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'Challenges and opportunities – the ongoing evolution of medical research'

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The last major restructuring of the science system was a generation ago, and that was primarily grounded in the then fashionable public sector reforms. Twenty years ago it was by no means accepted that public expenditure on science was an investment rather than simply being largely a cost. What is going on now is qualitatively different. Government has accepted that science is a core pillar of its economic growth and productivity agenda and this is largely not a matter of partisan debate.

Science now gets strongly supportive comment in the media. And the business sector is starting to respond – we are seeing an increased willingness, and indeed a demand, by business to see a greater integration of science with other aspects of innovation. However there are people left stuck in the 1980s, not seeing science as an essential part of the way ahead, and so we cannot be complacent.

The challenge is now to find the best path which links science and innovation to our national aspirations of economic growth, social development and environmental protection. An analysis of other small western advanced economies demonstrates a close relationship between a greater investment in science by both the public and private sectors and enhanced economic growth and productivity enhancement.

But equally the nature of science is changing and this creates challenges for both the scientist and the policy maker. Science is less bound by traditional disciplinary boundaries. The science and innovation eco-systems are now much more intertwined. Science is dealing with levels of complexities and non-linear systems not considered previously. The bioinformatics explosion, the need to deal with large databases, the use of complex models and the realisation that non-coding RNAs and RNA editing create new layers of biological complexity are obvious examples of this. This is leading to dramatically new paradigms of doing research. Larger and interdisciplinary research teams, and increasing reliance on rapidly changing and expensive technologies, are an increasingly normative part of science that advances a nation's interests.

But the questions that science is addressing also create real challenges for society – the conflation of the biological with the physical will lead to new forms of neural implants, stem cell biology, tissue engineering and regenerative medicine may well create impossible demands on the health sector, predictive biology based on genomics and particularly epigenomics will become more robust: these are all examples of where rapidly emerging science could well be in conflict with societal values. We have also grossly underestimated the impact of technological developments such as the internet on our social structure, on how people get information and relate to each other and on our mental health. And how do

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people distinguish between relatively reliable information, less reliable information and frankly misleading information on the net? These issues are real and change the nature of the relationship between the scientist and the community she or he lives in. These matters will get more intense over coming decades, and the need for scientists, particularly medical scientists, to be clear about their role in maintaining the social contract with the community will become greater. We have already seen this threatened and even broken in the confusion of issues in the climate change arena and the GMO debate.

A related issue is who owns the data when the research is funded by the State. This was highlighted in the Muir Russell report that followed the so-called “Climategate” affair a year ago. Particularly in medical research this is a growing issue: there have been examples of redundant sample collection, redundant surveys and data collection and failure to share: this issue of the scientific ego versus community interest is real and needs to be addressed. The State does not primarily fund medical research to support the ego of investigators – it does so to have a healthy and vibrant society and that requires a collaborative approach. It is worrisome that too many New Zealand medical researchers feel more comfortable collaborating outside New Zealand rather than within it and this is a concern that reflects a number of institutionalised attitudes. One suspects incentives will emerge that will encourage a shift towards a more collaborative approach.

Perhaps the biggest shift however is that about how the public and private sector science systems should interact. When I trained nearly 4 decades ago, it was considered to be crossing to the dark side for a scientist to go from a university to the private sector. In many countries that has changed – there is now an almost seamless interchange of good scientists from academia to business, and from business to academia. That an individual might spend formative years in the private sector then return to academic science is no longer seen as unusual. An individual is less likely to be penalized for doing so but there are still issues. We do need to work out how to give credit for time spent working outside the traditional model – equally we do need to protect and acknowledge the truly outstanding academics. We need a sharper focus on what defines value in a scientific career.

Sir Paul Nurse, incoming president of the Royal Society of London, Nobel laureate in Medicine or Physiology, and certainly a defender of and advocate for basic science, gave a speech in Kyoto a month ago at the Science Technology and Society Policy Forum in which he pointed out that one of the biggest challenges to the future of science was what he termed permeability. By permeability he was referring to the need for scientists to understand that the future lay in connecting science, business and government, not in creating walls around the academic enterprise.

While we need to be careful to protect intellectual freedom and basic science it can be done in a much more permeable way. The inwardly focused scientist will become much rarer. Early stage science need not be entirely dislocated from the applied environment. Indeed it is noteworthy that many of our most distinguished discovery scientists have also been those who have been outward looking.

Sadly, I worry that there is still arrogance within some components of university-based research that has the potential to penalise a person who is more applied in their efforts and certainly there is evidence that time spent in the private sector can disadvantage them in the peer review, grant and promotion systems. Over time this will change, as it has elsewhere.

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Change will happen because governments around the world are changing their expectations of the public science system. Governments are prepared to invest more in science only where either they can benefit directly or where there is private sector uptake of that science and scientists, and the university system in general must encourage and accept greater rotation of individuals, whether on a full-time or a part-time basis, to industry, to other public research organisations and to government. There are small steps already in this direction. I suspect that government in New Zealand will have to introduce incentives to assist this to happen. Certainly the division between Crown Research Institutes and universities is rapidly closing as a result of the reforms of the CRI sector in the past year.

It is worth remembering that the basic nature of our current science system was established fifty years ago and times have changed since then. In the 1970s and 1980s, academic science was generally seen as largely the bailiwick of individuals and small groups. Most public sector science was driven by curiosity, whereas most private sector research was driven by strategy. Individual investigator-led research is still prized but increasingly we are seeing aggregations into larger groups with strategic vision underpinning the research plan – the Centres of Research Excellence are examples of this being done successfully in New Zealand. Governments are expecting public science to support, feed into and promote private sector science. In some countries such as Singapore this is now specifically incentivised. The drivers beneath this trend are obvious, the implications are complex, it has changed the culture of science for many academics and for some, this is difficult to accept – but I suspect this trend is inevitable.

So where do I think medical science will go?

Firstly it is clear that New Zealand with only 4 million people cannot pretend to be world class and have critical mass in every area of science, let alone medical science. We cannot match the efforts of the Medical Research Council or the National Institutes of Health. I see little point in “me-too” or second rate science and we need to get more analytical of our efforts. The argument that we have to have a unique New Zealand perspective is over-used – we need to be more careful as to when it is justified and obviously there are cases when it is.

How will more focus be achieved? There will have to be a mix of top down and bottom up mechanisms because much medical science has its application well removed from its initial domain. I do not think business-driven assessment is competent to assess discovery or early stage science, and scientific peer review must be strengthened not weakened. However, questions of pathways to impact will become more important, particularly beyond the initial stages of research.

But to do impactful science will require critical mass and multiple disciplines and so some form of selection based on strategy, skill mix and impact will be needed. Will it be in the form of more CoRE-like structures or by some other mechanism? How will a balance be maintained between bottom up and impact-led definition of need? Even if there is a move to greater critical mass there is a need to provide for individual investigator-led research to allow new players to be identified and supported. These are not easy issues in a small science system.

Beyond that, New Zealand has real disadvantages in our lack of an internal market, geographical position and deficient capital markets. We have seen how the latter has led to failure in a number of biotech and biopharma developments where many of the failures were more about inappropriate governance, management and strategy and unrealistically

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low capital raising than about science *per se*. We have to learn from these examples and think of new models of doing science-based business – innovation is not just about science, it is also about process and management too. How will we make our private sector more science intensive? It is more than government incentives – it is about getting a more innovative and entrepreneurial business model that recognises the real added and rather weightless value of knowledge.

Let me give but one example. Currently we export food either as a commodity or because of added value based on consumer perceptions – venison would be such an example. But where will the food industry in Asia be in 20 years time? Part of it will be volume based and we cannot compete there. But an increasing element will be based on the growing demand for foods with proven value in health protection and in particular in dealing with the explosion of non-communicable disease. There will be half a billion people in Asia with diabetes within two decades and not all can be managed by drugs – foods as either preventatives or therapeutics will become important. New Zealand is extraordinarily well placed to do the research that would lead to such products and they are products that will have real added value.

Our future is in Asia, yet most of our international medical science has been focused on Europe and the US. Asia values our capacities to generate knowledge. Asia has scale, capital and markets and deserves our focus. Our business and academia have to look for new models that will allow the added value of science to be exported and returns made to the New Zealand economy. I suspect this will lead to New Zealand science not just building domestic multidisciplinary teams but also international teams.

But not all medical science is directly aimed at the productive economy. We must not forget the value of high quality defensive science. The events of recent weeks show how important bio-protection science is to our economy. Some medical research fits in this category. It is worth reflecting on how we ensure adequate capabilities in such defensive science.

One of my key roles as Chief Science Advisor is to work to improve the use of evidence in policy formation. Policy made in the absence of evidence is of course based solely on dogma. Policy made on bad evidence is no better than policy made on no evidence. So the evidence has to be good evidence, and that requires quality research in all relevant domains. Now I emphasise that evidence alone does not make policy – rather, it informs policy formation. Scientific advisers have to accept that governments can make policy decisions in the absence of evidence or even contrary to evidence. In a democracy, governments cannot go beyond the desire of the population and there are fiscal, ideological and political issues to consider.

Let me focus for a moment on social science which is one of the core disciplines of the health sciences but one not represented at this meeting. This is concerning as the conflation of the social and biological sciences is an increasingly important component of medical research worldwide. The issue of silos again emerges. We think that educational research is only about education, health research is only about health, and social welfare is only about social welfare, yet of course all of these and other domains interact. For example, policies about early childhood education are based on evidence within the educational domain. Yet there is a large body of research showing that early childhood education of the right type has in later life, major influences on health, particularly mental health, major influences on the risk of criminality, and major influences on the risks of anti-social behaviours. Some of these links have a biological basis on epigenetic processes.

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Equally, there is a large body of evidence that shows that progress through adolescence is influenced by all sorts of experiences earlier in life, and whether one looks at the outcome of adolescence in terms of teenage pregnancy, suicide attempts, binge drinking, drug abuse, or inappropriate sexual behaviour, one comes to the conclusion that many different and apparently peripheral initiatives, for example in the areas of early childhood education and developing eusocial neighbourhoods, can have important influences in improving the transition to adulthood. Again biological mechanisms have been implicated.

Yet we do not have the adequate capacity or the infrastructure to optimally integrate research activity across these domains. Indeed, we have rather poor social science research capacity and much of our public health research, while excellent, is seen in the very narrow domain of admittedly important medical issues, such as smoking or obesity and remains too isolated from the biomedical. One of the challenges is how to improve our ability to integrate research across multiple domains.

Disease-focused research now requires much more sophistication. Three modalities alone: the expansion of bioinformatics, epigenetics and genomics, the use of modern imaging modalities, and analysis of the gut microbiome are changing the way we will address chronic disease cause, target identification and intervention. But each requires enormous data-rich approaches, each requires major infrastructure, each requires multiple talents. A single experiment can produce millions of bits of data. Biology has become digital rather than analogue. Thus a new style of medical research is emerging – based on multidisciplinary approaches and operating not just in one lab but in multiple labs in multiple countries. Large consortia are forming.

Let me expand a bit on these comments by one example. Obesity will not be addressed by a simple public health approach any more than it will be addressed by a pure genetic or medical approach. We know two things about obesity – that not everyone has the same sensitivity to an obesogenic environment and that we all now live in such an environment. Those differences in sensitivity are in part genetic and in part developmental or epigenetic. By some estimates a significant component of the risk of obesity is based in these causes of individual variation. But what is also clear from the study of the biology of obesity is that these highly susceptible individuals are hard wired so that successful diet and exercise is for them very difficult – a simple public health approach will not work. Tackling obesity requires a multi-dimensional approach based on a mix of public health measures and attention to individual differences rather than simply blaming sloth and gluttony. We have yet to learn how to exploit this emerging knowledge to help such individuals. For many the concept of blame is misleading – their biology is different.

The challenge for medical research is how to one hand break the challenge down into manageable bits but on the other to ensure the multilevel systems approach. Systems biology is now at the crux of medical research – layers of complex biochemistry mixed with enormous data bases and the science of bioinformatics – biology is becoming digital.

As these changes in the way medical research is being conducted and funded occurs, this creates a real challenge for New Zealand. We have tended to fund individuals and small groups, we have tended to work in independent groups rather than consortia and focus on small questions – some outstanding work has and continues to be done but the potential for impact has been variable. Medical research is generally done in the highly contestable and institutionally focused environment of universities – breaking down these boundaries is not easy. New Zealand needs to work out how it will take its research to scale. That involves real

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and virtual critical masses and better forms of collaboration across institutions – the Centres of Research Excellence represent an initial step in that direction. The grand challenge approach used in Canada and elsewhere offers an alternate and exciting approach. The need to form stable international partnerships of excellence is also apparent, and more effective forms of technology transfer and technology exploitation are required.

A multiplicity of agencies are involved: beyond the HRC, other funders include the FRST, the Marsden and Lottery Health. Additionally, the Ministry of Health, and to some extent other social Ministries, fund extensive intramural and extramural research of unknown quality; some DHBs do the same. Despite this multiplicity of agencies, there no overall strategy underpinning this investment; consequently, gaps have emerged and this is worrying me. Much of this research is conducted in either universities or hospitals, but there is a rapidly expanding private sector component mainly by way of medical technology and software and a smattering of biotechnology firms in diagnostics and therapeutics. Indeed it is generally thought that medtech may be the sector where early productivity gains are most likely.

One of the problems we have is that we use a rather monovalent approach to assessing and funding medical and health research when in reality it is quite disparate from operational research to fundamental biology and bioengineering. An evaluation of the competitive funding system is likely in the next 12 months. How the Health Research Council fits within that system, and which aspects of the multiple types of medical research sit within the HRC, needs open discussion.

Before I finish there are two areas I want to particularly focus upon.

Biomedical research including bioengineering not only is at the base of much innovation in medical technology and biotechnology, where I believe wehave an enormous potential for productivity enhancement, but it also plays an important role in agricultural and other components of New Zealand's biological economy. It is an area that not so much delivers health benefits directly but rather fuels private sector opportunities. The Singaporean experience highlights the importance of biomedical research to attracting pharmaceutical and nutritional multinationals. It is of note that both Auckland and Otago Universities achieve their high international rankings because of the heavy influence of the quality of their biomedical research. Clinical physiology and pathophysiology should be the centre piece of a domestic life sciences industry strategy, particularly if it is linked to biomedical expertise, yet it is in poor shape – it has been run down by funding decisions over the past decade. The natural contextual advantages for New Zealand include good biomedical research, good clinical medicine and no-fault insurance.

A major area of potential activity remains to be exploited, which is innovative activity within the health sector itself. The UK experience has demonstrated that hospital systems contain individuals with many exploitable ideas, and "NHS Innovations" is an example of the hospital system developing a full exploitation chain that takes these ideas to business – especially in healthcare software and medical technologies. Based on the London experience, a small well developed team might identify and deliver to the market between 20 and 30 readily exploitable ideas from the system per year.

Health software and devices represent very quick routes to market compared to biologicals, and our discussions with Singapore indicate an enthusiasm for associations to help to go to scale in this domain. However, the goal of attracting major pharmaceutical, biotechnology

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and nutrition R&D back to New Zealand, either at the discovery or early clinical development stage, should not be ignored.

So to conclude: medical researchers need to be asking four questions of what they do, although the relative weighting will be different depending on the context.

- Is it really good and innovative research? Second rate research is really a waste of money.
- What new knowledge will the world really gain from this research?
- Can this new knowledge advance the public good?
- What are the exploitable opportunities that might arise from this research?

Given our small size and the need to focus, these questions must be the basis of moving ahead.

The world of science and innovation is changing – for New Zealand medical research to thrive it needs to be an integral part of this changed scene. This is not easy. How should we set priorities, how will we integrate what will have to be a mix of top-down and bottom-up approaches and across disciplines, does short-term funding allow this kind of research, how do we ensure the innovative rather than the conservative gets funded, how do we ensure transfer to impact is rapid via policy, via health care and via economic exploitation. These are non-trivial questions, but we need to find answers.

Thank you.

ENDS.

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