Perioperative medicine and UK plc.

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In March and May 2018, two open meetings were convened under the auspices of the National Institute of Academic Anaesthesia (NIAA) and National Institute of Health Research (NIHR) to consider how both clinical and non-clinical academics, research active National Health Service (NHS) clinicians, and industry representatives can continue to build on the investment underpinned by the NIAA in discovery science and experimental medicine. As an exemplar for drug discovery and experimental medicine, perioperative medicine has been transformed by extraordinary technological and pharmacological breakthroughs in both academia and industry; Mapleson breathing circuits,[1] propofol, the laryngeal mask,[2] remifentanil[3] and sugammadex,[4] to name a few. These advances have occurred, by comparison to many other specialties, at an astonishing pace. It is easy to overlook the impact of these huge technological leaps from the bench that have transformed anaesthetic – and wider- medical practice. Such innovation from industry, academia and the NHS are exemplars for the UK's ambition to secure health-life sciences as a pivotal industrial sector. Having reached – at least from a historical perspective- a likely plateau in progress in terms of technical equipment, there is an undeniable role for a new model of bi-directional, bedside-to-bench research contributing within the sphere of perioperative medicine, critical care and pain. As a potentially even more exciting era is emerging from both industrial and technological perspectives, here we consider the drivers that require discovery science and experimental medicine in anaesthesia to manoeuvre back into the fast lane of biomedical discovery.

UK healthcare as a pillar of the new Industrial Strategy

In November 2017, the UK government published a strategic policy discussion document (otherwise referred to as a white paper) entitled "Industrial Strategy: building a Britain fit for the future".[5] Arguably, this was the first explicit industrial strategy since the 1970s, having evolved from the recognition that much of industrial policy since the last quarter of the twentieth century had focussed on integrating foreign investment, competition promotion and market liberalisation.[6] This white paper sets out a long-term plan to boost the productivity and earning power of the UK by identifying strategically key sectors worthy of special attention and support. Two key Grand Challenges laid out in the white paper, the "Ageing Society" and "Artificial Intelligence" sit squarely within the healthcare domain. This is not surprising, given that the UK has one of the strongest and most productive Life Sciences industries in the world (Figure 1), with at least 5,000 companies generating in excess of £60 billion per year.[7] By 2046, almost 25% of the UK population is likely to be 65 years old and over.[8] The other compelling reason for this focus is the dawn of ultra-old age. More than one-third of UK children born in 2018 are predicted to live beyond 100 years.[8] These demographic shifts are likely to require significant -and disruptive- shifts in career planning, healthcare and retirement, brought into further sharp focus by the predicted increase in an unprecedented number of automated tasks.[9]

The Life Sciences Industrial Strategy is central to the ambition of the Industrial Strategy.[10] Professor Sir John Bell identified several strengths, and challenges, that this dominant economic sector in the UK needs to address. Broadly defined, 'Health Life Sciences' refers to the application of biology and technology to health improvement, including biopharmaceuticals, medical technology, genomics, diagnostics and digital health. The impact of non-clinicians and clinicians working at the interface with medicine to influence patient care is clear. Compared to other industries, the health life sciences sector is characterised by very high productivity, by virtue of the synergistic involvement of large and small biopharma, medtech and diagnostics, charities and academia. The UK NHS is central to this vision, as a non- insurance-based healthcare system within which healthcare research is deeply embedded through the NIHR. The preservation of the NIHR budget over the last 10 years is testament to the economic impact of NHS -related research.[11] Fundamentally, this is underpinned by international recognition that the NHS is capable of delivering homogenous, world-class healthcare. A key example of this type of integration is the 100,000 Genomes Project, with the creation of a unique genomic medicine service for the NHS.[12] Large-scale sequencing genomic data is now being married to longitudinal clinical data captured by the NHS detailing oncology therapy and outcome. This approach is already transforming conventional cytotoxic therapy, informing the rapidly growing field of immunotherapeutics and stratifying care using molecular markers developed to mitigate both cost and side-effects.

A rich history of drug discovery and technological advances in anaesthesia.

The rich transformative history of drug discovery in anaesthesia is unrivalled in modern medicine, characterised by work of basic scientists, anaesthetists in clinical and laboratory settings and academic innovators, as well as early technology adopters par excellence. In a remarkably short period of time, anaesthetic agents have evolved from dangerous, explosive compounds to the safe, reliable products we now use routinely. Similarly, the rapid development of ventilator technology, monitoring and airway devices has transformed practice out of all recognition. In 1980, two seminal articles in the history of anaesthesia – both published by the BJA- speculated that the laryngeal mask airway[2] and propofol[13] may be adopted more broadly! The recognition of John Glen's work on developing propofol, as recently recognisied by being awarded the 2018 Lasker~DeBakey Award for Clinical Medicine Research, underpins the fundamental importance of drug discovery and translational academic anaesthesia in the UK.[14] In the space of just 30 years, these discoveries have revolutionised our speciality to a point where the clinical challenges faced by our predecessors are very hard to appreciate. The development of sugammadex represents another pivotal step in anaesthetic drug discovery. While discovery of novel anaesthetic agents has declined over the last 30 years, revolutionary new technologies in neuroscience, such as opto- and chemogenetics, offer a real prospect of reversing this trend. The development of analgesics devoid of (or with reduced) side effects that typify morphine, including biased agonists[15] and nociception/orphanin FQ receptor agonists,[16] offers just one of several scientific approaches that academic anaesthesia can contribute to help address the public health crisis of escalating opioid abuse.[17] Anaesthesia continues to add to its record of rapidly adopting new technology, often in partnership with industry. The presence of notable current UK academics in anaesthesia/critical care on PATENTSCOPE, the database that provides access to international Patent Cooperation Treaty applications,[18] attests to an ongoing commitment to innovation.

A key role for experimental medicine

A pivotal element for the future of the UK health life sciences industrial sector is experimental medicine, which underpins this translational research strategy. Experimental medicine is defined by investigations undertaken in humans, complemented by model systems, to identify mechanisms of pathophysiology or disease, or to demonstrate proof-of-concept evidence of the validity and importance of new discoveries or treatments. We would add the underpinning bench science to the front end of the definition; target identification, drug discovery and device design/evaluation. This often requires a multidisciplinary approach through which the leveraging of health data provides another key contribution afforded by a healthcare system like the NHS. The bi-directional link between bench science and later stage testing of new treatments in patients is increasingly recognised as crucial to secure the translation of discoveries from basic laboratory and clinical science into benefits for human health.[19] Integrating these various approaches has already enabled several breakthroughs using a "reverse translational" or "bedside-to-bench" paradigm. For example, the relationship between drug side effects and various factors that explain inter-individual differences, including polymorphisms, genome-wide association studies and co-administered drugs, have generated novel mechanistic insights.[20] Large data mining has already enabled the potential repurposing, and basic mechanistic re-investigation, of drugs across many therapeutic areas, as well as computational biological approaches.[21] The Medical Research Council (MRC) is the lead public sector organisation for Experimental Medicine, co-ordinating activities on behalf of UK Clinical Research Collaboration partners.[22] Translational Research Partnerships (TRP) were launched in 2011 as a direct response to industry feedback to the UK Government. TRPs support collaborations with the life sciences industry in the early phase exploratory development of new drugs and therapeutics. In line with this, the Efficacy and Mechanism Evaluation (EME) programme, a partnership between the MRC and NIHR, supports clinical research that embeds mechanistic work into studies designed to drive rapid progress in healthcare delivery.

Future unrivalled opportunities within the realm of anaesthesia.

The combination of next generation sequencing, “-omics”, imaging technology and processing of large, longitudinal datasets offer an unprecedented opportunity to examine human pathophysiology at scale. Key clinical questions with commonality across specialities are frequently hampered by the inability to capture clinical data before pathology arises in an individual. The perioperative arena provides a unique opportunity to phenotype patients prior to clinical interventions and/or disease progress. In particular, there is an increasing recognition that the identification of endotypes, which are subtypes of a syndrome/disease but defined by a distinct functional or pathobiological mechanism, may radically change therapeutic strategies through the identification of new targets and/or biomarkers.[23] Of course, this is not a new concept, considering that blood typing transformed the administration of blood transfusions many years ago. However, the opportunity for more targeted, precision medicine is on the cusp of being transformed by the scalability of biological databases, extensive phenotyping methodologies (proteomics, metabolomics, genomics, rapid cellular assays), computational tools for analysing large datasets and additive manufacturing.[24] Unbiased analyses combining these technologies may powerfully interrogate relationships between targeted genomics and multiple phenotypes.[25] Identifying and/or developing tractable models of pathophysiology where *man is the new mouse* remains a critical challenge for translational biological understanding.[26] For example, the frequency of sepsis and subclinical organ injury that can now be revealed by many of the new technologies listed above, affording a unique, highly individualised approach to understanding early disease processes. Critical to this approach is challenging the endotype in question, often using readily available physiological tests. For example, perioperative medicine has extended the objective estimation of cardiorespiratory reserve beyond the cardiac transplantation population. Incorporating physiology from perioperative practice into experimental medicine studies has revealed specific endotypes that afford mechanistic insights into perioperative haemodynamics.[27]

Multimorbidity

Addressing the challenges of multimorbidity as a central feature of the "Ageing Society" has been highlighted by the Academy of Medical Sciences, United Kingdom as an urgent major health priority.[28] It is difficult to envisage a clinical speciality better poised than perioperative medicine to address this complex challenge at several levels. Multimorbidity is distinct from co-morbidity because there is no primary or index condition. The biological understanding of how multimorbidity influences responses to acute stressors is very limited, yet such insights are essential for developing both therapeutic and organisational strategies in ~72% of the older population with this unmet need.[29] Clinical care of multimorbidity will not only require a shift from specialists to generalists, but a similar skillset in translational research since identifying the determinants of the acceleration of multimorbidity is crucial. Perioperative clinical paradigms/models readily lend themselves to a centre stage for anaesthesia and related-specialties.

Neurodegenerative disorders

The escalating, age-related challenge of neurodegenerative disease also urgently requires new, tractable large-scale human models of investigation based on solid laboratory and translational science. Postoperative organ dysfunction leading to chronic inflammation and persistent pain appear to fuel cognitive decline.[30] Recent perioperative data has identified a clear link between established preoperative sub-clinical cognitive decline and postoperative delirium.[31] Whilst it appears unlikely that postoperative delirium alone precipitates persistent cognitive impairment and/or dementia after uncomplicated surgery, the opportunity to redefine the perioperative period as a neurophysiological challenge that reveals neurocognitive endotypes has emerged. The ability to identify, in huge numbers, older patients who appear to be on a trajectory to progressive neurocognitive decline offers unparalleled, population-based opportunities to intervene.

Moving forward

Over the last 10 years, a significant new cadre of anaesthesia-related clinician-scientists and basic scientists has emerged in the UK who are well equipped to contribute to discovery science and experimental perioperative medicine on an internationally competitive setting. Both charitable funding bodies and academic training reform have supported this development, underpinned by a concerted and sustained effort by the NIAA to enable successive generations to continue this trend. Indeed, the NIAA now celebrating its 10^{th} anniversary was set up to address a decline in academic anaesthesia and to urge our speciality to look beyond the operating room. Many of these investigators have married their clinical training with research interests that impact well beyond the conventional clinical silo model of research and discovery. The opportunities for the broad disciplines that our clinical sphere encompasses to contribute to the wider health life sciences industry have never been greater. The advent of both the Health Service Research Centre and Perioperative Medicine clinical trials network offers a powerful, NHS-integrated mechanism through which new technology and/or clinical approaches may be robustly tested and deployed rapidly. The launch of an Experimental Medicine/Discovery Science group is the latest initiative aimed at promoting the role that we can undoubtedly develop further in an arena that is not only 'mission critical' for improving healthcare, but more broadly an industrial sector that benefits from world-class perioperative care and emerging academia. To this end, specific funding calls and dedicated academic sessions focussed on Experimental Medicine/Discovery Science will be a regular feature of NIAA activities. There are several examples of groupings to serve the need of clinicians and clinician scientists, but fewer for the non-clinical anaesthetic researchers - this new group initiative fills that space. Moreover, membership encompasses clinical and non-clinical scientists with an ethos of working together. Inevitably, undergraduate and postgraduate educational reform will be required to equip practitioners at all levels in perioperative medicine to contribute optimally to a knowledge-driven future for both the NHS and life sciences industrial sector. Crucially, grasping the concept that these opportunities extend beyond the immediate and familiar clinical environment that our work encompasses is essential.

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