EMBO reports

outlook

The mousepox experience

An interview with Ronald Jackson and Ian Ramshaw on dual-use research

Michael J. Selgelid & Lorna Weir

Much of the debate about science policy in recent years has focused on 'the dual-use dilemma', which arises when well-intentioned scientific research has the potential to be misused by state and non-state actors for nefarious purposes. In the context of the life sciences, for example, the same discoveries that lead to advancements in medicine could also be used to facilitate the development of biological weapons. Although all life science techniques and discoveries might be inherently dual-use (Atlas, 2009), current debates are concerned primarily with cases where the consequences of malevolent use would be especially severe (Selgelid, 2009).

The dual-use dilemma is not new. When physicists observed atomic fission and the nuclear chain reaction early in the twentieth century, they realized that these discoveries might have beneficial applications in medicine and energy production; but they also realized that they could lead to the production of new, horribly efficient weapons. The manufacture and use of the first atomic bombs—and the nuclear arms race that followed—demonstrated that their fears were justified. According to the American biologist Matthew Meselson, this is not specific to nuclear physics: "Every major technology—metallurgy, explosives, internal combustion, aviation, electronics, nuclear energy—has been intensively exploited, not only for peaceful purposes but also for hostile ones" (Meselson, 2000). Similarly, recent advances in biology and genetics in particular raise the possibility of a new generation of biological weapons.

One of the most cited examples of dual-use research is that of Australian researchers who inadvertently developed a lethal mouse virus. In this now-famous study, the researchers used standard genetic engineering techniques to insert the gene for interleukin-4 (IL-4) into the mousepox virus. They hoped that the altered virus would induce infertility in mice—which are a major pest in Australia—and would thus serve as an infectious contraceptive for pest control. To their surprise, they discovered that the altered virus could kill both mice that were naturally resistant to, and mice that had been vaccinated against ordinary mousepox. When they published their findings, along with a description of the materials and methods, in the *Journal of Virology* in 2001 (Jackson *et al*, 2001), critics complained that they had thereby alerted would-be terrorists to new ways of making biological weapons and had provided them with explicit instructions.

> **…recent advances in biology and genetics in particular raise the possibility of a new generation of biological weapons**

Of particular concern was the possibility that the same techniques used to engineer the mousepox virus could be applied to create more virulent forms of poxviruses that afflict humans, including a vaccine-resistant strain of smallpox; one of the most devastating diseases in human history. Although it was eradicated in the 1980s, fears remain that former Soviet stockpiles—or genetically reconstituted forms of the virus—could be put to use by nefarious agents.

Given the historical importance of the mousepox experiment, we conducted separate interviews with the two primary researchers involved in the project—Ronald Jackson and Ian Ramshaw—in order to gain their perspective on this research. Although the interviews were conducted separately on 13 and 14 February 2008, we asked many of the same questions to both scientists. For the reader's ease, we therefore present their answers to some questions side-by-side below.

Michael J. Selgelid & Lorna Weir: How did you originally become involved with mousepox research?

Ronald Jackson: I started working with CSIRO [Commonwealth Scientific and Industrial Research Organization] in 1988 on a project to enhance myxomatosis to control rabbit populations—the myxoma virus is the rabbit equivalent of mousepox. Because rabbits aren't as well studied as mice, a lot of the reagents that we needed weren't available for the rabbit but had just become available for the mouse.

Selgelid & Weir: Can you explain the significance of the rabbit and mice problems in Australia?

Jackson: Rabbits were introduced in the mid-1800s and very quickly became an agricultural pest. CSIRO successfully introduced myxoma virus into Australia in 1950, which reduced the rabbit population, but then the virus and the rabbits started this co-evolution of rabbits developing resistance to the disease and the virus attenuating very quickly in response. By the late 1980s, the virus was controlling rabbit populations only moderately—and it wasn't effective at controlling population outbreaks. In agricultural areas, rabbits can be controlled moderately effectively using poisons and warren destruction, which can keep the numbers down. However, in the more arid zones of Australia, where there are very few people and little or no intensive agriculture, rabbits can cause major ecological problems.

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The mouse is also an agricultural pest in Australia. It was introduced from Europe and in recent history there's an outbreak of mice somewhere in Australia every three to four years.

Selgelid & Weir: Could earlier studies have made some of your mousepox findings predictable—particularly the lethality of the IL-4-altered virus?

Jackson: A group of scientists in England made a genetically complete vaccinia virus altered with IL-4, which was lethal, but you have to very carefully read their paper to see that this was the case (Bembridge *et al*, 1998).

Ronald Jackson completed his undergraduate studies in 1981, graduating with BSc (Hons) in Microbiology from Monash University, Australia. Ron was awarded a British Commonwealth Scholarship and completed his PhD in 1987 at the Department of Molecular Biology, University of Edinburgh, UK, studying the molecular genetics of the hepatitis B virus. He returned to Australia in 1988 to take a research scientist position with the Commonwealth Scientific and Industrial Research Organization (CSIRO) Division of Wildlife and Ecology—later CSIRO Sustainable Ecosystems—and was involved with the Pest Animal Control Cooperative Research Centre (1992–2005), developing novel biological control technologies. Ron worked with the CSIRO for 17 years, publishing in the disciplines of poxvirus molecular genetics and reproductive biology and presenting at both national and international conferences. During most of this period, Ron was also a visiting fellow at the John Curtin School of Medical Research (JCSMR), Australian National University, working closely with Ian Ramshaw and the Vaccine Immunology Group. In early 2008, Ron returned to the laboratory bench exploring new immunization technologies with Ian Ramshaw at the JCSMR.

Ian Ramshaw: [An earlier study] found that vaccinia virus [altered with IL-4] had increased virulence in mice. The major difference between mousepox (ectromelia) and vaccinia is that mousepox is a mouse pathogen. We found through initial studies that IL-4 increased the pathogenesis of mousepox. That was not a concern to us. The concern arose when we gave IL-4-altered mousepox to vaccinated mice. The experiments indicated that not only was the altered virus more virulent, but that the vaccines didn't protect against it. That was the critical discovery and big issue at this stage.

Selgelid & Weir: Did the same kind of controversy that surrounded your 2001 mousepox paper arise with these earlier publications?

Jackson: No one paid much attention to the Bembridge study. The lethality of the virus was only discussed in the results section. The Bembridge study was published after we had completed all our mousepox work; so we didn't know what the lethality would be at the time. All our work on mousepox was approved by what was then the Gene Manipulation Advisory Committee [the predecessor of the Australian government's Office of the Gene Technology Regulator] and in the original application we indicated that there was a possibility that this virus could be highly immuno-suppressive, resulting in a lethal infection. We didn't think it would happen, but there was a possibility.

Ramshaw: Our own previous research with mousepox raised no controversy at all. We were using a mouse gene that only operated in mice, so it would have no activity in humans. The issue of safety or dual use never even dawned at this stage.

The critical time was the day that the vaccinated mice died. Ron Jackson came up from the animal house and said, "The vaccinated mice are dying." We just looked at each other and said, "Wow." We were now aware of something that hadn't been previously identified. I didn't know of any other virus or system that could overcome a previously vaccinated regime.

Selgelid & Weir: How did you discover that IL-4 mousepox kills vaccinated mice?

Jackson: When we first did the IL-4 altered mousepox study with a small group of mice in 1998, they all died. This wasn't the desired result—our main goal was to sterilize the mice, not to kill them. So we put the project aside; we didn't have the resources to look at it. It was probably almost 12 months later when Alistair Ramsay and I conducted some relatively crude studies and showed that we got suppression of natural killer cells and total suppression of the adaptive immune response.

It was only as an afterthought that we decided to vaccinate some mice [against mousepox] and then challenged them with our altered virus. We infected them, and about a week later they started developing swelling at the inoculation site, which was highly surprising because they would normally show absolutely nothing. People keep asking: "Was it a surprise that this virus was lethal?" The answer is no: it wasn't a surprise that it was lethal to some mice. What was surprising was that mice that had been immunized were susceptible to infection. That's when we started getting really concerned and wondering what was going on.

> **"This was the first example of a virus overcoming vaccination, and this was very worrying"**

Selgelid & Weir: What was your reaction when Ron Jackson told you what was happening in the lab with the vaccinated mice?

Ramshaw: We said, "Boy this is scary—this is the kind of thing that science fiction is made of." This was the first example of a virus overcoming vaccination, and this was very worrying. And I suppose there was a little bit of excitement about it as well—it wasn't all doom and gloom. This is exciting stuff, no matter how evil or bad it may turn out to be. We went away wondering what to do about it. In those times there was no pathway in the structure of scientific institutions for resolving a case like this.

I gave a talk at a retreat when all our researchers were there. I gave them the results and asked them, "What do we do? Do we publish or don't we?" We came away with the consensus of the scientists, who probably weren't qualified, that there was already so much out there that could be used by bioterrorists that, I think I can quote, "One more won't make a difference". We informed the military and we never heard anything back. They probably wondered "Who the heck are these people?" or "What the heck is this?"

Selgelid & Weir: What were your concerns?

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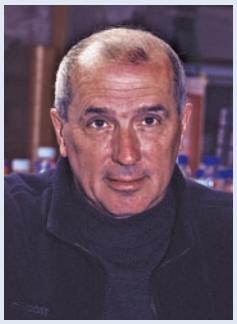

Ian Ramshaw is a professor and group leader of the Vaccine Immunology Group at the John Curtin School of Medical Research (JCSMR) at the Australian National University (ANU). He completed his PhD at the ANU in 1973 and developed a research career in immunology and the development of vaccines for infectious diseases, such as HIV. He set up a consortium to test the prime-boost immunisation vaccine strategy, developed at the ANU, which was funded by the US National Institutes of Health to carry out clinical trials in Australia and Thailand. He has also been studying the effect of coexpressing cytokine genes on the pathogenicity of viruses and published the seminal paper showing increased virulence of poxviruses expressing the gene for IL-4. Ian is Director of the National Centre for Biosecurity, which was established at the ANU in 2006 to facilitate greater academic engagement with biosecurity. The Centre's approach to biosecurity is multidisciplinary and collaborative. Centre members come from a variety of disciplines including microbiology, epidemiology, law, ethics, psychology and international security studies.

Jackson: There is a history of efforts to eradicate smallpox and concerns about smallpox use in biological warfare. This was always in the background in our minds, although what we were doing wasn't in contravention of the Biological Weapons Convention because it was for peaceful purposes and focused on animals rather than humans. But you would have to be an idiot not to realize the technology was transferable.

Ramshaw: Now a long time after the original finding, I thought about this and realized there is another dual-use dilemma—and one that hasn't received so much attention. We created a transmissible virus that doesn't kill the individual but makes them sterile. That's as bad as making a virus that kills the individual. The principles were shown for mice; the principles were shown for rabbits; and there's no reason to think that similar principles would not apply to humans. I'm only just realizing now that even before the so-called mousepox IL-4 experiments, we were already undertaking 'dual-use' experiments.

Another issue was that you would never want to release a recombinant virus that you couldn't recover into the environment. No matter how many experiments you do to show that these viruses don't infect humans or other animals, there would not be sufficient clarity about the consequences of environmental release. So the original work should never have started in the first place.

It soon became apparent that the government would never give permission to release a virus like this. The public would be too worried about the environmental release of a virus that causes sterility. The bright ideas scientists sometimes come up with just go astray, basically as soon as you get into the practicalities.

Selgelid & Weir: The reason the government would prohibit release is essentially a matter of politics influenced by public perceptions?

Ramshaw: It's not only public perception but scientific perception as well. Because such a virus would not be recoverable once you've released it, I wouldn't personally allow it to be released if I had that kind of authority. When you release a virus into an environment you don't know what will happen. You don't know what other animals will be infected. You don't know whether the genes will be incorporated in other viruses, whether somehow the virus will infect humans. The unknowns are too great to take a chance.

> "Another issue was that you would never want to release a recombinant virus that you couldn't recover into the environment"

Selgelid & Weir: As a scientist you must have a long history of thinking about the effects of the release of genetically modified organisms into the environment?

Ramshaw: I think we have learnt recently that scientists usually don't think enough about the consequences of their work. This mousepox incident several years ago was the first that brought my attention to these things.

Selgelid & Weir: Was anyone directly advising you at the institutional or governmental level at the time?

Jackson: The reality was that there was no one there to advise us. This was all before September 11, 2001.

Ramshaw: There was a lot of discussion at CSIRO. So they were well informed of this.

Selgelid & Weir: And there were no biosecurity issues flagged during the peer review process?

Ramshaw: No. The issue arose when a journalist from *New Scientist*—Rachel Nowak—came to me and asked what we were doing. I said we are working on HIV vaccines and we are doing this and that—and none of that was very interesting to her. And then I said, "By the way, we've made this discovery about genetic engineering making mousepox more virulent," and then her ears pricked up like no one's business. Afterwards I realized why this was. *New Scientist* itself has a great interest in problems associated with genetic engineering. Time and again they're raising concerns about the whole issue. She came back later and said she was going to do an article on this (Nowak, 2001). And I said, "Well, you have to wait until the paper comes out because that is required by the journals." I wasn't concerned about it. I certainly didn't expect the publicity that occurred.

But we informed CSIRO about what was happening. They made a series of announcements to newspapers to offset any damage that would occur with the publication of the *New Scientist* article. CSIRO's announcement created shock waves within the newspaper industry. The story appeared in our major Australian newspapers. It was picked up by Reuters and spread throughout the world.

CSIRO was concerned. [It] tried to contain the publicity and there were only certain people allowed to talk. I wasn't one of them, but that didn't stop me. I wasn't the official spokesperson, but I've got academic freedom and I'm happy to be open about this. I think the worst thing we can do as scientists is try to hide what we are doing.

Selgelid & Weir: Why is it important to you as a scientist to speak instead of keeping quiet?

Ramshaw: The public are already suspicious of scientists. If we try to hide what we are doing, it just leads to more suspicion. There's no problem about telling the public about what we can do with mousepox.

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I think it's an issue that they should be aware of and they should be aware that genetic engineering is moving at such a fast pace and that there are lots of issues that need to be addressed by non-scientists. We are not the sole god of what we can do and where we can go. We need lots of inputs; and the more open we are, the more respect we'll get from the public.

> **"The bright ideas scientists sometimes come up with just go astray, basically as soon as you get into the practicalities"**

Selgelid & Weir: You've spoken out recently about some experiments involving cowpox (Wright, 2004). What are your concerns about those experiments?

Ramshaw: There are elements within the US military research establishment that would like to take our mousepox finding further. Given what we've shown in the mouse, one wonders, "How general is this?" With regard to inserting the IL-4 gene into cowpox, the question is, why do it? We already knew that it would be more virulent. How super super-virulent do you want to get? I have heard talk that researchers would like to test the hypothesis that if you made a smallpox virus with this gene then it would be highly virulent. And they want to do it with monkeypox virus.

Selgelid & Weir: When did your mousepox paper become the focus of the media storm?

Jackson: When the *New Scientist* article came out, because it was a European publication, the interest was in Europe and Australia mainly. Because of what was happening with American politics at that time—something to do with the George W. Bush campaign—North America initially ignored it for a month or two. And then we went through a whole lot of media events in North America, and again it died down and it was almost forgotten about by the middle of that year. It wasn't until after 11 September 2001 and the anthrax letters in the USA that it was all picked up again. It then had a momentum of its own and it went on for years.

If it wasn't for the *New Scientist* article and September 11, our mousepox research would have been a blip; no one would have paid any attention to it. The reality is that we made a recombinant virus as a research tool. It was all done with appropriate approvals in contained conditions. Probably no more than 20 or 30 mice died during the course of these studies.

Selgelid & Weir: Did biosecurity concerns come up at any time during the publication process?

Jackson: No. The referees' reports said that this was a fairly mundane paper and they were dubious whether they should publish it or not. To be honest, we had merely shown a more extreme example of what had already been published. The only interesting part of that paper was the fact that the virus was lethal to vaccinated mice. We still don't know why; that's never been studied. Ian Ramshaw has done a little bit of work on this. But aside from that no one's ever really looked at it.

Selgelid & Weir: Have you been involved with any other dual-use experiments?

Jackson: We did another study later with a PhD student that showed that IL-4 altered mousepox is resistant to treatment with an antiviral agent called cidofovir (Robbins *et al*, 2005), which is a chosen antiviral agent for smallpox. That paper has been totally ignored.

Ramshaw: In another experiment we found that cidofovir did not influence our super mousepox virus with the IL-4. So it would appear that this virus is not only immune to vaccination, but would also not be readily treatable with the current drugs that we have for such viruses. This was published. We notified the journal that these were dual-use issues. We told them in the letter of submission, and the paper was published without issue.

Selgelid & Weir: And the reviewers didn't say anything on this occasion either?

Ramshaw: The reviewers didn't say anything about dual use. The reviewers reviewed the article scientifically. We countered any scientific concerns they had and the article was published.

Selgelid & Weir: How dangerous are potential misuses of the mousepox study compared to other dual-use science that routinely gets published? It is striking that this mousepox research has been right at the centre of so much debate about dual-use research.

Jackson: I'm sure if you went back through the literature you could find multiple dual-use studies that have the potential for being misused. I think that if we had stuck to the more technical language of 'ectromelia virus' and avoided the use of 'mousepox', then this may not have gotten so much attention because of the association with smallpox.

> **"I think there probably needs to be some sort of regulation, but I don't think that suppressing scientific research is the way to protect our society"**

Selgelid & Weir: In addition to the media attention, there has been a policy debate with regard to dual-use research. What are your views about governmental regulation and control of science based on security concerns?

Jackson: I think there probably needs to be some sort of regulation, but I don't think that suppressing scientific research is the way to protect our society. I think the more that is out in the open, the more people can think about what is going on and try to develop countermeasures. I don't agree with scientific censorship.

Ramshaw: Anything to do with genetic engineering is controlled effectively by committees that look at gene regulation. The problem is that if the experiments don't involve human pathogens or human susceptibility, then they will let everything pass. If we put our mousepox experiment through now, it would pass. The problem is that there is a susceptible population out in the wild. If that virus or other altered viruses had been accidentally released, they might establish a genetically engineered virus in the wild population. If you are making a virus and it happens to affect cattle, you can control that because you know where the cattle are and you can kill them. But releasing a virus into an area where there are susceptible animals that you can't bring back or control raises concerns that are never addressed by the government or gene regulatory authority.

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That should be a big red light to government or organizations or committees who deal with this.

> "Most people wouldn't know a dual-use issue if it was in front of them"

Selgelid & Weir: Are there any experiments that are possible to do but that you think shouldn't be done?

Jackson: Our work was totally harmless, because it was a mouse-specific virus. In addition, mouse IL-4 and the human IL-4 receptor are not compatible. It might affect a few other rodents but it is not going to cross over to primates. Looking at primate IL-4s would be a different matter because the virus would be able to replicate in primates. I wouldn't go anywhere near that.

Ramshaw: We made a virus with another molecule that behaves in many ways like IL-4. Instead of killing the animals quickly, it kills them slowly. It's a progressive, long-term poxvirus that the animals can't resolve. Other than that we haven't touched it. We've learnt our lesson and don't want to investigate this any more because what we might find out we may not want to know, simply because the value that we get out of further research on this isn't worth the possible or probable dual-use issues.

Selgelid & Weir: Would you publish results of studies like these?

Jackson: I don't know why you'd do those experiments in the first place. We already have a host-adapted virus with IL-4, in a host for which we have a reasonable understanding of the immune system. I can't understand what would be the application of such research.

Selgelid & Weir: Might there be biodefence motivations for doing research like this?

Jackson: You would have to ask a biological weapons expert. When you start working with things that can work in humans you are getting into very dangerous territory, unless there is a real biological imperative for doing the research. If there was a natural disease, which was infecting humans, then I can understand it. But you are never going to be able to do the research on humans anyway, so why do it?

Ramshaw: [Biodefence is] an excuse to work in these areas. What is defensive and what is offensive are often indistinguishable. So I personally believe that there should not be research in areas that look at increasing virulence of human pathogens. There's no point.

Selgelid & Weir: Do you think there is a place for classified research, if we are talking about bio-defence, for example?

Jackson: I think doing that sort of research is going a little bit too far—this is my own personal opinion. Although the justification is for defensive purposes, you would be developing systems that don't naturally exist. We can do enough with animal models to understand basic virology without stepping over to human or primate research. The only reason I can see justified to do primate work would be if there was a natural disease, or emerging diseases, affecting humans.

Ramshaw: One of the problems that most researchers have is that we don't know what the threats are. If you talk to a security analyst from government/defence they'll say "There are states that are doing this and there are individuals who are doing that." I don't know whether that's true or not. Therefore, I can't judge whether governments are justified in undertaking classified research against these "threats". I'd be reluctant to criticize governments if they are looking at ways of protecting against serious dangers, because I don't have the knowledge. I doubt there is much of a threat, but if there is a threat and they have knowledge that I don't have, then they might be justified in undertaking classified experiments to see if they can counter that threat.

Selgelid & Weir: I suppose you'd say the same thing about censorship?

Ramshaw: If the government prevented a researcher from publishing something, there would be no reason why the government could not, in confidence, tell the researcher about the situation the decision was based upon. The researcher may not accept the explanation but at least he would be provided with one. I just don't think the situation will arise. But if it did, hypothetically, the government should say to the researcher, "Here's a confidentiality agreement. Sign it and we'll tell you what the threat is. And if you are satisfied, fine, and if not, you can't tell anyone else what we've told you." Unless you're crazy—and I admit there are plenty of crazy researchers out there—you'll accept their decision if it is based on sound judgment. But I can't imagine a situation or a discovery that should not be published, including our mousepox study.

> "Forget about what we've done: taking viruses, making them more virulent. In the future, people are just going to make their own"

Selgelid & Weir: Why should it have been published?

Ramshaw: Anything scientifically interesting should be published. The IL-4 was interesting because it showed you how the immune system is controlled. Scientifically, it's an important result. It should also have been published to bring attention to the issues of what genetic engineering can do. I don't believe there are experiments that are aiming to increase the virulence of viruses or anything like that directly. Suppose that someone identifies a virulence factor of smallpox, thus revealing what makes the virus do what it does. That should be published.

There are many experiments that raise dual-use issues and unless you are—like me now—looking for them, you don't recognize them. Most people wouldn't know a dual-use issue if it was in front of them. We know that the myxoma virus only affects rabbits. We know why it doesn't infect humans. So we now know how to convert that virus into one that infects humans. The relevant studies are published, and there are very important scientific results showing why these viruses only affect rabbits and not humans. Studies like those are being published all the time and probably not even being recognized as a dual-use issue.

Selgelid & Weir: If there's a scientifically important dual-use finding that is, all things considered, worth publishing, do you think the dual-use issues should be flagged?

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Ramshaw: There is no question about dual-use flagging. I think that is a sensible way of going about it.

Selgelid & Weir: Flagging dual-use issues during review processes is one thing, but do you think they should be flagged in the actual publication?

Ramshaw: Why flag it in the publication? That's just flagging it for individuals who might use it. If *New Scientist* had not that day come across to talk to us, there wouldn't have been any controversy about our mousepox paper. So it's the public flagging of the issue that created the concern.

Selgelid & Weir: Do you think synthetic biology poses a new challenge for security concerns?

Jackson: The research that we were doing used technology that has been around for probably 30 years. People are now synthesizing whole bacterial genomes, which are 10–100 times the size of any virus that we know of. We now have the technology to resynthesize smallpox if someone wants to. There are other viral genomes [that] are highly infective from the nucleic acid itself. You can easily produce a herpes virus from the DNA. Where do you draw the line? Should we take all the pathogens out of the gene bank and hope no one notices?

Selgelid & Weir: Are there distinctive dangers associated with advances in synthetic biology?

Jackson: If you are talking about synthesizing whole genomes on chips, that capability is currently restricted to a small number of laboratories worldwide. This technology is very expensive. It's not something someone can do in their backyard.

Selgelid & Weir: Do you think that in the not-too-distant future the technology for synthesizing genomes will become as accessible as desktop synthesizers are at present?

Jackson: When I started my career, DNA sequencing was something only the richest labs did, using cumbersome, slow technologies. While I was doing my PhD the technology became accessible to general laboratories. Now, in the last 10 years, it's become an automated process. When DNA sequencing first started you'd get half a dozen bases. Then you got up to 200 bases when I was doing my PhD. Now you can get 1,000 bases these days. And they are perfect—and it's not sitting there looking at bands on gels and asking, "Is that real or false?"

Of course there are going to be further advances. Maybe in 20 years' time you will be able to type out your sequence, send it off, and have your bacteria synthesized and away you go. It would be a great way of making mutations in whole genomes.

> **"We haven't a clue of what's coming around the corner and that should influence our thinking about genetic engineering"**

Selgelid & Weir: Do you think there are major security implications given the rapid development of synthesis technology?

Jackson: You are really not asking the right person. All I can say is that you can look back in history and the moratoriums on genetic engineering back in the 1970s. It was all really a waste of time. All it did was hinder science. Of course, there are going to be advances in technology. People want to use it. How governments regulate it is up to them, not me.

Selgelid & Weir: What do you think about synthetic genomics?

Ramshaw: My major concern now is not necessarily the use of recombinant viruses and the technologies involved. It's in synthetic genomics: the capacity to synthesize whatever one wants without acquiring a virus. You don't need to acquire Ebola virus. You don't need to acquire foot and mouth disease virus. You can just make them in the laboratory, and it's going to get simpler and simpler. Forget about what we've done: taking viruses, making them more virulent. In the future, people are just going to make their own. The Australian government recently announced restrictions on the use of a variety of infectious agents. You can restrict access to those agents, but there's no restriction on the DNA. With this DNA I could make foot and mouth in the laboratory. It will become a virus if I inject it into a pig or sheep.

Selgelid & Weir: Does synthetic genomics have distinctive dangers in contrast to recombinant genetic engineering?

Ramshaw: Recombinant DNA technology needed more sophisticated techniques in the laboratory. In other words, we could make it but someone in Afghanistan couldn't. Synthetic genomics has made things so much simpler. An undergraduate student with access to synthetic genomics machinery—which everyone has access to via the internet—can make what they want. The smaller it is, the easier it is. But synthesis of even big viruses is now feasible, and it was even before Craig Venter announced that he had made a chromosome with a genome of 500,000 base pairs (Gibson *et al*, 2008). That's as big as any of the biggest viruses including smallpox, which is 250,000. But Ebola or polio or foot and mouth are roughly 10,000, which is in the realms of most synthetic companies. You can send an e-mail stipulating the sequence you want synthesized. The DNA sequence comes back. You put it in a small plasmid. You take that plasmid and if it is a human pathogen, you inject it into a human and it makes the virus.

Selgelid & Weir: So the genome is sufficient?

Ramshaw: With smallpox it might be a little bit more difficult. But with simple viruses, yes, the genome is sufficient. So what I'm saying is that synthetic genomics has overtaken the need for sophisticated recombinant viral or bacterial technology. That's the main thing to be concerned about in the future.

Selgelid & Weir: You've flagged distinctive dangers of synthetic genomics. Do you think there are distinctive or particular benefits to this area of science and technology?

Ramshaw: Yes, the benefits far outweigh the concerns. What previously would have taken two years to do is now done in two weeks. That's terribly important for researchers. You couldn't ban or control it. You just need to ensure there are regulations. This is an international affair that an institution such as the WHO [World Health Organization] should get onto. There's a whole raft of measures that might be used to assure that DNA imports/exports are

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innocuous, that one is not bringing in foot and mouth disease in or anything like that. We need some form of a regulatory system.

I often think about [Donald] Rumsfeld's statement about the "unknown unknowns". There is so much out there that we don't know. We might think we know there is an unknown that we are getting at, but there are unknown unknowns. We haven't a clue of what's coming around the corner and that should influence our thinking about genetic engineering. We've been fairly complacent up to now because nothing terrible has happened. But it's like a pyramid of sand: you keep putting sand on and you get a little fall off here and a little fall off there but one more grain of sand and the whole thing comes tumbling down. The big catastrophes are far, far less frequent than the minor incidents, but when they occur, we should be concerned. That's my philosophical comment.

Selgelid & Weir: Based on your personal experience, do you have any advice for other scientists?

Jackson: Back when we did this work it was a different world. Science was just science. I didn't even know the name Osama bin Laden. That paper in 2001 was published purely as a scientific paper. If it hadn't been for the result regarding fatality to immune mice I don't think it would have even gotten published.

When we did the research and wanted to publish it there was really no form of [biosecurity] review. There was no one to ask: "Shall we publish this or shouldn't we publish this?" The mechanisms just weren't in place, as we found out when we asked the government about this and no flags were raised. I don't think that would happen now.

Selgelid & Weir: What is the focus of your present research?

Jackson: I've been unemployed since 2005. In mid-2005 the unit I was working with was closed down. A few people were transferred to another division. There's no more research in biological control in Australia. From now on I think people will be very careful about doing controversial research. They'll do safe research because their careers are going to depend on it. In my case it was publish and perish. I just happened to be in the wrong place in the wrong time.

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