The Foundation for Science and Technology Debate on the Future Priorities for Medical Research

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I was asked to speak tonight about the future of the MRC over the next 25 or even 100 years. I make no claims to being a futurologist. If I could predict the future I would have probably given up science years ago and taken up betting on the horses, but I will try my best. Before starting on my thoughts for the future though, I want to affirm that the MRC is one of Britain's crown jewels, an important part of Britain's intellectual infrastructure, one of our national treasures. I can say this objectively, having not been directly supported by the MRC for at least a quarter of a century.

Let me begin by asking will there still be a need for the MRC for the next 100 years? The answer to this question is yes. Disease remains a major scourge for humankind and will continue to be so in the coming century. Science gives us the means to eradicate and control disease, and the opportunities that science will provide over the coming decades to achieve these objectives will be many.

One hundred years ago when the MRC was founded in 1913, biomedical science was in its infancy. For example, genetics and biochemistry were barely invented, and there was no conception of molecular biology, structural biology or genomics, all of which today contribute greatly to our understanding of biomedicine. Yet despite these limited beginnings, the advances of the last century have resulted in extraordinary improvements in life span and health care. So just imagine what is likely to be achieved in the next 100 years, given our present knowledge and the potential that we now have to dramatically improve that knowledge. It is important also to recognise that this applies not only to improving human health but also to providing opportunities in the UK for the creation of wealth.

One of the reasons the MRC has been so successful is that it has always recognised the importance of discovery science, that better understanding of how living organisms work is fundamental to controlling disease and to improving human health. In this talk I will focus on science, giving my view of some of the scientific problems where significant progress can be expected over the coming decades. When appropriate I will comment on their relevance for tackling human disease, although I expect that Keith Peters will deal more comprehensively with clinical outcomes.

One major research objective will be better understanding of the cell. The cell is the basic unit of life, and as the nineteenth century founder of pathology, Rudolf Virchow argued, it is the pathological behaviours of cells that form the base of many diseases. There are now real opportunities to advance our knowledge of how cells work, using a combination of techniques and approaches, including advanced microscopic visualisation of living cells, biochemistry and genetics. Because the cell is the simplest entity exhibiting the characteristics of life, many of the principles underlying how life works are likely to be found through study of the cell. A primary objective will be to combine the descriptions of molecular phenomena underlying cellular behaviour into a complete description of the cell and its operations. This will require an approach whereby the cell is considered as a complex system made up of molecular components that generate higher level biological functions. However, it is important that we are not satisfied solely with descriptions of molecular phenomena. Our real objective is to build on these descriptions to establish improved understanding.

What will be essential here is the approach that was dominant during the early years of molecular biology, one emphasised at the time by Sydney Brenner, that is the importance of information and the management of information. This means understanding how information is gathered, stored and used to generate purposeful teleonomic outcomes. The lessons learnt about information management in living systems obtained from the study of cells, will apply across tissues, organs and organisms as well. In my view, this approach will be informed by applying concepts developed by evolutionary and ecological scientists who have long studied complex living systems.

One major problem with the systems approach to cells is knowing what values of molecular parameters should be fed into subsequent analyses. For example, present approaches generally try to estimate the rate constants and concentrations that operate within the cell but these are difficult to accurately determine for all the parameters that will be necessary. A possible solution will be to reduce the complexity of descriptions to black boxes, focussing on inputs and outputs that can be measured, rather than trying to describe all the details of what goes on within those boxes.

Understanding cells will require work in a range of organisms including those that are single celled organisms such as bacteria and the yeasts, because the problems will be easier to solve with these simpler organisms than with Metazoan cells. But ultimately we need to understand human cells if we are to work out the basis of human disease. A good example is cancer. Cancer occurs as a consequence of genetic damage in cells which leads to uncontrolled cell division, and to cell shape and motility changes that result in the spread of cells throughout the body. These disease pathologies can only be understood and better managed through improved knowledge of how human cells work.

The poet Alexander Pope is sometimes misunderstood when his line, "The proper study of mankind is Man", is quoted in support of the importance of researching human beings rather than the rest of the living kingdom. In fact Pope was attempting to redirect human endeavour away from God, as is clear in the proceeding line, "Know then thyself, presume not God to scan". Nevertheless, it is right to focus biomedical research on the study of humans. In coming decades there will be a continuing need for the study of model living organisms especially mice, but increasingly we will need to take all opportunities to investigate human beings. I am not speaking here only of translational work, that is research aimed at achieving a particular diagnostic or therapeutic outcome, but also of research into human biology.

There are a number of promising possibilities for human biology in the future. First, is human genomics, that is exploiting knowledge of the sequence of the genome and its variation within human populations. There have been criticisms of those who advocated the sequencing of the human genome for promising too much too quickly. This is unfair. Although there were some who over promised the rapidity of applications, knowledge of the human genome sequence will be critical for future advances. The metaphor I use is that the human genome sequence is like having the list of the characters in a play; it is essential for the play to be written but is not sufficient. The task now is to use the cast list, that is the sequence, to help write the text of the play, that is understand how humans work. Identifying the genome variations within populations and correlating them with phenotypic variations, including predisposition to disease, helps inform the genetic contribution to disease. Sometimes this will be relatively simple, more often it will be complex, because many genetic differences are likely to contribute to disease onset. But as more data is gathered together over the coming decades, then these complexities will be gradually unravelled.

What will be especially powerful is to combine this deep knowledge of genetics with investigations of the effects of the environment, including variations in an individual's microbiome, on human health and disease. This is essentially the nature-nurture debate, which should not be seen as a conflict because it is obvious that both are important.

Rather they should be combined in major epidemiological studies to improve our power of prediction beyond what is possible if only genetics or environmental differences are examined. This is a big data issue, which the UK is well poised to tackle with its strengths in genomics and with the NHS, a unitary health care system that if effectively used has great potential for this type of research. Because the NHS is seen to be a service for the people rather than as a profit based system, I believe many of the public will be happy to contribute their own personal data for the ultimate public good. This approach will contribute to a more precise personalised medicine, tailoring treatment to the individual, based not only on their genome sequences, but on other physiological and pathological markers as well. Genome sequencing will also be illuminating about the pathways that may be implicated in disease predisposition, opening up new approaches to diagnosis and therapy. Because the cost of sequencing is dropping, it is not far-fetched to expect that soon everyone at birth will have their genome sequenced, although the ethical implications that this gives rise to must be handled with care.

A second opportunity in human biology, is to promote new approaches to human physiology using sophisticated imaging modalities. Imaging used in clinical care can also be employed for studies of human physiology. It needs to be combined with chemistry and radiochemistry to provide new markers that can monitor physiological states throughout the body. A more fanciful development might be to generate miniature micro-robots that can travel freely around the body, which are equipped with micro-sensors to assay their local environments. Perhaps they could also be equipped with microscopic worms that burrow into solid tissue to monitor more remote regions of the body in a relatively non-invasive manner. Given that these micro-robots would be controlled from outside the body, they might be further developed for use in micro surgery. More multi-disciplinary and inter-disciplinary approaches will be required to tackle such initiatives.

A third opportunity will be to use human stem cells combined with 3D tissue scaffolds to create prototypic human organs on the bench, not just for organ replacement as is often proposed, but also for physiological studies. Studies of such bench top 'human organs' would complement animal models, helping to better understand normal human physiology as well as providing possibilities for the treatment of degenerative disease. Genetic manipulation of the cells used to generate these organs will allow disease states to be more readily modelled, as well as allowing sensing systems to be built into cells to more precisely monitor cellular and tissue behaviours. These types of human studies will provide novel approaches to major diseases.

Understanding the brain is difficult. I think two contrasting approaches will be important in the coming decades. The first, given the complexity of the problem, is the use of simple model systems to study nervous systems, brains and behaviour, particularly invertebrate models such as the worm and the fly. The simple organisms can be studied whilst they perform behavioural acts in virtual environments, monitoring their brains and nervous systems in real time, correlating neuron activity at a fine level with sensory inputs and behavioural outputs. Another opportunity is the study of neural development using the transparent zebra fish embryo. Work on these simpler systems should help develop more general principles to underpin neuroscience and its application to mammalian systems including human beings. The second approach is to try and combine neuroscience studies of the human brain with studies of the mind. There is real promise here too but it is difficult and requires overcoming the cultural barriers between the often quite different scientists who are working on neuroscience and the mind.

Infectious disease continues to be a major problem, both in the developing world and in the UK too. New ways of combatting infectious agents are required, especially to deal with antibiotic resistance in bacteria. One promising approach will be the use of environmental or e-DNA. Only a rather small fraction of micro-organisms can be cultured easily in the laboratory, but their DNA can be extracted from natural sources

such as soil and then cloned and expressed in cultivatable micro-organisms. These can then be subsequently screened in the laboratory for antibiotic activity. The use of e-DNA should significantly widen the classes of antibiotics available.

These are my thoughts about some of the science that the MRC may be taking on in the coming decades.

Finally I want to consider how the MRC should operate in the future to be effective. It is an organisation which is Janus like, looking one way towards the clinic, and the other way towards the more basic biological and physical sciences. A stand-alone Research Council is best placed to achieve these dual relationships. As is the case now and has been generally in the past, the MRC needs to be led by a distinguished biomedical scientist. Someone who will provide scientific leadership and not just managerial competence. The MRC needs to put emphasis on the quality of the individual scientists that it supports and to ensure it employs a broad based approach, covering discovery research for long term progress, translational research for the medium term, and clinical research and trials for short term improvements in the management of disease.

Is there anything new the MRC should think about doing organisationally? I think it should consider using more public-private partnerships in clinical trials, working better both with the NHS and industry. The span of investigation in a clinical trial could be expanded beyond the focussed objective of a commercial company which generally has a specific translational application in mind, to include monitoring many more markers of human physiology. This information can be used to determine if the drugs or other interventions being tested may be relevant to other physiological systems or disease states beyond the focus of the company. This is a cultural change which emphasises major clinical trials as not simply a proof of principle, but as a research tool, a change that will require new practice and a shift in regulatory frameworks.

I end where I began by emphasising how important the MRC is as a valuable part of our intellectual infrastructure. Without question it will continue to make important scientific discoveries that will lead to great improvements in the human condition over the next century. But we need to recognise that the MRC and biomedical research in the UK face great competition from the rest of the world. This comes not only from scientifically developed nations such as the USA and Germany, who spend significantly more on science than we do in the UK, but also from nations such as China and India who are rapidly increasing their budgets and improving the quality of their research. This is something our political leaders need to take account of, not only over the next century, but right now in the next spending review.