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"Researchers Behaving Badly"

PRESENTED BY: Professor David Vaux

MERRILL CORPORATION
4/190 Queen Street, Melbourne
Telephone: 8628 5555
Facsimile: 9642 5185

MR GRONOW: Ladies and gentlemen, it is lovely to see you all here tonight. I am about to call upon our Legal Vice-President, Dr Elaine Fabris, to introduce our speaker, but before I do, I would just like to say this; we do not normally do this, but this is the first meeting of the society since the recent death of Dr John Emmerson QC who is our former President and our longest-serving ever Legal Secretary. John has contributed a great deal to our society over the last 40 years, and we will all miss him very much and I just ask you now to rise to your feet and join me in drinking a toast to John's memory. To Dr John Emmerson.

Now I will hand over to Elaine.

DR FABRIS: Good evening, everyone, I am very pleased to introduce our speaker, Professor David Vaux, tonight. Professor Vaux is an internationally acclaimed molecular biologist and biomedical scientist. He is Deputy Director of the Walter and Eliza Hall Institute of Medical Research and Senior Principal Research Fellow with the NH & MRC. He is also an Honorary Professor at the University of Melbourne and La Trobe and Monash Universities.

A little bit of background on Professor Vaux. He graduated in Medicine from the University of Melbourne in 1984 after spending a year in 1981 during his medical degree doing a Bachelor of Medical Science under the supervision of Sir Gus Nossal of the Walter and Eliza Hall Institute. He then was an intern at the Royal Melbourne Hospital in 1985.

He returned to the Walter and Eliza Hall Institute (the WEHI) to do a PhD. in Molecular Biology after his intern year, and then he continued his research at the

Stanford School of Medicine in the U.S. He returned to the WEHI in 1993. In 2003 he received the Victoria Prize for his research on cell death.

Professor Vaux and his group at the WEHI studied at the molecular level how cells self-destruct. Essentially, if cells fail to kill themselves when they should, they can accumulate and eventually turn into cancer, so obviously his research is incredibly important stuff. Professor Vaux is a Fellow of the Australian Academy of Science and in 2010 he received its highest award, the Burnet Medal. He has received numerous other awards, far too many to list tonight.

Professor Vaux is on the editorial board of three major scientific journals. He is a member of several different organisations, including the Committee on Publication Ethics, The Australia and New Zealand Association for the Advancement of Science and Australian Sceptics, which describes itself as: "A loose confederation of groups across Australia that investigate paranormal and pseudo-scientific claims from a responsible scientific viewpoint".

Professor Vaux is an expert in research ethics and he lectures worldwide in that subject area. He has very finely tuned antennae for picking up possible scientific misconduct. For several years Professor Vaux has advocated for the establishment of an office or an ombudsman in Australia for research integrity. We are all looking forward very much to hearing from Professor Vaux about various tales of researchers behaving badly and what can be done to improve this and advance scientific integrity.

Please give Professor Vaux a very warm welcome.

PROFESSOR VAUX: Well, I am absolutely delighted to be here. I am a little bit daunted because you are not my usual audience. Now, normally I go around with my laser pointer and I bought the powerful one so if I start asking questions it is out of habit, and if you feel your retina burning then I am asking you, okay?

So this talk is going to be not on my research field but on this area of research ethics or lack of ethics, I guess. This is a paper published by John Ioannidis who is a statistician currently at Stanford University, "Why Most Published Research Findings are False", and he has gone on to actually show that it can be proven that most claimed research findings are false.

So every year about a million new papers appear in PubMed and Johnny Ioannidis has proven that most of them the conclusions are wrong. He made this assumption based on statistical grounds, but he assumed that scientists are both honest and competent, and if you do not make those assumptions then this might be an underestimate of the size of the problem.

So to actually look at some real data, this is a commentary published in Nature by Glen Begley. Glen Begley is a clinician/scientist who trained at Royal Melbourne Hospital and afterwards he became the head of Oncology at Amgen, one of the world's biggest biotech companies.

He published this commentary because they found at Amgen, where they are trying to find new drugs to treat cancer or new targets that the drugs might hit. They would read about them in the academic journals, and then

the first thing they would try to do is reproduce the published results from the academic scientists, but they found that they often could not reproduce those findings.

So they looked at about 60 landmark papers published in Cell Science, Nature and New England Medical Journal and tried to reproduce the results, and if they could not they contacted the authors of those papers and said, "We will do this confidentially. We will keep it anonymous, but we will offer you all of the resources available at Amgen to try to reproduce your results, so you help us do it or we will help you do it".

And they found that even with the cooperation of the authors, they could only reproduce the findings in 11 per cent of papers. So 90 per cent of the papers that you pick up and read, and these are the scientific papers, these are not the clinical papers, are going to be not reproducible, right? So this is a huge problem, and so this talk is about why this might be the case.

One thing that got me into this sort of thing was this edition of Nature from 2004, so the next dozen or so slides are going to be from various papers in this one edition of Nature. Now, any of you who have read Nature knows that there are papers in physics and biology and chemistry, but many of them have figures that look typically like this.

Now, so here is a figure and here are some bar graphs, and at the end of the bar graphs there are these little T-shaped things and these are called error bars. Normally when I give this talk I go into great detail about what error bars are and why you use them, but you really do not have to know anything about that. What you

do have to know is that all error bars look the same, and in this case, if you look at the figure legend you will see here that these error bars are showing mean values plus or minus standard deviations. So this is from one paper in this one edition of Nature.

Here is another figure from another paper, completely different paper but the same edition of Nature, and in this one, like many papers in Nature, there are again graphs, and in these graphs here there are these little T-shaped things. These are error bars. And in this case if you look at the figure legend you can see that the bars represent mean plus or minus SEM, or standard error of the mean. So in the previous paper, the error bars were standard deviation, but in this paper these error bars are standard error of the mean.

Here is another figure from the same edition of Nature but a different paper, here are these little T-shaped things These T-shaped things, of course, are error bars, and if we look at the figure legend we can see that these error bars are CIs, or confidence intervals. So you will notice that the error bars in every case look the same, but in one paper they were standard deviations, one they were standard error of the mean and in this one they are confidence intervals.

Here is another figure from the same edition of Nature. In this graph here, there are these little T-shaped things. These are error bars, but if we look at the figure legend it does not say what the error bars are, and if you look at the materials and methods of this paper, it does not say what the error bars are.

Here is another figure from the same edition of

Nature, graph, error bars, but the figure legend does not say what the error bars are, so there's no way of knowing if these error bars are standard deviations, standard error of the mean, confidence intervals, range or something completely different.

Here is another one. Same edition of nature, different paper, and here are the graphs with error bars, but the figure legend does not say what the error bars are, and the materials and methods do not say what the error bars are. So it turned out that in that one edition of Nature there were 10 papers that had figures that showed error bars but only three of those papers said what the error bars were.

So the thing is, to interpret these papers, you need to know what the error bars are, and presumably one of the authors calculated the error bars and thought there was a reason for it and drew them in, but all of the other authors did not notice that it does not say what the error bars are. The three reviewers of the paper did not notice that they did not say what the error bars are, and none of the editors at Nature noticed that seven out of ten papers in Nature that show error bars do not even say what they are.

So what this means is that most papers that appear in Nature, maybe seven out of ten papers appearing in Nature, haven't been carefully read by the reviewers or the editors or the authors of the paper because these are all multi-author papers. So once again it suggests there is a big problem with quality control in even the most prestigious journals.

So when I see this sort of thing, I get all steamed

up and then I write letters and most of the time the editors ignore my letters but in this case they published this correspondence. I wrote that by not ensuring that all papers that have error bars describe what they are, Nature publishes material that cannot be properly assessed by its readers.

So they were good enough to publish this and they were good enough to improve their guidelines to authors and to reviewers, and now it is much less common to find papers in Nature that show error bars but do not tell the readers what they are. Many other journals have also improved their standards.

Now, sometimes I think I might have shot myself in the foot because in the old days it was easy to work out which one of the thousands of papers that get published every week you should ignore, because you could just look for ones that showed error bars but did not say what they were, and you could ignore them because they have not been read carefully by the authors or the reviewers or the editors so why should you bother reading them yourself. You might as well throw them away. So now they say what the error bars are but there is no reason to believe that the papers are of any higher quality than they used to be.

So that was back in 2004 and, as I said, most big journals have improved their guidelines to authors and reviewers and it is less common to find papers where there are error bars but they do not describe them. But still, they come about.

Here is a paper published in PNAS, the Proceedings of the National Academy of Science of the US. This one is published in 2009 and this one is contributed by Bert

Vogelstein. Bert Vogelstein is probably the most highly cited cancer researcher on the planet. If you are a member of the US Academy of Science, as Bert Vogelstein is, then you can contribute some papers to PNAS and you also get to choose the reviewers. Some people have argued that this makes things much more efficient because papers rarely get rejected if you choose the reviewers, but other people have argued that this can lower the quality of papers appearing in this journal.

In this paper here, here is Figure 2, here is a graph, here are these T-shaped things, these error bars. We look at Figure 2 but it does not say what the error bars are. We do not know whether they are standard deviation, standard errors mean confidence intervals or something else. So one author, presumably the first author, has drawn them in but they have not told the readers what they are and none of the other authors can have read the paper carefully enough to notice that it doesn't say what the error bars are.

So once again, I got steamed up and I wrote to Randy Schekman, who is the editor-in-chief of PNAS. I said, "Can you please publish a correction so it is possible to interpret the data, otherwise readers may be left with the impression that papers appearing in PNAS have not been carefully read by the authors or reviewers. Yours sincerely", blah, blah, blah.

He is good enough to reply, "Dear David, you have been kind enough to point out this error on more than one occasion and in spite of our efforts to tighten up the instructions, authors continue to ignore us." Right, so this is the editor-in-chief of PNAS talking to a member of

the US Academy of Science. So it is a big problem.

But from this, I have learnt that by looking at error bars you can learn a lot of things, even unrelated to statistics. So the first lesson I have learnt is that if a figure shows error bars and does not say what they are, throw the paper away. But I always do look at error bars because you can get hints about all sorts of other things.

Now, this is a paper published in Nature in, I think it was 2011, and it is from Massachusetts General Hospital, Harvard Medical School, the Broad Institute of Harvard and MIT. This one is looking at tumours in mice and it is lucky that this is before dinner rather than during dinner or after.

The first thing that struck me as peculiar was they are measuring tumour size in these mice but they are measuring - so these graphs, the little T-shaped things here, they are very small ones, these are error bars and they say what the error bars are in this case. The error bars in this case are "mean plus or minus standard deviation of three independent experiments". So they have done three independent experiments, three independent tumours and they have measured the tumours. But what is surprising is they have measured the tumour size in millimetres.

I will just show you a blow-up of that picture, so this is the picture here, and they have outlined the tumour in blue. If I was going to measure the size of a tumour in a mouse or in a human or any other organism, then I would not measure its length, especially an irregularly-shaped tumour like this one. If I had

dissected out the tumour, as they have over here, I might weigh it and say how many milligrams it weighed. Or I might measure its volume and talk about the volume of the tumour. But it struck me as very peculiar that they are measuring the length of a tumour in millimetres because are they measuring it from here to here, or from side to side, or from back to front?

Yet, when they have measured this, their standard deviations are really tiny and weeny. So they are measuring these independent tumours with an accuracy with standard deviations of less than a 10th of a millimetre and yet these tumours are incredibly irregularly-shaped. I bet if three independent people measured the length of this tumour you would get answers that would be wildly different.

So this struck me as being very peculiar and so I wrote a letter to the editors at Nature, but before I show you that, if you look at the supplementary material there were some hints as to why their results were often so reproducible.

So here is the picture from the supplemental material and here you see four mice up the top, and these tumours all do look extremely similar, and these mice down the bottom, three out of these four mice also have tumours that look extremely similar. You can see the alteration, it is exactly the same position on these three mice. These mice, the tumours all look very similar. If you look at the droppings at the bottom of the cage, they're also extremely similar. So these people are capable of doing very reproducible work.

So I wrote to the editors and said something funny

is going on and it turned out that there was and so they published a correction and this is the correction that they published. In the correction, now they are measuring tumour volume instead of tumour length and this makes a lot more sense. You can see that the standard deviations are much bigger, so they are getting variation, as you would expect if you are looking at independent tumours. Over here again, tumour volume and big standard deviations, which is what you would expect.

But this raised another problem and the problem here is that, if any of you have used mice in research, an adult mouse weighs about 20 to 30 grams, 25 grams I guess on average. Anybody who has used animals in research knows that you have to get signed off by an animal ethics committee. You have to carry out the experiments ethically. You have to make sure the mice do not suffer unnecessarily. You have to be able to justify any pain that you cause to a mouse based on the potential of the results that you get. It is very highly regulated.

But if you look here at the size of the tumours, some of these mice must have had tumours of over seven cubic centimetres. Nature were good enough to publish a picture of those mice. Before I get to that, in their correction they say, "We have been unable to verify without doubt that the image in supplementary Figure 9B shows four different mice". So they are unable to verify that they did not just take a picture of one mouse and show it four times, right. So again you cannot trust them.

But Nature has not retracted the paper. They have just published this correction. Here is the correction

showing the mice. Now, there might be some members of an animal ethics committee here tonight but the rules are, whether you're in Australia or in the US or in Europe, that you cannot have tumours that are over about one and a half cubic centimetres. Yet some of these mice have tumours that are seven cubic centimetres in size. This is animal cruelty. It is gross animal cruelty. This should be criminal. It probably is criminal and these people should be locked up. Yet this is presented in Nature, who gives it tacit approval by publishing it with no comment.

These mice here, you can see these dark patches, these are ulcerating tumours. Again, all of the ethics committees say that if any mouse has an ulcerating tumour, you have to euthanise that animal. You are not allowed to have animals with tumours over about one and a half cubic centimetres in size of their tumours.

So by publishing this and giving it tacit acceptance, I think Nature does a disservice to the entire community because use of animals in research is a real privilege but it is an important one that is protected because otherwise medical research won't progress. Now I do not know what PETA would make of this, but Nature seems to think it is very acceptable. Nevertheless, I have written to them from time to time.

Here is one reply from one of the editors of Nature. This is 16 October 2012, and this is in response to the correction: "This is just to let you know that in one of the upcoming editions of Nature we will publish a correction to this paper in which the authors state that the experiments were not performed in compliance with the Institute's guidelines". So that was on 16 October, again

not retracting the paper, but just noticing, "Oh, well, we have not done it ethically and here it is".

Then here we are in November 2013, "Dear David, I want to take the opportunity to update you. We have not yet made a final decision on how to proceed", and here we are in June 4 2014, "Dear David, I realise it is taking far longer than any of us would like. We will update you as soon as things are finalised and there will be an editorial on Nature's position regarding animal welfare". And yet still nothing has happened.

Now I am going to talk about another very famous researcher. This fellow is Michael Karin, again one of the most highly cited and biggest cancer researchers in the United States. He mainly works on signalling and activation of transcription factors, especially one called NF Kappa B. He has published over 500 papers, 28 of his papers have been cited over 1000 times and if any of you have published scientific papers you would know that that is a lot.

He is ranked first world-wide by the Institute of Scientific Information and in the listing of most cited molecular biology and genetic research papers published in prestigious journals. So I was reading one of his papers which was shown to me by a colleague in the lab, and he said that his results were different to the ones published in Cell which is the most prestigious biomedical journal from Michael Karin's lab. And this is one figure from that paper and I will just blow up some of the figures.

It struck me that some of these bands – so this is called the western blot, and all of these bands should be the results of independent experiments and yet if you

looked at this band here it looked very similar to this band over here. And over here in this other blot in the same figure you can see this scratching on the top of the lane here, looks very similar to that, and I am not sure if you will be able to see the background here, but the background spots and pixels are all identical between these lanes. Yet the bottom of the lanes are different and in this other figure here you can see the same scratches. It looks almost as if someone has just taken a copy of this one and then using Photoshop they have pasted it down here.

Of course I do not know what has happened because I haven't got access to the original data and I don't know which of the authors might be responsible so of course I wrote to Dr Karin and said, "Dear Dr Karin, In this publication there appear to be duplicated bands in figures 2A, B, and D, (See attached figures). Could you please determine whether the published figures are a fair representation of the primary blots and if they are not, determine who is responsible and whether there are other suspect images and papers and take the necessary appropriate action." Yours sincerely.

He wrote back, "We have already checked other allegations regarding this publication." So somebody else has noticed there are odd looking things in this paper and have contacted him and they have already checked them out but they have found them to be totally baseless. "The first author is no longer in possession of the primary data."

Once again, in most places not keeping your primary data fits in with the definition of misconduct but how did

they know that these things were totally baseless if they were no longer in possession of the primary data? And yet, as I said, all of this has been examined and no data manipulations were found.

Then a little bit later he forwarded on a response from the first author and he said, "Michael, please have them check out carefully and I will just annotate the figures down below." So where I had seen these two bands that look extremely similar he says, "In figure 2a the band in lane 1 appeared to be a little bit wider than the one in the other lane. And for these two that look absolutely identical, in Figure 2b the different pattern at the bottom" – so down below where it is different – "demonstrates that they were from two different samples", and yet there is no explanation of why the tops look exactly the same. And in these two bands here are exactly the same patterns and pixels, no idea why they circled the lanes 1 and 2 in figure 2d plotted by FAD. Complete denial.

Normally I know that if I receive a message from someone saying, "We dispute what you have found", or "we have seen something funny in one of your papers", I know my reaction is to feel physically sick because as a scientist you know that your integrity is the thing you hold dearest and the role of a scientist is to find the truth so I was very surprised by the very dismissive and blasé attitude from Professor Karin, so I wrote to another guy I know well, John Dahlberg who is the Director of the Division of Investigative Oversight at the Office of Research Integrity in United States. He replied to me and he said, "Dear David, thank you for sending us additional

allegations." Again this was a shock because I had not sent any before, and he said, "We have been working with the University of California San Diego on this matter but you have added additional concerns about this paper."

So not only had I had concerns but apparently somebody else had, and they had been raised with the Office of Integrity in the United States. Of course Australia does not have an Office for Research Integrity so in Australia you cannot even go this far.

It turned out that nothing has been done. This paper has not been retracted. The investigations by UCSD and the Office for Research Integrity in the States have not found that anything is wrong whatsoever.

I ran into John Dahlberg at a meeting and he basically said that the lawyers that Michael Karin had were better than the ones that can be afforded by the Office of Research Integrity.

But it turned out if you look at other figures from the same paper then there are other problems and these have come to light because people nowadays log onto the internet and if you look at the internet then you can find out what is really going. So in Figure 3D all of these panels are the same as in Figure 4A and yet these cells have received different treatments, and if you look at the gene knockout mice, this is a double knockout mouse, a mutant mouse and he is a wild type embryo but you can see this figure, these two pictures are absolutely identical so there is a huge number of problems with this paper but the journal has not retracted it or corrected it, neither has Michael Karin, neither has the Office of Research Integrity, neither has the University of California San

Diego.

Now I will move on to another character and there might be some of you who recognise this character. He is an author on this book that again some of you, the medical graduates might recognise from their days studying as medical students or for physicians' exams. This is Harrison's Textbook of Medicine and one of the editors on this is Eugene Grunwald.

Eugene Grunwald is the most frequently cited author and cardiologist. He is probably the biggest and most famous cardiologist on the planet, and as I said, one of the editors of Harrison's Textbook of Medicine.

He was involved in one of the earliest cases and biggest cases of research misconduct that led to the establishment of the Office of Research Integrity in the United States, and that was the case of a young trainee cardiologist working with him called John Darcy. He joined Grunwald's lab in 1979. Darcy produced five major papers in his first 15 months at Harvard. Some of Darcy's colleagues became concerned about the accuracy of his results. They went to the lab Director, Robert Kloner with their suspicions. Kloner found that Darcy had been altering the dates on his laboratory work to make a few hours work appear to be several weeks of data.

Grunwald and Kloner investigated Darcy's work and found no other evidence of fraud nor did a committee of Harvard Faculty appointed by the Dean of the Medical School. But further discrepancies were reported and that led to an investigation by the NIH and ultimately led to the establishment of the Office for Research Integrity.

The NIH review, so an independent review rather than

one by the colleagues found that Darcy had fabricated large amounts of data from experiments which he had never conducted. Harvard's investigation as well as that of Grunwald and Kroner were criticised for being inadequately rigorous and for recording that they had fully reviewed data which later turned out to be non-existent. Harvard retracted 30 of Darcy's papers and abstracts in February 1983 and a review of Darcy's earlier work at Edinburgh University led to the retraction of an additional 52 papers and abstracts published during his tenure there, so there is a history of research misconduct in Eugene Grunwald's lab, but of course in that case it was John Darcy who was responsible.

These issues give a look at the culture in a laboratory and if you see ongoing cases then it makes you worry about the culture and the system rather than individuals. There was an article on Amrinone which was a new drug for heart failure, was published in the New England Medical Journal of Medicine in 1978 by Braunwald's Group and this is the paper here. Amrinone is supposed to increase the power of pumping of failing hearts.

The article said that the five authors were employed in the cardiology department at Harvard Medical School but two were actually full-time employees of Sterling-Winthrop, that is the company who developed the drug, and had never worked at Harvard. Two of the three that did work at Harvard were also paid consultants of the company and these conflicts of interest were not declared.

In 1979 a letter from cardiologists in Los Angeles was published in the New England Medical Journal. The letter reported fatal side-effects from Amrinone and this

is the letter from Stanley Rubin and colleagues. A stockbroker had seen the sudden increase in price of Sterling-Winthrop's shares after the paper from Braunwald Group was published in the New England Medical Journal and thinking that it must have been a break-through drug, she asked her husband's cardiologist, Stanley Rubin, to obtain the drug for him as he had severe heart failure.

Rubin persuaded the company to let him have Amrinone on a named patient basis and soon after receiving the drug his patient died, and so he wrote to the New England Medical Journal. So, they sent the New England Medical Journal, the first report of side-effects of Amrinone, but soon after submitting the manuscript, Sterling-Winthrop contacted them, so Rubin and colleagues, and asked them to withdraw it, and that is because the New England Medical Journal had sent Sterling-Winthrop a copy of the report.

So, once again, you will see that there are these covert relationships between the most prestigious research institutes, the most prestigious journals, the pharmaceutical companies and the investigators themselves.

Initially the journal refused to publish the letter but when Rubin said that if they did not he would go to the press, they relented.

A British cardiologist Peter Wilmhurst - and he is the one has been most critical at having Amrinone eventually withdrawn - started to do research in the UK on Amrinone in 1978, and Sterling-Winthrop provided him with the drug. He found that Amrinone did not help his patients with heart failure and frequently caused threatening side-effects.

He reported to Sterling-Winthrop, because they had

funded the study, that he was unable to find evidence that Amrinone worked in patients with heart failure, and he reported serious adverse events. Company employees asked him to exclude some patients from the analysis which would have produced an apparent but spurious increase in contractility - basically any patient with side-effects or with a failure to respond, they wanted to remove those patients from the study - he refused and so the company threatened to sue him.

The Netherlands Committee for the Evaluation of Medicines saw Peter Wilmhurst's paper on the side-effects of Amrinone, so this is the paper from Peter Wilmhurst, and when they compared his results with the clinical report cards on his patients that had been submitted by the company - and remember the company is funding Peter Wilmhurst's study and so they had all of his records and they supplied it to The Netherlands Committee for the Evaluation of Medicines - when they compared his results with the clinical report cards on his patients that had been submitted by the company, they found discrepancies; the company had sent The Netherlands Committee forged clinical records for Wilmhurst's patients with the information on adverse events deleted.

In 1984 the company told the FDA that there had been over 1400 serious side-effects in patients given Amrinone in trials, and they would cease the trials and applications for the product licences world-wide, so they dumped the drug because it basically does not work and it has serious side-effects, like causing death of patients.

They still went on and marketed the drug for another two years in Africa and Asia. In 1983 Sterling-Winthrop

produced a modified form of Amrinone called Milrinone and there is a paper on Milrinone, again from Eugene Braunwald's lab, and it was agreed before the research on Milrinone had been completed that it would be published in the New England Medical Journal. So, there is a very cosy relationship between some researchers and some journals.

I believe that one of the biggest reasons that there are so many papers published that are not reproducable is because what determines whether a paper is accepted for publication is who the authors are and where they come from, rather than the scientific contents of the paper.

So, it was agreed before the researches had been completed that it would be published in the New England Medical Journal, and that was by Arnold Relman, the editor-in-chief. When the first two referees recommended rejection, the editor Arnold Relman sent the article to two more referees. They also recommenced rejection, but the journal published the paper on Milrinone as previously agreed.

Since then Braunwald has published another 750 papers and this is one of them. This is from 2012 where he writes, "It has been brought to my attention that there were differences in my financial disclosures of a number of articles previously published in the Journal of the American Medical Association and this warrants explanation".

So he goes on to say, "Relationships present during the 36 months prior to submission of the latter two articles include research support from Merck, AstraZeneca, Johnson & Johnson" and so on, and so on, and so forth. "These were not listed because I did not consider them to

be relevant to these two articles. I did not understand that all financial interests" blah, blah, blah, "should be disclosed. I hope this clears up any possible misunderstanding".

So, again it has taken something like 30 years for Braunwald to understand that you have to declare your conflicts of interest because otherwise readers of these journals won't know that you are paid by the drug companies.

My last example tonight is talking about Vioxx. In the 1990s, Merck developed a COX-2 inhibitor drug Vioxx, for the treatment of arthritis. This is the key paper here, again published in the New England Medical Journal, and this is November 2000. Merck employed ghost writers to create journal articles that were favourable for Vioxx. A ghost author is an author who actually writes the paper but their name does not appear on the authorship list, so that these papers would often be written by employees of the company, and this is especially true for reviews, and then they would often invite key opinion leaders to act as honorary authors, and they would put their name on the paper and they would get a cheque for doing so. So, after writing the paper they would recruit honorary leaders in the field to act as the senior authors.

In a 2008 review by the Journal of American Medical Association, which, again, you can see from the huge number of papers published in that journal from Eugene Braunwald, they have had a chequered history, but in a review in the Journal of American Medical Association of 96 published papers about Vioxx – right, so it is amazing how many were published – Vioxx from Merck, they found 92

per cent of the papers on the clinical controls disclosed their financial support, but this is the minority of the papers, but only half of the review articles disclosed Merck's sponsorship or involvement in creation of the paper or whether the authors were paid by them.

So, this one has an Australian angle to it. This is a report in a magazine called The Scientist, this is an international sort of news magazine and in it it had the story that Merck had published a fake journal. Merck paid an undisclosed sum to Elsevier to produce several volumes of a publication that had the look of a peer reviewed medical journal but contained only reprinted or summarised articles, most of which presented data favourable to Merck products, that appeared to act solely as a marketing tool with no disclosure in this fake journal of company sponsorship.

So, they funded a number of these journals that all contained articles, reprints of articles, that were favourable to Merck products but there was no disclosure that this is all funded by Merck, and then the journals were made to look like, you know, a proper journal; they had an editorial board, they had all of the look, and so for a lot of clinicians they did not realise that this was advertising material and not objective material.

Australians who took Vioxx sued Merck and its Australian subsidiary. In documents submitted to the court it was revealed that, "Merck had paid an undisclosed sum to Elsevier to produce several volumes of publication that had a look of a peer reviewed medical journal, but contained only reprinted or summarised articles".

So, The Scientist got its story from Australia when

these things came out in the courts, and one of these journals, and there was a number of them, was the Australian Journal of Bone and Joint Medicine. It also carried ads for Merck products, Fosamax and Vioxx, that appeared solely to act as marketing tools with no disclosure of company sponsorship.

So, this is one of the ads here and this up the top is a nice picture of a couple that are now waltzing because they have been treated with Vioxx, they have waited a long time for this dance, and so this is one of the advertisements in this fake journal.

This is the cover of the fake journal, and this is the editorial board. I have blanked out a lot of the names here, because maybe there are members of the editorial board here in the audience, but you can see there are many; there is Royal Melbourne Hospital, Brisbane Hospital, Austin Hospital. So these are the key opinion leaders here in Australia.

I have got no reason to know that any of these people actually knew that they had been listed by the journal. I know one of them knew but I won't say which one, but for all I know they were included here, they were not paid and they had no knowledge of this. But you can understand that if people are offered to be on an editorial board, if they are given a cheque, this will help their CV, it will help their prestige, it will help their mortgage.

So sometime later there was a paper, again in the New England Medical Journal, this is an expression of concern because they are referring back to their earlier paper, the first one, the main one on Vioxx, where they

are criticising the authors because the authors had three patients who had heart attacks while they were on the drug that they knew about before they submitted the final version of the paper but they did not mention that to the journal. So they withheld information about serious cardiac side effects from the journal.

Eventually, a report from the FDA on Vioxx was published. A report on Vioxx risks that was previously blocked by the FDA was published online after the agency withdrew its opposition. The study found that as many as 140,000 cases of heart disease in the United States and as many as 56,000 deaths were caused by the painkiller during the five years that it was on the market.

So again, this is not an exaggeration in that this is the FDA. This is published in the Lancet. These are real deaths not just theoretical ones. So 56,000 deaths. Vioxx was taken off the market in 2004 after it was linked to an increase in heart attacks and strokes. Merck paid $4.85 billion to settle the US cases and a further $1 billion for its legal costs.

Now, I will just get back on my hobby horse and talk about the situation in Australia because that last example of fake journals, that was in Australia. I come across many cases of researcher misconduct in very different forms in Australia but in Australia there is very little that you can do because the only people who are in charge of this are the institutions that employ the individuals involved and of course they are publicity adverse and they want to keep things quiet and sweep them under the carpet.

Australia would benefit greatly from having an Ombudsman or an Office for Research Integrity. It would

not have to be as big as the ORI in the United States and certainly the Office for Research Integrity in the States is not a panacea. They still have their problems, as you saw with Professor Karin.

But an Office for Research Integrity would provide advice to whistle-blowers on how to report concerns. It would provide advice to the accused people because if you are wrongly accused, where do you turn to? It would provide advice to institutions on how to carry out investigations because it seems to be that in any individual institution, they have an accusation, they carry out an investigation. It turns out to be a complete disaster. They learn a lot from it but then by the time the next case comes around, there is different individuals involved. So an Office of Research Integrity or an Ombudsman could provide advice to institutions and could provide advice to ethics committees.

It would allow all published work and research involving animals or humans to be covered. Currently, there is a code called the Australian Code for Responsible Conduct in Research but it only covers research covered by the NH&MRC and the ARC. It does not cover research funded by companies or by the CSIRO or by charitable organisations but there should be a body that covers all research, especially all research that involves humans and animals.

An office could collect data so we know what is the incidence; where is it occurring; what can be done to try to prevent it? It could provide oversight. If an institution is not carrying out the investigation properly, then the office could become involved and do

things right. It could provide an avenue for appeal. It could act as an avenue for concerns to be reported both locally and internationally. Currently there is no way, if somebody in Canada notices that there is a problem with some paper published in Australia, that they can have anything done about it.

It could also modify and improve the Australian Code for Responsible Conduct of Research. This is now about 12 years old and there are many problems with the way the code is written. There are many inconsistencies, there is too many Latin terms, and that should be improved.

So thank you all for your attention, I hope the animal pictures have not put you off your dinner and I am happy to answer questions.

MR GRONOW: Professor Vaux has kindly agreed to take questions. Naomi has the microphone and perhaps if you could give your name and profession when you ask a question.

MR NAYLOR: Professor, my name is James Naylor. I have come as a guest tonight but thanks for an interesting presentation. I was actually prescribed Vioxx after an operation to reconnect an obscure tendon I had ruptured playing tennis, in my ankle. I stopped taking it before I finished the course and I did not make a claim in the lawsuit that followed but what intrigues me is you talk about the need for an Ombudsman or an office to handle these issues in Australia. What concerns me also is what happens to scientists who have actually done breakthrough work, like Dr McBride with Thalidomide, and then somewhere down the track they have maybe been tempted to go with some dodgy data? Who hears of Foundation 41? Is that out of business? You are talking about cultures of a - the

issue of the culture in research institutes and just recently, this would be in the last couple of months, I can't think of the fellow's name but there was a scandal where - in the last couple of years, where some Japanese group of scientists had some breakthrough, I can't remember what it was about, but the researcher came under scrutiny and this fellow, I think he might have been the leader of the unit, he killed himself recently. I mean, this is really serious.

PROFESSOR VAUX: Yes. Right.

MR NAYLOR: What happens to people who, sure, they have done the wrong thing but they have been - - -

PROFESSOR VAUX: No, you raise a number of incredibly important points. So first of all, it is important that people realise that research misconduct is a spectrum and it goes all the way from incredibly trivial, like intentionally not citing your competitors or citing yourself more than you should, so you know, that is very trivial, to really serious which leads to patients given drugs that cause them harm.

It is important that the responses are proportional and appropriate. For issues where things are not causing harm to patients, the environment, to animals, where it is an error on the research record, then in those cases, then the scientists should be encouraged to make a correction or retract the paper. But if they do that, then that should be the end of the matter.

The thing is that people learn from experience and if there is an organisation that can gather experience on how do you provide support people to tell people that there is a path to redemption, "This is the way you go

about it. This is the importance of protecting your original data, to protect yourself against spurious or vexatious accusations."

So the thing is the office is not there as a police force. It is more there, or should be there, as a fire brigade. Somebody who you can call when you see a problem. Their job is not to punish, their job is to put the fire out, to correct the scientific record but also to correct behaviours because the only way researchers will want to have a career in research is if they think it is a fair process where they will get due credit, you know, to stop plagiarism, to stop other sorts of behaviours.

It is not easy.

MS SNOW: My name is Pam Snow and I am very fortunate to be here tonight as a guest. I am an academic at Monash University, in the Faculty of Medicine. It is very hard to disagree with most of what you say but there is one aspect that I think maybe you did not touch on. That is the aspect of academic workloads. I review probably six or eight papers a year. I turn down a small number for logistical reasons or because I think the content or the analysis is outside my sort of comfort zone. But I get no brownie points at all from the university. As my husband will attest, it is all done after-hours on weekends. I do my best but universities need to acknowledge that as part of the global academy of science, it is academics who provide this peer review process but we are not rewarded for it at all by our institutions.

PROFESSOR VAUX: Yes. No, I could not agree more. I did not really go into incentives but the incentives cause people to bend things. So in Australia, for example, 3,000 PhD's

are awarded in the life sciences every year. There is only one career programme for medical researchers and that's the NHMRC Fellowship Programme. Thirty positions open up every year in that programme. The average age for entry to the lowest rung of the research, NHMRC Research Fellowship position, the average age for entry to the lowest rung is currently 47.

Right, so you have got all of these people that have incredible pressures on them. You know, how do they pay their mortgage. Their success rate in NHMRC project grants is currently around 16 per cent, right, and they have to get grant after grant just to pay the salary to pay the mortgage so they can put food on the table.

So there's tremendous pressure to, you know, if you are sending in the last draft of the paper to satisfy the reviewers' requests and they are requesting more and more. So you can see how people start to just bend things the way they need to be.

So we need to look at career structures. We need to look at incentives. We need to make it easy for people to do the right thing rather than the wrong thing. As you say, there is no credit for doing all of this peer review. We estimate at the Walter and Eliza Hall Institute that about 25 per cent of our time is spent either writing grants or reviewing grants and even more time if you count reviewing papers.

The other thing with peer review papers, and I think this is one thing that could be done that would improve things a lot, is that currently what determines whether a paper is accepted or not is whether you know the authors or whether you know the institution. We should have

double-blind peer review of papers, just as we have double-blind clinical trials.

And one day, maybe in 20 years, we will have double-blind peer review where you judge a paper based on its scientific content alone and we will look back and say, "How could we possibly have had this system which is so easy to corrupt where you just get a cabal where, 'I will accept your paper, you accept my paper and we will reject everybody else's'".

MR SCOTT: Thank you very much. David Scott from St Vincent's in Melbourne. I am a clinician and an academic researcher and I'm obviously disturbed by a lot of what you said. I think it's not new to many in the field that this is an emerging and accelerating process.

Just a very brief comment. The last thing you said is that it used to be double-blind reviewing and it has gone to open reviewing now. We now know the authors of the papers that we review but it used to be that we did not know the authors of the papers that we do.

PROFESSOR VAUX: Some journals.

MR SCOTT: But my question is more about not so much the researcher behaving badly, which you've clearly demonstrated, but what you touched on which is the Editorial Boards behaving badly and particularly journals like the New England Journal of Medicine.

These journals are all driven by what is called the "impact factor" and the impact factor is how much impact, how many citations a particular article or journal article will get. And that makes the journal itself more prestigious, more powerful, obviously attracts funding and so forth.

An impact factor is a very pervasive and insidious drive to publish papers which are controversial and may lack scientific rigour, and I think a lot of the thrust of this should be to empower individuals like yourself to be able to actually question these Boards and demand answers from them about their failure to apply the appropriate level of scientific rigour because it concerns me greatly.

There is a huge thing called "positive publication bias", which you are well aware of, where if you got a positive result in a paper it is much more satisfying for a journal to publish it. It is much more likely to be cited, which will improve the journal's impact factor.

As a researcher I know two-thirds, if you are lucky, two-thirds will be negative studies, they won't get published. If you do a review of public positive and negative papers in the literature, the negative papers are about one-tenth of what they should be.

PROFESSOR VAUX: Yes, I completely agree with everything you have said. I just want to add one little thing as a point of optimism, is that the clinicians are responsible for now having registration of trials before the trials are conducted, and in that way it should be much harder for negative trials to just be put in the bottom drawer and never see the light of day.

So, the other thing, sort of light that has recently come about is the web because now it is possible to publish everything on the web, you can put a lot more data up there. It is also possible to have post-publication peer review. So there is a number of websites where people can write up comments and now they are linked to PubMed so that if anybody does have concerns they can

anonymously raise them and raise awareness. So, you know, I think there is some grounds for optimism but as I say, currently 90 per cent of papers that are published can't be reproduced.

MR GRONOW: We'll have one last question.

PROFESSOR VAUX: Two one last questions.

MR GRONOW: Two last questions, all right.

DR COURT: I will be brief. Doctor John Court, I am a paediatrician.

PROFESSOR VAUX: Yes, John.

DR COURT: I am editor of Journal of Paediatrics and Child Health publication.

PROFESSOR VAUX: Yes, and diabetic camps.

DR COURT: My question is that, as editors, one is so very reliant on reviewers and one is pressed between whether they are working in the same field but may be competitive or otherwise. My question really is, do you see merit in actually publishing the names or the critiques of reviewers when a paper is accepted?

PROFESSOR VAUX: No and yes. So I do not think there is any benefit, I do not think there would be any point in publishing the names of the reviewers because then everybody would just write beige reviews. But I do think the comments should be published, the comments of the papers that are accepted for publication and also the comments on papers that are rejected. The comments should become the property of the authors and so that would act as a disincentive to people publishing ridiculous critiques.

MR MOLONEY: Professor Vaux, thank you very much for your paper. My name is Moloney, I am a member of the Victorian

Bar and I have two questions and a few sentences thereafter which might reveal the basis for the questions.

The first question is, do you know how many independent external research misconduct inquiries are conducted in this country?

PROFESSOR VAUX: No.

MR MOLONEY: I see. That is quite extraordinary.

PROFESSOR VAUX: Nobody does because they are all secret. There is no - - -

MR MOLONEY: And, secondly, are you able to indicate the degree of difficulty with having the incorporation of the NHMRC Guidelines, which are a very, very useful tool, into the model for the funding of every other form of research in Australia? And I will explain why in a minute.

I chaired an independent research misconduct inquiry with two eminent scientists. It is an extremely burdensome task. The three panel members, myself and two others, have no immunity from suit.

PROFESSOR VAUX: Yes, so that is one thing is - - -

MR MOLONEY: You have the risk of being sued at all times for all purposes. The only other inquiry I am aware of was chaired by Sir Gerard Brennan, the former Justice of the High Court.

PROFESSOR VAUX: Yes, the Bruce Hall case.

MR MOLONEY: And he was sued up hill and down dale. He had the benefit of protection from the University of Sydney. In my inquiry there was serious scientific fraud which involved the in-depth examination of data for weeks and weeks and weeks. It involved the commissioning of solicitors to assist the inquiry. It involved the retaining of counsel to assist the inquiry. It involved a

hearing that went for over a week and the researcher in this city his career was at an end once the matter was heard, and an extensive report was written and found and the papers were removed.

The medical people and the scientists say this is awful, why does this take so long? But then when you get into it, it is inevitable that things - and that was quite quick because the science is in issue, and the career is in issue, and the institution's reputation is in issue.

So you suggest that an Ombudsman may be helpful to do that I think - and the premise for that is that it centralises the capacity for complaint and its resolution. Who funds the Ombudsman? I have thought long and hard about this over many, many years to see whether there was a better way to handle this problem that I faced and my two enquirers faced. We were lucky because we had the NHMRC funding the research. But for that funding all the rules would have had to have been made up by me. A frightening burden.

And so I am interested to know, and I know your position as a Senior Research Fellow, how is it practically possible to plug the NHMRC rules in for all research in this country?

PROFESSOR VAUX: So again you raise a huge number of pertinent issues, so, first of all, in my opinion the Ombudsman and the Office of Research Integrity would rarely carry out investigations themselves, they would mainly provide oversight just as the Office of Research Integrity does in the United States and as the Ombudsman for the DFG does in Germany, for example - again, they are not panaceas, they have problems themselves - but things tend to, in my

opinion, go much more smoothly there.

It would have been great had the University of New South Wales had been able to pass on their inquiry to get advice on how to conduct an inquiry to get some advice in place, like provide support people for the accused and support people for the whistleblower, to indemnify all of the panel members. Again, you know, I know Judy Whitworth who was also on the Panel with Sir Gerard Brennan, and she was threatened with Supreme Court injunction and just had to shut up. The only reason we know what they found was because the matter was tabled in the Senate by Kim Carr. So, I think, if I was in charge of a university or in charge of an institute, I would love to be able to say "Look, we have got a case" to be able to go somewhere to get advice; they could keep a pool of experienced personnel to be able to carry out the investigations.

Timeliness was another thing that you raised, and while there are issues to do with people's career ending and reputations of universities, in some cases you've got to consider clinical trials.

There is one case currently going on where the Deputy Vice Chancellor had found prima facie evidence or data underpinning a clinical trial, and that trial was allowed to recruit patients for an entire year while the panel was investigating, but they did not inform the Human Research Ethics Committee. So, there is not only an obligation to the individual involved and the whistleblowing institution, you also have to consider the rights of the scientific community as a whole, and particularly of patients and animals.

There is an enormous number of issues and ways that

things could be improved. I think we should learn by looking at other countries, other countries that do it better. There have been plenty of countries where there have been big scandals where they have put things in place, where things seem to be going better than they are in Australia.

MR GRONOW: Thank you very much.

PROFESSOR VAUX: One very last question.

FEMALE SPEAKER: Thank you. I am pleased that ultimately a woman was able to speak. Professor Vaux, can I congratulate you on your phenomenal paper and the fact that you have got the courage to speak out on this issue, because we all suspect that there is an enormous amount of lack of integrity which seems to be systemic in so many aspects of our society nowadays, but I think you have articulated what you have said today in a very very powerful and cogent way.

Can I just say that I would entirely support your drive towards having an ombudsman for research integrity, but may I say that I think we need a lot of integrity across the board, both in the legal and other spheres, politics, et cetera, and maybe we need an ombudsman that actually heralds integrity generally because that is a value that we seem to have in great decline in our society.

It is a comment, one that whereby you have added to my concerns.

PROFESSOR VAUX: You know, the thing is that people talk about integrity in lots of fields, and the thing is you can have "bottom up" approaches and you can have principles and "everybody should be good", and so on, but that is just

not going to work because if you have speed limits but no police, no cameras, then people will speed.

On the other hand, you can't have a Gestapo where everything is cameras and watching and flying squads come in and look at the data, so I think you do need top down, you need bottom up, you also need this fire brigade model where every researcher needs to know where to go to get good advice.

MR GRONOW: I would now like to call on Dr Phoebe Mainland to thank our speaker.

DR MAINLAND: I think our society expects health research as part of a quest for truth with the intention of advancing health with decisions based on valid information and information that is gathered and reported ethically.

Professor Vaux has uncovered questions of honesty and trust of research, not only in the gathering of the research but also in the publication, so, no wonder some have shattered illusions of data in reports which leads to suspicion and unfortunately contamination of the whole process of those involved in medical research or by medical research. Unfortunately, this can lead to almost an insult to those researchers who have integrity, as well as hijacking the advancement of health.

Thankfully, people like Professor Vaux have approached this by challenging and calling on the journals, particularly for publishing dubious results, and also by a request for an office or an ombudsman for research integrity in Australia.

Professor Vaux, I would like to thank you for your efforts in all of this on a global scale, but particularly for your presentation to the Society tonight. Thank you.

MR GRONOW: Thank you, ladies and gentlemen. Dinner will be served shortly.

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