The importance of integration

Author: Patrick Vallance[A]

DOI: 10.7861/clinmed.2023-23.6.harv

ABSTRACT

Introduction

William Harvey was a great scientific integrator and so I have no hesitation in choosing integration as the theme of my Oration. In his quest to understand the action of the heart and the distribution of the blood, Harvey used anatomy, physiology, mathematics, observation and experimentation. Perhaps the two most striking examples of the breadth of his thinking were the use of cold-blooded animals to enable him to observe the actions of the heart in slow motion, and his use of calculation to demonstrate that the sheer volume of blood leaving the heart would necessitate making nearly 500 pounds of blood a day if it was not circulating. His 1628 masterpiece integrated evidence from multiple sources and approaches and was compelling, but it shook accepted wisdom and took another 20 years to become widely accepted.

Harvey was at heart an experimentalist and he wanted medicine to be underpinned by science. In his bequest to the Royal College of Physicians he reminds the orator that physicians should be exhorted 'to search and Studdy out the secrett of Nature by way of Experiment' and he expresses the view that 'concord makes small things grow whilst discord brings the greatest ruin'. Some have seen his work as the origins of what is currently called 'systems biology'.[1]

Of course, the notion that integration of evidence is important is not a surprising one to the clinician; the taking of a history, physical examination and investigations must all be integrated to reach a diagnosis and devise a treatment plan. This often needs to take into account other diseases or pre-existing conditions that don't fit neatly into one organ system or discipline; integration is a daily activity for doctors. Nearly 100 years ago Sir Robert Hutchison in his Harveian Oration noted that 'specialism is inevitable; but though favourable to the accumulation of facts, it is bad for the philosophy of knowledge'.[2] So what is the role of integration today and why does it matter? I tackle this question using personal observations from my time in academia, industry and government.

A single layer of cells

Three hundred and fifty years after Harvey's *De motu cordis*, a 64-year-old pharmacologist called Robert Furchgott made a curious observation for which he was later awarded the Nobel Prize. He found that the aorta of a rabbit would relax in response to acetylcholine only if the innermost layer of cells of the blood vessel, the endothelium, remained intact.[3] If this endothelial layer was removed the aorta would either not respond, or in some cases appeared to contract. By a series of elegant experiments, Furchgott demonstrated that it was the release of a local hormone or autacoid from the endothelial cells in response to acetylcholine that relaxed the underlying smooth muscle cells. Initially called endothelium-derived relaxing factor, it was later identified as a simple inorganic compound, nitric oxide.[4,5] This field of research arose from the use of bioassay, a whole blood vessel strung up in an organ bath and examined for its ability to contract or relax. It was initially integrative rather than reductionist.

This was the observation that triggered my research career. I wanted to understand whether endothelial control of the muscle in blood vessels occurred in humans and what that might mean for physiology, pathophysiology and pharmacology. I was fortunate to have an enlightened, creative and supportive supervisor, to have contact with a colleague who had synthesised an inhibitor of nitric oxide synthase, and to have access to a technique that allowed me to measure the effects of nitric oxide blockade in the arterial and venous system in humans *in vivo*. Suffice to say that the experiments demonstrated that the continuous release of nitric oxide from endothelium is crucial to keep arterial vessels in a dilated state, maintain arterial blood flow and help keep blood pressure down.[6,7]

Myriad questions followed from these early experiments: what controlled the amount of nitric oxide produced, which diseases might be caused by or cause excess or lack of nitric oxide, could new therapies be designed, how conserved was this process through evolution, and many more. The subsequent decade for me was taken up with an attempt to answer some of these questions.[7] It meant moving from the two or three techniques that I had initially used to embrace chemistry, molecular biology, gene editing, animal studies, clinical trials, electronic health care records, structural biology, immunology and virology. I was not an expert in any of these disciplines and needed to work with colleagues who were, something that was made easier by working at University College London, a multi-faculty university brimming with experts. It was clear to me that if I was to answer the questions that I thought were important I could not become bound by a single technique or approach; attacking the question from multiple angles would be required. Integration was essential in order to address the questions.

Author: [A]chair, Natural History Museum, London, UK

Four big questions

Dabbling with chemistry to explore nitric oxide biology was exciting, but what would it take to make a medicine? I learnt the answer to this question when I moved from academia to industry. During the 11 years I spent in the pharmaceutical industry, I identified what I consider to be the four key stages in making a medicine. The first stage is to ask 'What are you going to target?' – which disease, which pathway and which molecular target. This stage of the process is being transformed by genomics[8] and the ability to identify causal pathways in disease, but even so it remains an inexact science and more often than not the target doesn't deliver what you had hoped. The second stage is to address the question 'What molecule/gene/cell are you going to pick as your candidate drug?' Once you have designed the molecule and selected it as your candidate drug, all the promise and heartbreak of your work are embedded in the physical structure and properties of the molecule you choose. If you get it wrong, you live with the consequences. A focus on molecule quality is essential. The same is true with a cell therapy or a gene therapy, where the exact gene construct or the precise cell chosen can be the difference between success and failure. The third key stage is to ask 'Can you demonstrate that the drug has the expected effect on the target in humans?' This is the stage of experimental medicine and usually requires intensive study of the drug in small numbers of volunteers. It is the stage that is often the natural home of the clinician scientist and involves defining the drug's potential, identifying how to measure its effects and determining in which patients it is likely to have the most benefit. And finally, if your drug makes it through to large-scale clinical trials, you need to know that it is safe, effective and beneficial in large numbers of patients. Crucially it is important at this stage to determine what the overall benefits to a healthcare system may be.

Historically the process of going from idea to medicine has taken at least a decade and often much longer, and the success rate overall is lower than 5%. At the beginning of the process, when selecting a target to work on, the biologists and chemists benefit from having a clinician present. At the end, when large-scale trials are being undertaken, the late-stage clinical development team will need to engage with chemists, biologists, toxicologists, engineers and others as the unanticipated properties of the medicine emerge. Lessons are learned along the way and the process is iterative rather than linear. Integrated teams are essential and the integration here is focused on the product: its quality, efficacy and safety, of course, but also whether it can be made at large scales. The importance of teamwork, the need for multiple disciplines to work together, and the crucial role of the integration of engineers with scientists were all important lessons for me, whether we were making small molecule drugs, antibody treatments or cell and gene therapies. Failure at any one point could mean failure of the project.

Although new technologies and approaches will accelerate the process of medicines invention, one unexpected benefit of the long time it takes to make a medicine is deferred gratification. Two recent examples for me in the last year, 5 years after I left industry, were to see the progress of the first new class of antibiotic in 30 years into phase III trials that were so positive they had to be stopped early, and to see a long-acting injectable drug for HIV[9] hailed by WHO as an important tool for prophylaxis in at-risk populations. Perhaps as the extraordinary advances in artificial intelligence allow integration and understanding of huge data sets to provide better prediction of molecular structures and properties[10] and a faster anticipation of putative biological function, the timelines for gratification will shorten and the success rate will increase.

Everything

If medicine needs science, then what about government? As the UK government's chief scientific adviser from 2018 to 2023 I found no area of government policy or operations where science, engineering or technology could not make a difference. How we make our houses, design our towns and cities, educate our children, secure our defence, monitor and manage the environment, move ourselves and freight around the country, generate clean power, communicate with each other and access information, protect and enhance our health and care – indeed all departmental activities require the input of science. A modern thriving economy also depends on science. Seven out the top 10 companies in the world are science- and technology-based and there is a positive correlation between national investment in science and technology and overall productivity. And our resilience as a nation requires science. In my 5 years in post, science came to the fore during challenges to national resilience which included Novichok poisonings in Salisbury, the potential collapse of a dam in the Toddbrook reservoir, drones over Gatwick airport just before Christmas, worries about supplies of critical minerals, and of course the COVID-19 pandemic.

It follows that if science is needed so ubiquitously across government, then a modern government needs to be good at it. In 2019 the Government Office for Science published a report entitled *Realising our potential through science: a review of government science capability*.[11] It identified that many departmental budgets within government had decreased over the previous decade, that mechanisms for scientific input into departmental work were often underdeveloped, and that only 10% or so of the fast-stream graduate intake to the civil service had a STEM degree. In the intervening years things have improved; there is now a target for 50% of the fast stream to have a STEM degree, budgets have increased, there is a chief scientific adviser in every department and the system is more robust. Furthermore, the role of science has been recognised in key strategy documents, including the Government's Integrated Review,[12] which recognised science and technology as a major need for the UK's international success, and the civil service has committed to increasing science capability and capacity throughout government. Recognising that what happens inside government is only part of the picture, the Science and Technology Framework[13] spells out what needs to happen nationally and there is now a dedicated department of Science Innovation and Technology with a remit to make sure that the academic and industrial science bases are supported and grows. This must be a priority for any government. Integration of science into government thinking, structures and processes is *sine qua non* for successful modern government.

Two examples

The last few years have seen a pandemic ravage the world. It caused many deaths and great suffering and had substantial knock-on consequences. The strong science base of the UK was essential to inform the response. Academia provided experts from public health, medicine, mathematical modelling, social

and behavioural science, virology, immunology, engineering and many other vital disciplines. This ability to access a breadth of expertise and bring it together quickly meant a core of integrated advice was available throughout the pandemic. The fact that we routinely run clinical trials in the NHS and have expertise in trial design meant that the most informative COVID clinical trial, the RECOVERY study,[14] was run from and in the UK and found which drugs worked and, just as importantly, which did not. The existence of vaccine discovery groups in academia and a skilled private sector with pharmaceutical science, engineering and manufacturing expertise allowed the vaccines task force to effectively marshal the discovery, development, procurement and rollout of effective vaccines. The Government's Office for National Statistics, together with a private sector workforce (displaced because of the closure of non-COVID clinical trials but with the expertise required and the availability to be deployed quickly), ran a world class survey to monitor infection rates, and scientists in Public Health England were important for testing and tracing. The National Core Studies were deliberately integrative and brought together academia, government and the private sector to answer key questions ranging from mechanisms of environmental spread to evolving immunology to the nature of long COVID, and supported infrastructure for clinical trials and data provision. All of this and more will be required to prepare for future pandemic risks and lessons must be learned, but none of this would have been possible without the pre-existing structures and skills in the health system, academia, industry and parts of government. Each part played a role, and each part was dependent on the others. And although this is an example of science being needed for national resilience, it is also relevant for the economy. The way in which drug trials and vaccines were accelerated in the UK meant that international industry started to invest again in the UK biomedicine.

If COVID was an emergency lasting 2–3 years, the climate crisis is one that will go on for decades, and the WHO has recognised that it presents a major threat to health and wellbeing globally. Just as in the COVID example, the triad of a strong fundamental science base, a strong industrial science sector, and a scientifically informed and enabled government will be critical. Academics identified the problem of climate change; they will be needed to understand both mitigation and adaptation responses, and will explore key remaining unknowns around areas like cloud formation and effects, sub-kilometre forecasting and environmental tipping points, and behavioural scientists will help inform responses of societies around the world. Technological solutions will need to be invented and implemented at scale, and this requires a thriving innovative green technology sector as well as the large companies that are needed to implement solutions at whole-population scale. And government science will need to plan at a whole-systems level in order to support demonstrator sites for new technologies and to facilitate the technical implementation of everything from hydrogen through to effective electrification. Government science will also need to continue to pursue the longer-term solutions for decarbonised energy that will be required even after 2050, in areas including nuclear fusion.

Unexpected areas

One final unexpected (to me) area of government funded research is the museums. In my time at the Natural History Museum I have seen first-hand the value of longitudinal collections and new collections. It is possible to extract small samples of nucleic acids from bats that have been stored for many decades and scientists are exploring the evolution of coronaviruses in bats from around the world, a use that those collecting the bats could never have dreamt of. Other collections have allowed the construction of a bio-intactness index that measures how much species loss has occurred in different parts of the world. The challenge for current collectors is to develop archives and collections that someone will be grateful for in the future, and might use in ways we cannot imagine today.

Despite the loss of biodiversity, new species continue to be identified. I have seen collections of sponges obtained from the depths of the Clarion-Clipperton zone in the Pacific Ocean where more than 70% of the specimens are previously undescribed species. Much to my surprise I saw one with 10-cm-long spiked tubes emerging from its body and learnt that these were made of glass. For reasons of energy efficiency these sponges use silicon rather than calcium carbonate and are able to make glass through enzymatic processes at 2°C–could this present an interesting opportunity for biological engineering?[15]

Conclusion

Specialism and reductionist science are essential, but so too is effective integration. The nature of the integration required varies depending on the objective, but the principles of integration are the same and require a skilled workforce. In academia, the presence of a strong and wide fundamental science base is essential because the ingredients for integration are often not predictable. Funding mechanisms must support integrative research and not create multiple jeopardy by viewing each component of a project through a separate specialist lens. Academia alone is not enough and the presence of a strong innovative industrial science base in the country is needed. Investment structures and incentives that understand and support the long-term and varying risk profile of innovative science and technology companies are urgently required. Ease of movement of individuals across sectors is important and should be recognised in career paths. And government needs to be scientific. It doesn't just need more scientists and engineers; it needs every part of government to be scientifically literate and aware.

Finally, of course, integration depends on people. A skilled workforce is required and it must be diverse, inclusive and open. Difficult problems are not solved by monolithic groups; diversity and inclusion is the bedrock of effective integration. As Desmond Tutu wrote, 'differences are not intended to separate, to alienate. We are different precisely in order to realise our need of one another'. ■

Acknowledgements

I would like to thank all the students, collaborators and colleagues that I have worked with in the public and private sector whose work is alluded to in this article. I would also like to thank my mentors and supervisors who helped shape my thinking and work.

References

1 Auffray C, Noble D. Origins of systems biology in William Harvey's masterpiece on the movement of the heart and blood in animals. *Int J Mol Sci* 2009;10:1658–69.

2 Walshe FMR. The integration of medicine. *Br Med J* 1945;1:723–7.
3 Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980;288:373–6.
4 Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proc Natl Acad Sci* 1987;84:9265–9.
5 Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987;327:524–6.
6 Vallance P, Collier J, Moncada S. Effects of endothelium-derived nitric oxide on peripheral arteriolar tone in man. *Lancet* 1989;334:997–1000.
7 Vallance P. Exploring nitric oxide in health and disease. The Goulstonian Lecture 1996. *J R Coll Physicians Lond* 1997;31:321–7.
8 Szustakowski JD, Balasubramanian S, Kvikstad E *et al*. Advancing human genetics research and drug discovery through exome sequencing of the UK Biobank. *Nature Genetics* 53;942–6.
9 World Health Organization. *WHO recommends long-acting cabotegravir for HIV prevention*. WHO, 2022. www.who.int/news/item/28-07-2022-who-recommends-long-acting-cabotegravir-for-hiv-prevention [Accessed 1 October 2023].
10 Jumper J, Evans R, Pritzel A *et al*. Highly accurate protein structure prediction with AlphaFold. *Nature* 2021;596:583–9.
11 Vallance P. *Realising our potential through science: A review of government science capability*. Government Office for Science, 2019. Available from www.gov.uk/government/publications/government-science-capability-review [Accessed 1 October 2023].
12 UK Government. *Global Britain in a competitive age: the Integrated Review of security, defence, development and foreign policy*. UK Government, 2021. Available from www.gov.uk/government/publications/global-britain-in-a-competitive-age-the-integrated-review-of-security-defence-development-and-foreign-policy [Accessed 6 October 2023].
13 Department for Science, Innovation and Technology. *Science and technology framework–taking a systems approach to UK science and technology*. DSIT, 2023. Available from www.gov.uk/government/publications/uk-science-and-technology-framework/the-uk-science-and-technology-framework [Accessed 1 October 2023].
14 RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021:384:693–704.
15 Francis WR, Eitel M, Vargas S *et al*. The genome of the reef-building glass sponge Aphrocallistes vastus provides insights into silica biomineralization. *R Soc Open Sci* 2023;10:230423.

Address for correspondence: Sir Patrick Vallance, Chair, Natural History Museum, Cromwell Rd, South Kensington, London SW7 5BD.
Email: Patrick.vallance@nhm.ac.uk