with the quirkiness of legal pursuit of every single word in a DSM-IV diagnostic category. The diagnosis is required to be made by psychiatrists with expertise in the field, but it's not a legal diagnosis. There is a framework that the diagnosis is made by a clinician. In the courtroom there can be a challenge to the diagnosis made by a medical expert of one kind or another, but the diagnostic process is in the hands of the person who has made the clinical assessment.

(Professor Donald)

A couple of times today people have raised this question about whether the SoP should in some way include a phrase that requires a diagnosis to be made by a certain person. My initial response to that is no, I don't actually think it's within our legal framework to do that. I think that it would fall outside of our powers and one of the things that the RMA should be very careful of is not to make up powers for itself.

Issues related to particular factors

ISSUE
Circularity of vascular dementia definition

My question about the vascular dementia SoP is this, does not the very diagnosis of the condition satisfy one or other of the factors? My understanding is that the condition cannot exist without either the presence of cerebrovascular disease or having suffered a CVA.

RESPONSE

(Dr Ward)

There is some circularity in that the definition suggests that the dementia is due to vascular causes, but then the SoP spells out within the factors the particular types of vascular conditions that could cause vascular dementia, and refers back to the factors in the CVA SoP.

(Professor Donald)

If you are saying that the issue is that everybody in the room has atherosclerosis, then you've all got some reduction in flow to your brain. Most of you don't have symptoms from that atherosclerosis and many of you will never get any symptoms from the atherosclerosis that you've got, which is interfering in some way with the smooth flow of blood to your brain, but the question is when does your IQ fall to the point where some clever doctor calls you less clever than he is, for example, and says you've got dementia. The point at which dementia is diagnosed will vary, obviously, you just get more and more forgetful. It's one of those situations where there is no line that says every time somebody diagnoses dementia that it will be the same point on the deterioration. We have a problem dealing with atherosclerosis because everybody's got it and in some senses it's pathologically a disease, but for most people it's not causing symptoms today. Some people will never get symptoms, they'll die of something else first, and creating a SoP for atherosclerosis wouldn't get us anywhere. So we're left with a SoP for vascular dementia, which is an artificial line, when your doctor thinks you're dumb enough to call you demented. Our point is that the definition of disease is not simple, and putting it into a legal instrument in words that are clear and can always be interpreted the same is quite difficult.

ISSUE
Exposure of fire fighters to aviation fuel and fire retardants

Has the RMA given any consideration to the Statement of Principle for non-Hodgkin's lymphoma as it relates to exposure to AVTUR, AVGAS and/or fire retardants used to suppress aviation fires, and the effects of exposure to these substances as it relates to the health of RAAF fire fighters? If not, in the light of the evidence that's coming out from the United States, Europe and Canada and the United Kingdom relating to the risk of fire fighters dying from prolonged exposure to these chemicals, is it possible that the RMA will give consideration to examining the information from these other countries with a view to considering a change to the present SoP for non-Hodgkin's lymphoma as it relates to RAAF fire fighters and/or other ADF personnel?

RESPONSE (Professor Donald)

The evidence concerning the relationship between NHL and solvents, AVGAS, benzene-containing fuels and

numerous occupational exposures was examined in the last review in 2003. The SoP hasn't been reviewed since 2003 but those issues were addressed in the last review. A fire retardant is a substance that helps to delay or prevent combustion and the term covers a number of different substances, including water, so that the particular chemicals need to be specified. No particular studies using the general term fire retardants were identified in the last investigation. So, in other words, there may be substances which are there by name in the literature but not under a categorisation of fire retardants when we search for fire retardants as part of the PubMed search.

A general problem with occupational categories such as fire fighters as proxies for exposure is that numerous chemical exposures are involved and it's not possible to identify those which might be related to the disease in question. Fire fighters are exposed to a vast array of chemicals and we can't deal with them as a class of veterans, we have to try and find those chemicals. Now, often the brand name chemicals are complex mixtures, so it gets a bit more complex even than just knowing the brand names. Aviation fuel contains a mixture of about 80% aliphatic hydrocarbons and 20% aromatic hydrocarbons and numerous performance enhancer additives including xylene, benzenes and diethylene glycol. Our staff look at as many of the individual chemicals as they can find identified in the literature.

It is in general more generous to specify the actual exposures as a risk factor, because any occupational activity which involves an exposure to the risk will then be covered. In other words, there are other people who would be exposed to the same chemicals as fire fighters, so if we specify the chemical we cover everybody who is exposed. The RMA routinely considers sound medical-scientific evidence from all sources, local or international and you can tell us more about these recent studies which we don't yet know about. If you write to us and tell us where to find them, we'll look at them.

ISSUE
Ischaemic heart disease as a cause of cerebrovascular disease

It's not uncommon for a person treated for ischaemic heart disease to die unexpectedly for cerebrovascular accidents as a result of undiagnosed cerebrovascular disease. It would seem logical to expect that suffering from ischaemic heart disease would be a factor in the SoP for cerebrovascular disease.

RESPONSE (Professor Donald)

Indeed, they are both caused by atherosclerosis, but they happen independently. Now, sometimes it does occur in clinical practice that a patient who has had a myocardial infarction suffers a drastic fall in blood pressure and will also then go on and have a stroke because of the low blood pressure. That does happen in clinical practice but it's not a very common event at all. So, yes they are both caused by atherosclerosis, but they are not causal, one between the other, they are separate outcomes of the same underlying vascular abnormality and they're treated, therefore, as separate diseases. They've got very similar risk factors, but it's those risk factors that cause the stroke, not the myocardial infarct.

ISSUE
Risks of secondary smoking

While secondary smoking is included in some SoPs, the overall public perception fuelled by prominent cardiologists indicates a much higher risk. Could the RMA please address the perceived versus the real risks from secondary smoking?

RESPONSE (Professor Donald)

People hold opinions about all sorts of things and the legislation has specifically got rid of opinions from prominent specialists, as some of them became quite literally an embarrassment to the system. Some of the cases that triggered the Auditor-General's response came from certain prominent specialists because the government of the day asked me to look at those cases before this legislation was drawn up. They said, "What's going on in these cases?" And I said, "I hesitate to answer the question. It's one of two things, these people don't know what they're talking about or they're committing perjury, I don't know which it is." That was the advice I gave at the time, and that was partly the reason why this legislation came to pass.

I don't know about the public perception, but there is a difference between active smoking and passive smoking and they are not the same thing. It's different smoke, it's different concentrations and the composition of the smoke that goes into the lung is actually different. The number of studies that are done on passive smoking is much less than the number of studies done on active smoking, and of course the measurement of dose is absolutely different in the two. For active smoking, you can measure the number of cigarettes per day, which is subject to the problems of recall bias and people's memories, but at least you have a fairly successful measure. With passive smoking the dose gets down to whether you can see it or not. There's no way of measuring accurately the dose of passive smoking, so epidemiological studies based on passive smoking start with a huge hurdle to overcome just in dose measurement. Getting a group of people together who have all experienced the same dose of passive smoking is actually very unlikely to be achieved. You probably can't even get a cohesive group together without bias in the selection of who's in the group for passive smoking and who is not. So, you just can't compare active and passive smoking in any simplistic way.

The second part of the question is can we add the doses from active and passive smoking together? That would

be like adding up a barrel full of apples and a barrel full of oranges and figuring out what you would get at the end - perhaps a peach or something. There's just no way of taking two quite separate entities and putting them together. That would be coming out with some sort of magic and we can't do that, we've got to stick with epidemiology.

We put passive smoking in as a factor where there is evidence that shows that it could cause that disease. There are studies which show that lung cancer is increased in people who have increased passive smoking levels. Where we get some epidemiology which is comprehensible we put it in, but we can't make it up if there are no studies. We have to have some facts on which we can examine the question of whether there is an indication that the hypothesis is positive.

ISSUE
Potable water factor

Is it the intent that the vessel must have been in Vietnamese waters for a cumulative period of thirty days? Did the veteran have to consume the water for a cumulative period of thirty days? Did the water have to be consumed during operational service? How long was the contaminated water in the tanks? How much of the water was used for cooking purposes?

RESPONSE (Professor Donald)

This gets back to the question of intent. Our position is that we don't say how you get the exposure, you just have to drink a certain amount of the water or get a certain dose of the dioxin from the water but it is not our business to say how you get it or which boat you get it in. That's the business of the evidence concerning the relationship to service.

ISSUE
Repetitive trauma and spondylolisthesis

In my opinion repetitive trauma has not been given appropriate consideration (weight) by the RMA in respect of causation and aggravation, particularly in relation to the type of repetitive trauma a service person may receive within his specialised type of work in either combat or eligible service. Does the RMA take this into account when investigating and structuring the SOP factor investigation?

The factors in the SoPs for spondylolisthesis make no mention of repetitive trauma, however Veterans Affairs Canada have defined repetitive trauma as a causal and aggravation factor for Spondylolisthesis. Given that we are told continuously that Australia has a generous legislation in respect of returned veterans under Reasonable Hypothesis standard of proof, can the RMA explain this anomaly?

There was a helicopter pilot in Vietnam who had continuous back pain during his service in Vietnam but because it's not covered in the SoP for spondylolisthesis, it can't be accepted as a causation factor.

RESPONSE (Professor Donald)

Repetitive trauma is a problem, but you've got to be careful about the word trauma because it doesn't mean repetitive exercise. It doesn't mean repetitive doing of something that doesn't cause injury. Trauma implies a wound or a break in the surface. It doesn't mean walking down the street or carrying a pack down the street without damaging your cartilage. I've had a look at the so-called more generous Canadian factor and it isn't more generous, because it's not just about repetitive lifting. What it requires is seeing a doctor after you've done this repetitive exercise because you've damaged your back. If you read the Canadian factor, you have to have injury and you have to see a doctor within two days of doing the repetitive trauma. There's a very close relationship between doing the repetitive trauma and having the injury - within 2 or 3 days. Because you have to have seen the doctor it's a much more restrictive arrangement.

Breaking the cartilage or breaking a bone or chipping something or twisting the ligament or damaging the joint is trauma. We compensate things that follow trauma, but with ordinary walking down the street carrying a suitcase or carrying a 20 pound pack on your back, unless you get pain in a joint at that time, there's no evidence that it's causing you injury. In fact the evidence would suggest that it is actually strengthening your joints by strengthening the muscles around the joints. Muscle strength around the joints is very important in their protection, and bone and cartilage strengthen with usage. There is a difference between the normal use of joints without injury and repetitive use of joints with a consequent injury.

If we took the trouble to say that there had to be high energy trauma, I'd be pretty confident that the studies that are available indicate that low energy trauma does not cause spondylolisthesis, because we would have put them in if it did. The studies that are available to us must say that the dose has to be high energy trauma, but if there is other evidence out there that says it's low energy trauma, then let us know and we'll change the factor as soon as we see the evidence. In fact, there is a factor in the SoP for competitive sports involving repetitive and forceful movements.

Summary of Workshop on Critical Appraisal and Causal Inference

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16 April 2008

The purpose of the workshop on critical appraisal and causal inference was to give participants the opportunity to experience at first hand the process of deciding whether or not a factor should go into a SoP. Participants were divided into six work groups of around ten people, and each group was assigned a facilitator from the RMA or the RMA secretariat, as well as an ESO spokesperson. Two articles had been selected for study, one article concerning the relationship between drinking alcohol and hypertension (Nakanishi et al 2001) and another article concerning the relationship between exposure to diesel exhaust and lung cancer (Richiardi et al 2006).

Each group was asked to convene for an hour and half to critically examine its allocated study using the criteria in the Critical Appraisal Checklist as a guide (see over). Although the groups looked at all the questions in the checklist, each group was asked to focus on one of three particular sets of criteria; "What is the study about?", "What are the main results?" or "Can the results be explained by anything else apart from the risk factor under consideration?" The group was also asked to make a decision about a final factor, based on the paper they looked at. They had to decide if they would support the inclusion of a factor in the RH or BOP instruments for that particular condition (either, both or neither). They were also asked to suggest a form of words and the dose if time permitted.

A report-back and discussion session was subsequently conducted, chaired by Professor Kaldor. This session consisted of a number of activities:

- the group spokesperson presented a five minute report on his or her group's findings on their assigned question from the Critical Appraisal Checklist
- the factor that the group had agreed upon was discussed with the other groups' factors
- an RMA researcher or member presented a summary of the evidence for causation for each paper, and showed how each paper fitted in with the rest of the literature concerning that particular association

In fact, all three groups which looked at the Nakanishi paper decided to put a factor in the RH and BoP instruments for hypertension and all three groups which looked a the Richiardi paper decided not to put a factor in either instrument for lung cancer. It was recognised that this result might differ from the actual factor in the SoPs because the groups were being asked to make a decision on the basis of just one study, whereas the RMA makes a decision based on all of the available evidence.

Group members participated actively and enthusiastically in the discussions. Feedback suggested that participants found the workshop to have been a fun and informative way to learn how to critically analyse a scientific paper, and they also developed a better understanding of the systematic approach that the RMA takes to SoP development.

Critical Appraisal Checklist for Workgroups

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 (exposures) 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?
- Do the results provide information that could be used to determine
  - the amount or duration of exposure at which the risk of disease significantly increases, or
  - the length of time between exposure and the onset of disease?

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?

Organisations Represented at 2008 Forum

ADF	Australian Defence Force
APPVA	Australian Peacekeepers & Peacemakers Veterans Association
ASASA	Australian Special Air Service Association
AVADSC	Australian Veterans & Defence Services Council
CMVH	Centre for Military and Veterans' Health
DoD	Department of Defence
DFWA	Defence Force Welfare Association
DVA	Department of Veterans' Affairs
Legacy	Legacy Coordinating Council
LEGION	The Royal Canadian Legion
NZRSA	New Zealand Returned & Services Association
	Office of the Ombudsman
PVA	Partners of Veterans Association
RC	Repatriation Commission
RMA	Repatriation Medical Authority
RSL	Returned & Services League of Australia Limited
SMRC	Specialist Medical Review Council
TIP	Training Information Program
TPI	Australian Federation of Totally & Permanently Incapacitated Ex-Servicemen and Women
VAC	Veterans' Affairs Canada
VRB	Veterans' Review Board
VVAA	Vietnam Veterans Association of Australia
VVFA	Vietnam Veterans Federation of Australia
WWG	War Widows' Guild

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Abbreviations and Acronyms

BoP	Balance of probability
DSM-IV	Diagnostic and Statistical Manual, 4th Revision
MRCA	*Military Rehabilitation and Compensation Act 2004*
PTSD	Post-traumatic stress disorder
RH	Reasonable Hypothesis
SMSE	Sound medical-scientific evidence
SOP	Statement of Principles
VEA	*Veterans' Entitlements Act 1986*