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# Oxford Medicine

THE NEWSLETTER OF THE OXFORD MEDICAL ALUMNI

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**Professor Sir David  
Weatherall:  
1933–2018**

**Nuffield Department  
of Women's &  
Reproductive Health**

**Clinical training at  
Oxford. Reflections  
from the new DCS**

## President's Piece



*John Morris,  
OMA President*

**Welcome to the Spring Issue of Oxford Medicine, our twice-yearly magazine intended to keep all those who trained in medicine in Oxford in touch with each other, and abreast with what is going on in the medical school.**

In particular in this issue we have a tribute to Professor Sir David Weatherall, who died in December 2018, and for whom there have rightly been numerous national and international tributes. The four people who have provided the tributes for Oxford Medicine are all people who were his close clinical and scientific colleagues for many years: John Clegg, with whom David worked on the synthesis of the alpha and beta chains of haemoglobin to understand causes of thalassaemia; and John Ledingham, Jim Holt and David Warrell who were his clinical colleagues in the Nuffield Department of Medicine, dealing with the huge variety of clinical problems that present themselves to any major tertiary referral centre. Sir David was a supreme example of a physician scientist and his name is now appropriately memorialised in the 'MRC Weatherall Institute of Molecular Medicine' which is just one part of his enormous legacy. In this period of the inevitable increase in specialisation David's breadth of clinical knowledge and expertise was truly outstanding and an inspiration to all who knew him. Some people of this stature can be somewhat aloof, but this was never the case with Sir David. On several occasions I had the good fortune to discover that, despite being so deeply involved with the clinical school, he could equally well turn his mind to and give succinct advice on matters concerning the preclinical school and its teaching.

Medical science is changing very rapidly and it is therefore

very important that all parts of the medical school change and develop equally rapidly to keep pace while, at the same time, ensuring that the basics remain strong and that personal care for each patient is maintained. I therefore urge you to read and ponder the article by Catherine Swales, our new Director of Clinical Studies, whose article considers the challenges and opportunities in what she describes as the 'exciting times ahead' as she seeks to fill the 'big boots' that her predecessors Tim Lancaster and Tim Littlewood have bequeathed to her.

It's not only personnel but also the names of departments that change as the medical school develops. Those of you who fondly remember your rotation through "O&G" in year 5 and were inspired to specialise in that aspect of medicine will, I am sure, be interested to read Stephen Kennedy's article on what is now the Nuffield Department of Women's and Reproductive Health to note not only the emphasis on health rather than disease but also the remarkable growth and development from the origins of the department in 1937 to the present day.

I'll take this opportunity of reminding those who have previously paid a £30 membership fee to OMA that this is now history. You should have had a letter about this but, if you do have any queries, please contact OMA on [oma@medsci.ox.ac.uk](mailto:oma@medsci.ox.ac.uk).

Finally, may I encourage you all to think about and then contribute a piece to Oxford Medicine so that we can all keep abreast of the many and varied great things that our alumni are doing in different parts of the world. It's a real joy that so many of you come back for the reunions and it's always a pleasure to catch up with past students, friends and colleagues. It's been my privilege to serve as President of OMA for a number of years and I look forward to keeping in touch with you in the future, either personally or through Oxford Medicine.



## News

### Oxford-Harrington Rare Disease Centre to research rare diseases therapies

The University of Oxford and Harrington Discovery Institute at University Hospitals in Cleveland, Ohio have announced a new affiliation to advance therapies for rare diseases. The joint program combines capabilities to improve treatment options globally for patients with rare diseases.

There are about 7,000 known rare diseases, with new diseases being discovered every day. More than 350 million people worldwide are living with a rare disease, and approximately 50 percent are children. A rare disease affects one in 10 Americans, or 10 percent of the US population. Similarly, Europe has approximately 30 million people who suffer from a rare disease. The majority of all rare diseases are genetic in origin, which means they are present throughout a person's life. Only five percent of rare diseases have a treatment approved



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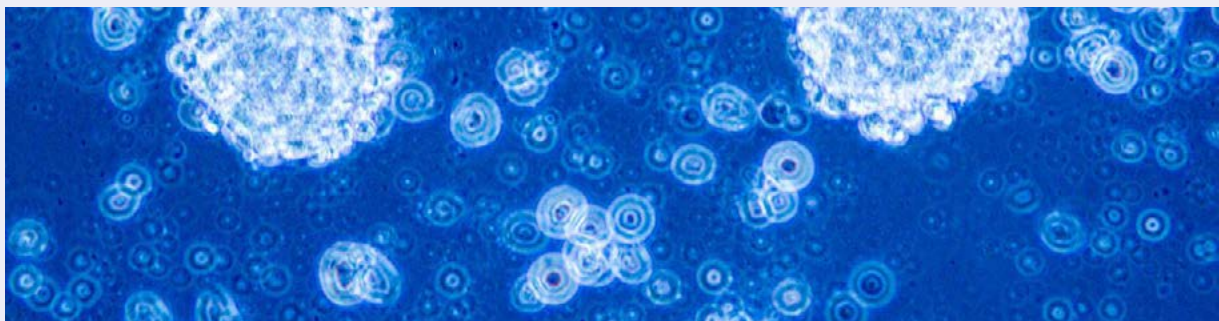
by the US Food and Drug Administration (FDA) and similar estimates have been made for treatments approved by the European Medicine Agency (EMA). Therefore, someone with a rare disease today faces a lifelong, often life-threatening, condition with little hope for a cure, or even an effective treatment option.

### New technique to analyse cancer cells' life history could help provide personalised cancer treatment

A team of researchers from the Medical Research Council (MRC) Weatherall Institute of Molecular Medicine at Oxford University has developed a new technique that allows scientists to reliably track genetic errors in individual cancer cells, and find out how these might lead to uncontrollable growth.

Despite recognising that cancer cell diversity underlies treatment resistance and recurrence of cancer, previous attempts to track errors in individual cancer cells were very inaccurate, or could only track a few cells at a time. This is the first time that researchers have been able to reliably track DNA errors, or 'mutations' in thousands of individual cancer cells, while also measuring how these mutations lead to disruption to how DNA is read within individual cancer cells in a tumour.

The study, published in the journal *Molecular Cell*, describes how this new technique, TARGET-seq, can not only detect mutations within individual cancer cells from patients, but also work out the full list of gene products in individual cancer cells (the transcriptome). Tracking these genetic errors, and their consequences, is important, because despite the latest medical advances, completely getting rid of cancer cells is sometimes extremely difficult. As there are many different kinds of cancer cells in a tumour, they can all behave differently and have different kinds of resistant to treatment. Understanding the genetics of individual cancer cells in such detail will help clinicians personalise cancer treatments for each patient.



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## Oxford researchers receive £6M British Heart Foundation funding to further develop cardiovascular research

The British Heart Foundation (BHF) has awarded the University of Oxford £6 million to further develop the Oxford BHF Centre of Research Excellence (Oxford BHF CRE) for the next 5 years. Professor Hugh Watkins, Director of the Oxford BHF CRE said “We are delighted to have achieved this renewed support from the BHF.

“We will use this fantastic opportunity to build on all that has been achieved in Oxford since the BHF CRE was initiated in 2008, by supporting our cardiovascular researchers to target selected areas where we believe we are poised to deliver world leading progress.

“The previous BHF Research Excellence awards have been transformative, as we have been able to use their unique flexibility to build capacity and engineer

research opportunities and to achieve a common sense of purpose, and thereby enhance ambition and momentum.”

The Oxford BHF CRE channels this BHF funding into nurturing future cardiovascular research leaders, creating and supporting opportunities for collaborations across the globe, and ensuring access to the key enabling technologies which are critical to allow researchers to compete at the highest level.

John Radcliffe (1653–1714) was the most successful physician of his day and the doctor to the likes of Queen Anne. After his death in 1714, the bulk of his fortune was left to his Trustees for charitable purposes.

## Mobile Malaria Project team begin their journey



The Mobile Malaria Project team, led by Dr George Busby from University of Oxford, will travel over 6,300km across Namibia, Zambia, Tanzania and Kenya to investigate the challenges facing those on the front line of malaria control in Africa – where 90 per cent of the world’s cases occur.

The 2018 Royal Geographical Society Land Rover Bursary recipients have begun their eight week journey. Driving a specially-equipped Land Rover Discovery, the team will research the potential of portable DNA sequencing technology. Their bespoke vehicle is equipped with a mobile genetic sequencing laboratory and extensive modifications. These modifications will allow the team to trial portable DNA sequencing technology, in collaboration with African research centres, to better understand how the technology can be

used in different locations. This will provide important information about malaria parasite and mosquito populations, including drug and insecticide resistance.

For more news articles from the Medical Sciences Division: [www.medsci.ox.ac.uk/news](http://www.medsci.ox.ac.uk/news)

## Professor Sir David Weatherall: 1933–2018



*Prof Sir David Weatherall (second from right) with HRH the Princess Royal at the official opening of the (then) Institute of Molecular Medicine*

### The Clinician

*Written by Professor John Ledingham, Dr Jim Holt and Professor David Warrell*

#### Appointment as Nuffield Professor

Some sixty years ago, most of Oxford's undergraduate medical students chose to complete their clinical studies in London or elsewhere, rather than staying in the small local clinical school. Since then, Oxford's Medical School has grown in size and reputation to become the world's top rated institution. How did this happen? It was due largely to the efforts of three professors of medicine: George Pickering, Paul Beeson and, in particular, David Weatherall.

David was unknown in Oxford until 1971. At the Association of Physicians meeting in Sheffield that year, the third paper on the agenda was by DJ Weatherall, JB Clegg and PF Milner on "New' molecular mechanism as the basis for a genetically determined haemolytic anaemia". In a presentation that struck the Oxford physicians in the audience as being scintillating, David described a new abnormal haemoglobin (Constant Spring) found in members of a large Jamaican family with severe haemoglobin H disease.

In early 1973, Paul Beeson, the Nuffield Professor of Medicine, confided in Jim Holt that he intended to retire back to the United States. He remarked that it would be rather nice if his chair went back to blood disease which was his predecessor LJ Witt's interest. "How about that young chap Weatherall from Liverpool who gave the splendid paper on haemoglobinopathies at the Association of Physicians meeting?" Jim was due to lecture in David's department in Liverpool in early April and was authorised to mention the impending retirement. He invited David down to Oxford for a weekend in May and hosted a dinner with Renwick Vickers, John Badenoch and John Ledingham, at which the conversation focussed more on Mozart's operas than medicine. Next day, John arranged meetings with the Regius, Richard Doll, and with Beeson. David was encouraged to apply by the eminent professor of Medicine in Liverpool, Sir Cyril Clarke. Unfortunately, the Regius's preferred candidate was a senior figure from a London teaching hospital, whose appointment had been promised as virtually a *fait accompli*. However, the other electors; who included Ledingham, Badenoch, and

Hugh Sinclair, chaired by Alan Bullock; were swayed by the argument that it would be more stimulating to bring in a promising younger man whose name and reputation were not yet made, but might be established in Oxford. David was duly appointed in early 1974, but, as the October start of the academic year approached, he had received no letter of confirmation from the University. He wondered whether it was safe to send in his letter of resignation. His secretary, Mrs Coggley, rang the VC's secretary but was told haughtily: "It was announced in the Times, what more does he want?"

### Incoming priorities

In the meantime, John Ledingham had been made May Reader and became acting head of the Nuffield Department of Medicine. In a letter to John, David delineated his priorities as incoming Nuffield Professor: to make the department outstanding clinically, in teaching and, only in third place, in research! He had gone into medicine primarily to heal the sick, regarded himself as "basically a humble haematologist", and hoped that they would work together as equals. Despite their contrasting backgrounds, education and styles, David and John proved, in the years to come, a highly effective diarchy, in which David was never domineering.

### The clinician in action

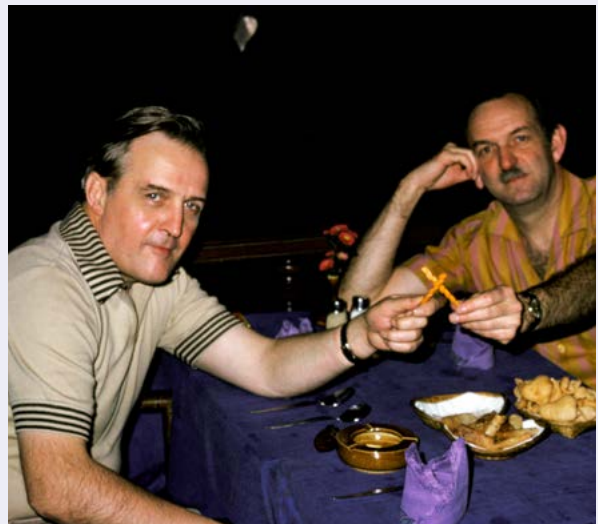
David's junior staff recall that, at the bedside, his approach to the patient was homely and unaffected. Like his predecessor Paul Beeson, he showed great concern for their feelings and anxieties. His attitude was always thorough, methodical, and thoughtful, and he never gave the impression of being rushed. He discouraged excessive investigations, but was rigorous in pursuing with the house staff the results of tests that he had recommended. David would probe the history and check physical signs when necessary. He was adept at analysing complex clinical findings to arrive at a diagnosis but, despite his encyclopaedic knowledge, was always willing to seek outside advice from specialist colleagues, and to admit rare errors in diagnosis. As a senior registrar in Liverpool, he remembered writing up investigations and treatments only to have them contested or cancelled by Cyril Clarke his consultant. He was responsible for David's tendency to therapeutic nihilism, and his rejection of claims for treatment that went beyond the evidence. David wrote that "Cyril believed in minimal intervention. His advice to his new house staff on the use of drugs came, he claimed, straight from the mouth of one of his teachers at Guy's, who, as he got older, restricted his personal pharmacopoeia to morphia and sodium bicarbonate, and was not too liberal with the bicarbonate".

David virtually never missed a take round, routine ward round or Thursday NDM clinical meeting, and would insist on flying back from the United States to chair a Wednesday grand round. He developed excellent relationships with the medical and nursing staff and with his secretaries, creating a warm atmosphere on the firm.

### The Oxford Textbook of Medicine

In the late 1970s, John was approached by Richard Charkin of Oxford University Press to edit a new "Oxford Textbook of Medicine", to succeed "Price's Textbook of the Practice of Medicine". He was disinclined to do this due to other commitments, but David felt that the medical school deserved a locally produced textbook and that the Oxford brand should not be surrendered into other hands. As a result, Weatherall, Ledingham and Warrell became editors of this magnum opus. They used to meet on Saturday mornings in David's office to select authors for a book that had to be authoritative and comprehensive, with memorable descriptions of the clinical phenotype as well as discussion of pathophysiology and treatment. Inevitably, amusing and destructive anecdotes were exchanged about some of the proposed authors, and many a fine reputation hit the dust.

David Weatherall was the very model of that endangered species, the clinician scientist. He never relinquished the ideal, expressed when he was appointed here, of making the Oxford Medical School a world leader in clinical practice, teaching, and research.



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*On board "The Rice Barge" on the Chaopraya River, Bangkok, Jan 1979. Concluding the formal agreement between the Wellcome Trust (Peter Williams, right) and the Nuffield Department of Clinical Medicine (David Weatherall, left) to fund the first of Oxford's tropical medicine research units*



## The scientist

Written by Professor John Clegg

David Weatherall's first encounter with thalassaemia – while serving in the RAMC in Singapore on National Service – was the stimulus for a life-long fascination with genetic blood diseases. In 1962, when he began a training fellowship at the Department of Medicine at the Johns Hopkins Hospital in Baltimore, thalassaemia was already known to be a genetic disorder affecting haemoglobin, with two broad classes, depending on which globin subunit, alpha or beta, was involved. But, despite much theorising, there was no direct experimental evidence for any of the proposed mechanisms.

During most of his three years at Hopkins, David (and many others) had struggled unsuccessfully to get the established methods used for haemoglobin synthesis in rabbits to work with human blood samples. In fact, a simple technical problem was responsible and, early in 1965, he learnt to his surprise that it had just been solved by a protein chemistry group in a different Hopkins department across the road from the hospital! A mutual friend put the two in contact. In the few months left before he had to return to Liverpool, they carried out the definitive experiments showing that the basic defect in thalassaemia was *imbalanced* synthesis of the alpha and beta globin proteins. The methods that the Weatherall group developed at this time subsequently became the basis for the prenatal detection of haemoglobin disorders: this was, until the later DNA era, the major reason for the

remarkable decline in new cases of thalassaemia in some Mediterranean countries.

Ironically, the key paper that described the 1965 experiments was published too late to make the first edition of David's authoritative book 'The Thalassaemia Syndromes'. Nevertheless, its impact may be gauged from the comment of a speaker at a New York Academy of Sciences meeting on the biochemistry of thalassaemia a few years later. It was, he said, 'the fountain-head of all this'. Almost fifty years on, it had lost none of its significance: the citation for the American Society of Haematology's 2013 Coulter Award to David described it as 'a truly ground-breaking and transformative report'.

In the ensuing years, the Weatherall group published over 200 research papers on various aspects of the genetics, molecular biology and pathophysiology of thalassaemia. Many of these arose from collaborations and contacts David had made during fact-finding trips he had undertaken for the World Health Organisation. Occasionally, some of this work crossed over into other areas of medicine and biology. In one, a chance conversation with a doctor from the New Hebrides (now Vanuatu) led to large-scale surveys of thalassaemia and malaria in the S. W. Pacific. This, and subsequent clinical case-control studies in Vanuatu and Papua New Guinea, provided convincing proof of the 'malaria hypothesis' –

first mooted in 1949 by the geneticist J.B.S. Haldane – that carrier states of thalassaemia offer some protection against malaria.

David Weatherall was always patient-driven and he helped to set up a number of treatment and diagnostic centres in developing countries. Most notable, perhaps, was the National Thalassaemia Centre in Kurunegala, Sri Lanka. David was a regular visitor: it was ideally placed and suited his research on one of his long-standing interests, HbE /beta-thalassaemia. This, the commonest form of the disease in S. E. Asia, affects hundreds of thousands of individuals and has a remarkable clinical heterogeneity despite having precisely defined (to the single base pair) genotypes. David had received long-term funding for this project sometime before his 'retirement' in 2000. As anyone who knew him well could have predicted, he was still at work on it at the time of his death.



*David Weatherall with a group of staff and thalassaemic children in the Children's Ward in the District Hospital at Kurunegala, Sri Lanka*

Oxford Medicine would like to thank the authors for their personal contributions about Sir David. If you would like to read further details about Professor Weatherall's life, we'd like to recommend the following articles:

On the Oxford university website:  
[www.ox.ac.uk/news/2018-12-10-professor-sir-david-weatherall-1933-2018](http://www.ox.ac.uk/news/2018-12-10-professor-sir-david-weatherall-1933-2018)

On the Centre for Tropical Medicine and Global Health website: [www.tropicalmedicine.ox.ac.uk/news/sir-david-weatherall-1933-2018](http://www.tropicalmedicine.ox.ac.uk/news/sir-david-weatherall-1933-2018)

On the Nuffield Department of Surgical Sciences: [www.nds.ox.ac.uk/news/blog/sir-david-weatherall-1933-2018](http://www.nds.ox.ac.uk/news/blog/sir-david-weatherall-1933-2018)

## 2019 Medical School Prizes

The Examiners in the Second Examination for the Degrees of Bachelor of Medicine and Bachelor of Surgery in Year 3 have awarded the following prizes in Hilary term 2019.

### George Pickering Prize 2019

Recipient: Ain Neuhaus (Somerville College)

The George Pickering Prize is awarded annually for performance in General Clinical Studies Examination in Medicine and Surgery (Year 6)

### Ledingham Prize in Medicine 2019

Recipient: Harry Fagan (Merton College)

The Ledingham Prize is awarded for outstanding performance in Medicine in the General Clinical Studies Examination in Medicine and Surgery by the Examiners appointed for the Second BM examination in Year 3.

### Mortensen Prize in Surgery 2019

Recipient: Imogen Mechie (New College)

The Mortensen Prize is awarded for outstanding performance in Surgery in the General Clinical Studies Examination in Medicine and Surgery by the Examiners appointed for the Second BM examination in Year 3 in Hilary term following a prize viva.

### Margaret Harris Memorial Prize 2019

Recipient: Calum Robertson (Green Templeton College)

The Margaret Harris Memorial Prize is awarded annually for performance in General Clinical Studies Examination in Medicine and Surgery (Year 6).



## Nuffield Department of Women's & Reproductive Health



*Stephen Kennedy, MA (Oxon), MD, MRCOG  
Head of Department, Professor of Reproductive Medicine & Co-Director of the  
Oxford Maternal and Perinatal Health Institute (OMPHI).*

In its field, the Nuffield Department of Women's & Reproductive Health (NDWRH) is one of the largest academic departments in the world. NDWRH encompasses multi-

disciplinary research across the full spectrum of women's health. Our work has four overarching themes: Cancer, Global Health, Maternal & Fetal Health and Reproductive Medicine & Genetics. We focus on genetic studies; the dissection of molecular, biochemical and cellular mechanisms underlying normal and aberrant reproductive tissue function; clinical studies in women's health and pregnancy, and growth and development across the first 1000 days of life (from early pregnancy to age 2).

Our clinical and laboratory programmes are primarily

based in the Women's Centre, John Radcliffe Hospital; Weatherall Institute of Molecular Medicine; Wellcome Trust Centre for Human Genetics, and the Big Data Institute, and there are collaborations with many other University departments, as well as institutions outside Oxford.

Our staff carry out translational research in close collaboration with clinicians in The Women's Centre. For example, Ahmed Ahmed focuses on understanding the molecular mechanisms that drive the genesis and formation of micrometastases in ovarian cancer and developing novel targeted therapies for the disease. Manu Vatish studies the mechanisms responsible for placentally-derived pregnancy complications such as gestational diabetes and preeclampsia, with a view to producing new diagnostic tools; their work with Roche Diagnostics in preeclampsia recently won the



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HSJ Best Healthcare Provider Partnership Award. Krina Zondervan, Cecilia Lindgren & Christian Becker work with Bayer AG to identify novel therapeutic targets for benign gynaecological diseases (endometriosis, uterine fibroids and polycystic ovarian syndrome). Antoniya Georgieva is producing innovative automated methods for interpreting the fetal heart trace in labour whilst Aris Papageorghiou, working with Oxford engineers, aims to develop low-cost technologies for fetal ultrasound scanning in low-middle income countries (LMICs).

Many of our observational and interventional studies are conducted in the Oxford Safer Pregnancy Alliance (OSPREA) Unit in the Women's Centre established with funding from the NIHR Oxford Biomedical Research Centre as a collaboration between the Trust and NDWRH. Its mission is to encourage all pregnant women attending the hospital to contribute to research, training, audit and service development. Adding to our profile, this year, we created The Centre for the Endocrinology of Human Lactation (Director, Fadil Hannan), funded by the Family Larsson-Rosenquist Foundation. The centre will investigate the molecular endocrinology of human lactation in healthy and malnourished women; generate new molecular tools to assess lactation adequacy, and define the lactation-dependent mechanisms regulating maternal and infant health outcomes. The Foundation has also generously agreed to endow a Chair in the subject in perpetuity from 2021.

The department also delivers cutting-edge research in reproductive medicine: new techniques for pre-implantation genetic diagnosis (Dagan Wells); immunology of recurrent miscarriage (Ingrid Granne); chronic pelvic pain (Katy Vincent) mitochondrial genetics (Joanna Poulton), and cryopreservation of ovarian and testicular tissue (Suzannah Williams, Kevin Coward). In addition, the Williams Group aims to save the endangered Northern White Rhino by using ovarian tissue to yield large numbers of oocytes for in vitro use.

To complement our activities in reproductive medicine, in 2008, we established an MSc Course in Clinical Embryology, a world-class programme that has won numerous University awards for teaching innovation and excellence. This 1-year taught MSc provides graduates from scientific and clinical backgrounds with advanced theoretical and practical understanding of human reproductive biology, embryology, infertility and assisted reproductive technology (ART). We place great emphasis on 'hands-on' practical training in laboratory techniques associated with scientific research, clinical diagnosis and ART. Amongst the 126 graduates from 42 countries, some work as clinical embryologists or for global fertility companies, others are studying for higher degrees in the UK or overseas.



© Nuffield Department of Women's and Reproductive Health

#### *INTERGROWTH-21st Project*

The department has a particular focus on improving maternal and perinatal care globally. Working with clinicians and scientists from 18 countries worldwide, the INTERGROWTH-21st Project (Stephen Kennedy/ José Villar/Aris Papageorghiou) has produced clinical tools for standardising how human growth, nutritional status and development are monitored across the first 1000 days of life. These tools have been adopted by WHO, CDC and countries, such as Brazil, Sri Lanka and Scotland. As importantly, the project has shown that the colour of a woman's skin plays no role in determining the variation in growth currently seen worldwide, especially in LMICs, compared to the social conditions, health and nutritional state of the population. The failure to recognise this truth is a human rights issue.

To enhance our commitment to women's health across the world, The George Institute for Global Health (TGI) joined NDWRH in 2016. TGI is a Sydney-based research institute, employing 600+ people globally with units in India and China, and projects in approximately 50 countries. TGI is challenging the status quo in healthcare to find the best ways to prevent and treat non-communicable diseases (NCDs) and injury, and to influence policy and practice worldwide. An early example of our work together is SmartHealth Pregnancy (Jane Hirst, Robyn Norton), a tablet-based clinical decision support system in antenatal and postnatal care for use by rural healthcare workers in India.

Reflecting our broader interests in the life-course of women, in December 2017, on the 80th anniversary of our establishment as a University department, we changed our name, through an extensive democratic process, to NDWRH from the more limited Nuffield Department of Obstetrics & Gynaecology.

Together, NDWRH and TGI UK plan to establish an Institute for Global Women's Health (IGWH) in a new, purpose-built facility (for which we need to raise £50 million) that will serve as a national and international hub for efforts to develop effective, affordable solutions



© The George Institute for Global Health

for the major health issues facing women and girls worldwide, and train future leaders in the areas of research and sustainable development relating to the health of women and girls.

The IGWH will bring together world-leading biomedical, social and data scientists with complementary strengths and extensive global networks, with an initial focus on four priority areas that span the life course, which builds on our current respective strengths: 1) Transforming the management of pregnancy; 2) Earlier detection and treatment of gynaecological diseases (including cancer); 3) Enhancing the knowledge base on human lactation and its relationship to future disease, and 4) Reducing the burden of cardiometabolic diseases in women.

Lastly, the department is intensely proud of its Silver

Athena SWAN Award. We have spearheaded a range of innovations, including: a) a new suggestion for improvements scheme (Brainwaves) and engagement platform (Peakon); b) refurbishment of departmental space (Project Rejuvenation), and c) most importantly, a commitment to tackle some of the challenges facing the HE sector, namely short-term contracts and limited career development opportunities for postdocs. The changes already introduced have generated greater satisfaction, as evidenced by our staff surveys, and influenced everyone's approach to the important issues that affect both women and men, particularly gender equality, work-life balance and the working environment. As a result, the department is an exciting place to work with a clear, ambitious mission to improve the health of women and girls globally.



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## Using machines to generate biomedical intelligence



By Gil McVean

*Professor of Statistical Genetics, Nuffield Department of Medicine, and Director of the Big Data Institute*

**It's been a busy period here at the Big Data Institute, or BDI, Oxford's recent addition to the rapidly growing biomedical research campus.**

Over just a few days we hosted a board meeting for a major pharmaceutical company, held a kick-off meeting for a collaboration with another, gave a tour to representatives from HM Treasury and BEIS, participated in a NICE expert working group on real-world evidence, and were part of a successful Oxford-led bid to establish a hub for AI in biomedical imaging.

It seems that everyone wants to know about AI, machine learning and big data in health research. And it's not surprising. The dramatic advances we've seen in the ability of algorithms to identify and use complex patterns in images, documents, streams of financial data and other data-rich domains are beginning to transform the way in which biomedical and health data-related research can be carried out.

From solving mundane but critical tasks, such as maximising the efficiency of healthcare delivery, to the holy grails of automated drug design or individualised therapy, AI is being deployed across the world with enthusiasm, hype and occasional success.

Within Oxford, we've been fortunate enough to have in place many of the pieces we need to make real the promise of biomedical AI. This includes an incredible history of population health research, leading back to Richard Doll and the British doctors' study on smoking,

with an emphasis on clinical trials and population-scale longitudinal measurement; huge strength in the statistical underpinnings of AI, often referred to as machine learning; a community of clinician-scientists who have the insight and drive to understand the need and to help facilitate and shape data-driven research programmes; and a university's worth of fantastic engineers, informaticians, epidemiologists, genomicists and so on, excited by collaborative research and hungry to see their insights make a difference to patients.

The BDI acts as a hub for such activity, supporting the necessary training, computational infrastructure and information exchange, while also leading research programmes ranging from mapping the burden of antimicrobial resistance across the world, to developing mobile apps for measuring the parts of memory that are fastest to decline in dementia.

To a large extent the needs of an AI-driven research programme in healthcare are not so different from any other data-driven problem. Take, for example, the challenge of automated feature prioritisation from imaging modalities, such as pathology or radiology. We want the computer to help the clinician spot features of importance, building on sets of expert-curated training data, coupled with learning algorithms that improve with experience. This requires a close loop between the engineers, clinicians, algorithm

developers and, of course, access to the critical high-quality data sources.

This is the type of problem AI has proved hugely competent at solving – it's a game, like chess or Go, where the rules are set and the machine has to learn the best strategies. Clearly, issues such as repeatability, reproducibility and generalisability are important, but we don't necessarily require the machine to explain why a particular decision has been made. We just need a good decision, fast.

But many of the core problems in biomedicine are fundamentally different from this class of task. Consider the problem of investigating whether some patients respond better to one type of drug than another. Resources, such as the UK Biobank, which are measuring vast amounts of biological, clinical, behavioural and medical data on hundreds of thousands of people, give unprecedented power to find complex patterns. So if we were to use AI to ask whether there are differences in the medical trajectories between those patients given drug A or drug B, the answer would almost certainly be yes. Put another way, by looking at the entirety of a person's data, I can probably work out whether they were given drug A or drug B with reasonable confidence.

But that doesn't necessarily mean that these differences were the result of taking the different drugs. Perhaps

drug A is more often given to those who are likely to do well because they have fewer other diseases, or because its use just happens to be preferred in a couple of hospitals that have particularly good specialists and care pathways for the disease.

In this and many other medical problems, the critical intelligence we need is an understanding of causality – the health benefit likely to arise from a particular intervention. And this doesn't fall naturally from AI. Rather, it is something that only clinical trials, despite their cost and time, can assess.

So what is the role of AI in such work? There are two key areas, both of which the BDI is pursuing. First, we can use AI to make us much smarter about generating therapeutic hypotheses to take to trials, building on a growing wealth of data types that give us clues to causality (such as genomics, longitudinal data, experimental screens and high-resolution biological measurement). Second, we use AI to make trials themselves better, by finding the patients most likely to benefit, the readouts able to measure impact the fastest, and by analysing the clinical data arising to refine hypotheses and iterate.

AI is ultimately just a tool, but it's one that allows us to do science better and get the benefits out into the real world faster.

This article comes from 'The University of Oxford Guide to Artificial Intelligence'. If you would like to view more articles in the guide, please follow this link: <http://po.st/GZ2xku>

For more information about the Big Data Institute: [www.bdi.ox.ac.uk](http://www.bdi.ox.ac.uk)

## Clinical training at Oxford: old skills, new tricks and a hard act for me to follow. Reflections from the new DCS



*Dr Catherine Swales, Director of Clinical Studies*

It's not easy taking over a success story. There's something much more comfortable about leaping in to the rescue – to a school that has unhappy students, miserable faculty, poor outcomes and multiple high-level recommendations from the GMC.

Within that context, what could possibly go wrong? To put my succession into the Oxford context however, when I was appointed one of my closest friends in the Division commented: "You'll be fine, just don't crash it!"...

But there is a risk of being at cruising altitude – and complacency, even a hint of unassailable arrogance, is our worst enemy. If we're not careful, coasting at the dizzying heights, the ground will come up to meet us. It's not just a risk of actual loss, but also of projected loss – we need to be thinking not only what does the School need now and in the next few years, but actually what does British Medicine need in the next 15 or 20 years, and how can we produce happy fulfilled graduates who meet those requirements? Our landscape is changing rapidly: academically, politically (how long did you think I'd wait before mentioning Brexit?) and financially. Add in a healthy, and appropriate, blob of patient and public perception and we're in uncertain terrain indeed. But there's the joy. The challenge of meeting these interdigitating pressures, with students first and foremost and absolutely at the heart of it, that's the best bit of all.

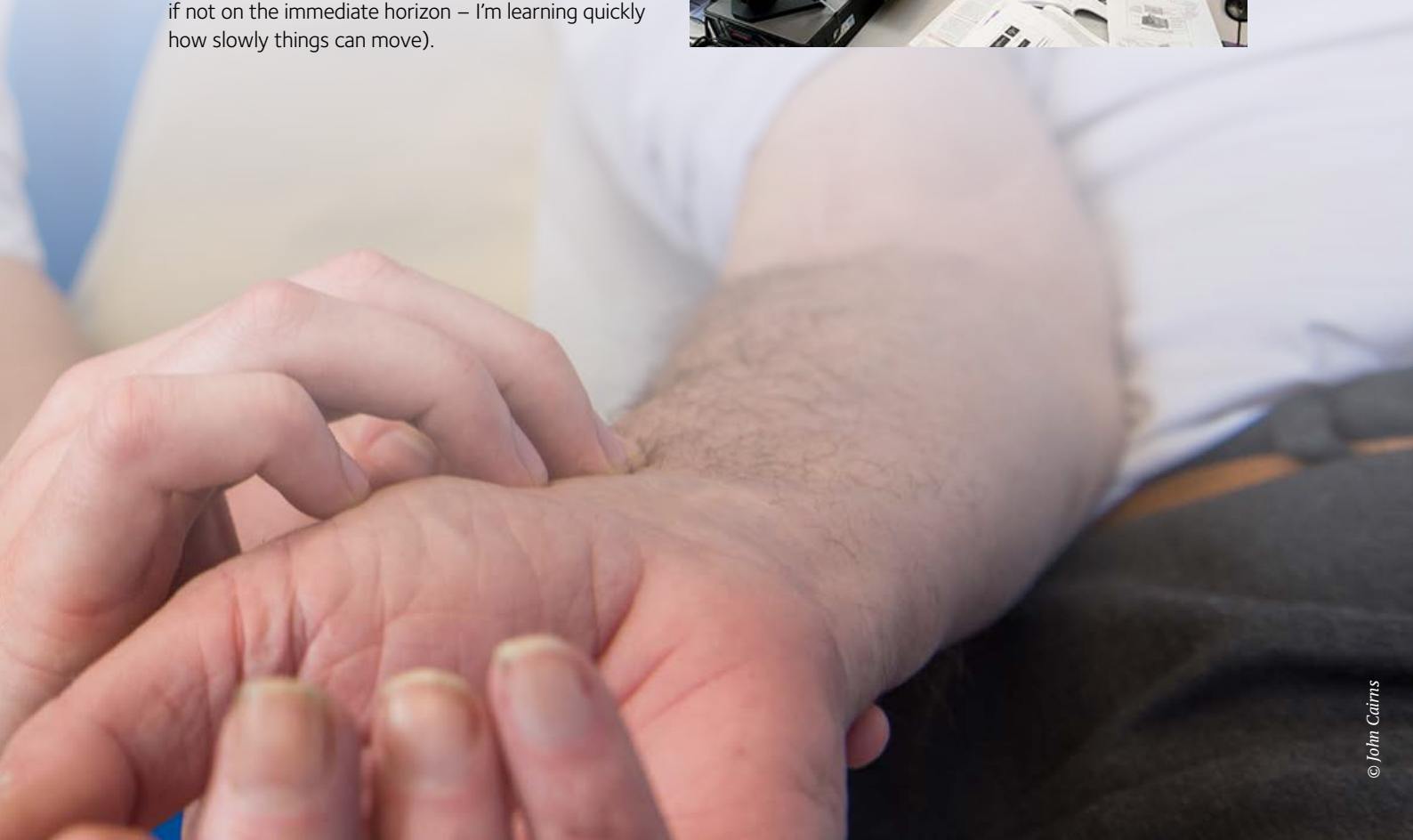
From a student perspective, a crucial element is a sense of belonging. Meaningful experiential learning matters. When they feel part of the team, of the firm, that they have something to contribute whilst they learn, the 'doing as well as the knowing' becomes second nature – and then that patient is never forgotten, a drug interaction is always remembered, a style is adopted, and professional character built and cemented. Sadly, this form of cognitive apprenticeship is under threat from a number of factors (some of which are beyond the control of the Medical School or supervising consultants), not least the way patient care is delivered. Teams are more fluid than previously, patients are in hospital for less time, and their presentations are more complex, with the rise of multimorbidity and frailty. This is the point at which virtual learning environments and simulation training can step in – and we're funding and developing these initiatives, which will improve student learning hugely. But as innovative and exciting as these things are, there remains no substitute for spending time on the ward and in clinic, speaking to patients ('expert' or otherwise), and not retreating to the library and text. Oxford Medicine wouldn't be the same without an Osler quote – and he made the point that "...he who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all...". The line may be gendered, but the message is timeless. There is something to be learned from each conversation or examination or review of every patient,



and our students must recognise that too in order to benefit most; they need to be taught how to learn again in this new world. And we in turn need to learn how to examine afresh – arguably our assessment methods are currently too snapshot, and fail to adequately address broader skills, including professionalism. The postgraduate arena has recognised the value of ongoing work-based assessments, reflective learning and portfolios and we must too – and will.

So, aside from skilled, thoughtful, kind and resilient clinicians, what else might British Medicine need? A cadre of clinical academics for certain – and Oxford has always been good at not only setting people on that path, but also keeping them there (OUCAGS has an unrivalled rate of progression into independent investigators for example). But there will also be a need for clinician pharmacologists, and for bioengineers. With changing times, we need to speak to the pluripotency of our students and offer them research or alternative opportunities at several stages through their training. Intercalated DPhils already exist, and a handful take up this opportunity each year – but dedicated funding for these placements, plus research internships, an MB DPhil program with Industry experience, even formal training in Leadership and Business Management Skills are all on the cards (even if not on the immediate horizon – I’m learning quickly how slowly things can move).

I’ve already quoted Osler, but I’d like to end with Pooh Bear, who once said: “When you see someone putting on Big boots, you can be pretty sure that an Adventure is going to happen...”. And we all have very exciting times ahead, and I have very big boots to fill. This piece would not be complete without my thanks, and those of countless students, to “The Tims” – my predecessors Tim Littlewood and Tim Lancaster, for developing and sustaining both a School and graduates who made us very proud, and their patients feel very cared for. Our heartfelt admiration and gratitude to you both. In your own ways you both taught me for several years, and whilst there may be changes ahead, I fervently hope that this apple doesn’t fall too far from such wise and kind trees.



## Olivia Pryer (St Edmund Hall) is a 4th year medical student and was a member of the Race Crew for the 2019 Women's Boat Race

### What is your average day?

During the week, I typically wake up at about 5.45 and quickly get ready and have some breakfast, and then leave the house for our morning training session. This will be about an hour long either on the rowing machine or doing a circuit. I then come home and get ready to go to the hospital (and have a second breakfast!) The structure of the course varies throughout the year, so I then either have a few hours of lectures in the morning, or if I'm on a rotation I will go to the ward round. I then see if there are any patients I can follow up on either by taking bloods, or doing an examination or taking a history, which are the crucial things which we are meant to become confident with during fourth year! In the afternoon we have our second session of the day, this time rowing on the water. Both the women's and men's teams and the lightweight squads are based at the university boat house in Wallingford, which is set on a wonderful stretch of the Thames. Each session will have a different focus, looking at improving our technique or endurance, or practicing speed work in preparation for races. I'll then come home and do some reading about the cases I saw during the day, before eating dinner and getting an early night!

### How long have you been rowing?

I learnt to row at my school when I was about 12, so I've been rowing for almost 10 years now! However, I took some time out during my last year at school and my first and second years at Oxford to focus on studying, but missed the sport far too much and returned to it in the third year of my degree.

### When did you decide to study medicine?

I think I was relatively quite late to decide that I wanted to apply for medicine at university. I had known I wanted to study science for a while, but had thought that I would apply to study chemistry instead. I first started considering medicine when I was about 15, and did some work experience at my local hospital to see if it would be something I was interested in. I had a wonderful week, particularly sitting in on some clinics with doctors who were eager to teach and talk to me about medicine. I thought that I could see myself as a doctor, and it would be something I'd enjoy learning about, and so far I haven't been proven wrong!



### What drew you to the course at Oxford?

Having wanted to study a science, I was attracted by the first three years of the course, which essentially functions as a science degree. I wanted to learn about how to treat patients whilst having the scientific knowledge to underpin the decisions that we make. Since transitioning into the clinical school, I have found this very useful, as it has made me question why a patient is treated in a certain way and how certain treatments and medications work.

### Do you know what speciality you'd like to head into?

No I don't! I have tried to keep an open mind throughout fourth year, and I have been surprised already, for example I didn't think I wanted to be a surgeon but my surgery rotation has made me consider this as an option. I think though that really I would like to be a physician, and I am attracted to fairly broad specialties such as general practice or geratology. I find it really interesting to have to consider multiple aspects of a patient's well being, and find a solution that makes the patient as well as possible.

### Where is your favourite place in Oxford?

I enjoy spending time outside, so I have a few favourite places in Oxford. I am at Teddy Hall and I love the garden surrounding the library (which also happens to have a graveyard in it!) I like the Botanical Gardens too, which vary so much throughout the year, but I also spend an awful lot of time with friends in the many cafes around the city!



## “Professor Witts also had female house physicians!”

### Dr Julie Neale, BMBCh 1960

I read John Hampton's memories of being an HP at the Radcliffe in 1963 and I'd like to record that both Carole Robertson and I were also Professor Witts' house physicians, myself in 1961, Carole earlier still. This was the era when female students (at least) firmly believed that most house jobs were decided in the pub across the road from the hospital, and unescorted women did not go into pubs alone. However, “the Wittery”, as it was known, was a wonderful firm to work on: Sydney Truelove for colon and Crohn's; Sheila Callender for haematology; John Badenoch for classical medicine; Don Acheson who kept us all on our toes; and numerous visiting doctors. All these made ward rounds a treasure-trove of expertise and stimulation. It seemed to us that none of the consultants ever forgot anything! Practically, we became dab hands at transfusing aplastic anaemic patients every 3 months, searching for veins that were hardly visible after many transfusions. Those were also the days of rubber giving sets and resharpening needles!

As an HP I lived in ‘The Rotunda’, a building that had been divided into 8 rooms like slices of cake around a central staircase. Mine was the first and smallest, on the principle that I would be called out most frequently; it was also at the bottom of the stairs! I was summoned by one ring of the phone in the corridor whereas the HP in the 8th room – ENT I think – was summoned by 8 rings on the assumption that they would rarely be required in the middle of the night. Needless to say the ringing woke us all! Time off was dependant on others covering, but I did manage four commemoration balls that summer. We may have worked very hard but we also played hard and I, for one, enjoyed every minute. Unlike John I also enjoyed the food – but then I had had three years of eating either in the fish and chip shop where the ‘young gentlemen from the hospital’ got a knife as well as a fork, or at the adjacent curry house which later had 2 prosecutions for putting cat food in the curry. One joy of the residents mess was, after a tiring day, to collapse with a coffee in front of the small television to see what? – ‘Emergency Ward Ten’. As some may recall, the opening shot was of the Radcliffe front entrance and some episodes were written by one of the consultants.

My next job was as Professor Allison's first (I think) female HS, when he was just starting. Alf Gunning was the first assistant and very different from the Prof. This was not such an enjoyable period; too many deaths. I remember particularly a lovely young woman who was the first surgical patient I saw as a student. She had mitral stenosis and had had a valve split, but had



*March 1958: Julie Neale at the start of her clinical studies with Sir John Badenoch (Director of Clinical Studies) and Sir George Pickering (Regius Professor of Medicine)*

developed mitral incompetence and efforts to repair this were unsuccessful. Alf was enormously supportive to all of us who were shocked and very sad. As junior staff, we thought that the hierarchy scarcely noticed us but, two years later when I was working in Newcastle, I was invited by Prof. Pickering to attend an interview for the Radcliffe Travelling Fellowship. It was the winter when England froze for several months and I had a very long drive to Norham Gardens where I was introduced to the other candidate as “Dr Neale, whose stiletto heels have ruined the floor of the Professor of Surgery's houseman's office”. I did not get the Fellowship!

We felt well prepared for house jobs partly because student locums were given a lot of responsibility from the word go. I recall doing some of the admissions of surgical patients because the HS could not do them all. We also took bloods and put up drips. Once, when doing a paediatric locum, I was warned that an unauthorised man was visiting a child and to be on my guard. One evening a man in a raincoat walked into the ward and straight up to the child, whipping out a stethoscope as he did so. Trying to be tactful but alert I went up to him and asked “Excuse me, are you this child's GP?” He turned to me and said “My name's Grimshaw and I am a thoracic surgeon at this hospital. If I may give you a word of advice young woman, never use the term ‘GP’, always ask if they are the ‘family doctor’.”

John Hampton says his 6 months with Pickering were the best in his life – I agree so far as my medical career is concerned; wonderful medicine surrounded by clinicians who were all at their peak, and who provided constant encouragement, stimulation and critical thinking.

## News from Osler House



### Alexander Mafi, Osler House President 2018–19

We're now deep into the academic year which means some exciting events for Osler House. Our sixth years finished their finals in February and were greeted in Osler House by a prosecco reception to celebrate the end of exams. Many of them are now jetting off to various corners of the globe on their electives with more due to fly out in April. Our fifth years have also celebrated being halfway through clinical school with a big 'Halfway Hall' event at St Edmunds Hall. We're looking forward to putting on a 4th year Easter dinner and our annual Osler Ball this summer.

The new Tingewick firm took over in January and are now in full swing organising social and fundraising events, hoping to beat the incredible £42k target set

by their predecessors. (This money will be split between Medicines Sans Frontieres and South Oxfordshire Food and Education Alliance.) Osler House recently played host to a sea of very green students dancing into the night at the Tingewick organised St Patrick's Day bop. All the proceeds this year are going towards Aspire Oxford and Oxford Sexual Abuse and Rape Centre.

In other news, Osler now comes with a brand-new water fountain to accompany our new gym. Plans are also in the works to upgrade the gym, the main dining area and to introduce a new coffee machine to ensure our clinical students are kept sufficiently caffeinated.

My thanks go out to the Osler committee for their continuing hard work over the year!

left © Nigel Blackwell, right © Academy Of Medical Sciences/John Cairns Photography



Richard Blackwell



The Da Vinci Robotic Platform is used for colorectal surgery

## Richard Blackwell Pharsalia Professorship will enable a ‘scientist surgeon’ to lead the way in the treatment of colorectal disease

**The University of Oxford is delighted to announce the creation of a new professorship in the medical sciences, thanks to the generous support of the Pharsalia Charitable Trust.**

The chair has been supported by Nigel Blackwell, Senior Trustee of the Pharsalia Charitable Trust, and will be named after his father, Richard Blackwell.

Richard Blackwell’s international bookselling and publishing business originated from Blackwell’s university bookshop on Broad Street, Oxford. His lifelong support of the University included replacing the two missing Muses, Melpomene and Euterpe, on the empty plinths on top of the Clarendon Building in 1974. He also awarded multiple gifts to Oxford colleges in 1979 – Blackwell’s centenary year – and his donation to St Cross College enabled its merger with Pusey House, thereby repaying Blackwell’s ‘debt of gratitude’ to the University.

The impact of the Richard Blackwell Pharsalia Professorship in Colorectal Surgery will be substantial, assuring major investment in advancing knowledge and expertise in colorectal conditions and related health issues. The value of this work in informing other areas of research beyond this specific area of medicine will also be considerable.

Colorectal cancer is common and the subject of a well-established national screening programme. Early stage tumours can be cured, and this field of surgery has witnessed great strides in high-technology and minimally-invasive techniques. Moreover, research into colorectal polyps, adenomas and tumours provides an important window into cancer mechanisms, the results of which are instructive in the investigation of other types of cancer.

The development of targeted therapies for inflammatory bowel diseases – chronic relapsing conditions affecting young people, such as ulcerative colitis and Crohn’s disease – is also yielding breakthroughs. Among these is the treatment of patients through timely surgery

using key hole techniques, the results of which can immeasurably improve quality of life.

Professor Freddie C Hamdy, Nuffield Professor of Surgery and Head of the Nuffield Department of Surgical Science, says: ‘The addition of a statutory chair is a major benefit for Oxford owing to the University’s existing excellence in surgical science and bio-engineering.

‘Colorectal cancer is a curable cancer. That’s one reason why the new chair is so exciting to us. We have long wanted it but lacked the resources. The holder of this chair will be a leader developing a research group, a ‘scientist surgeon’ – another reason for encouragement because, traditionally, surgery and research have been separate endeavours.’

For Nigel Blackwell, the endowment of this chair in his father’s name has great personal resonance: ‘My father, Richard Blackwell, was a man of virtue and principle, generous and self-effacing. His faith and beliefs were shaped by the experience of wartime service in the Royal Navy, where he saw action and hardship and was decorated for bravery.

‘Returning from the war, he kept the promise made to his father at the age of seven that he would ‘help him in his business’ and it became his life’s work to build a large, complex and successful international bookselling, library service and publishing organisation. The founding of this chair means his name and achievements will always be remembered.’

The endowment of the Richard Blackwell Pharsalia Professorship in Colorectal Surgery is also generously supported by the Lee Placito Medical Fund. The chair will be a fellow of Linacre College and it is anticipated that the position will be filled before the end of 2019.



### Contacting OMA

Oxford Medical Alumni  
University of Oxford  
Sherrington Building  
Parks Road  
Oxford OX1 3PT  
oma@medsci.ox.ac.uk  
+44 (0) 1865 282 541  
[www.medsci.ox.ac.uk/oma](http://www.medsci.ox.ac.uk/oma)



## Events and Reunions in 2019

### June

Friday 7 June **50th Anniversary Reunion**  
(1967 and 1968 clinical school intake)

Saturday 15 June **10th Anniversary Reunion** (2009 qualification)

### September

Saturday 21 September **The Osler Lecture** given by Professor Irene Tracey, Head of Department & Nuffield Chair in Anaesthetic Science, Nuffield Department of Clinical Neurosciences, University of Oxford

Saturday 21 September **Oxford Medical Alumni Drinks Reception**.  
Join us after the Osler Lecture at St Luke's Chapel.

Friday 20–Sunday 22 September **Meeting Minds: Alumni Weekend Oxford**

### October

Saturday 5 October **40th Anniversary Reunion** (1979 qualification)

### November

Saturday 23 November **30th Anniversary Reunion** (1989 qualification)

Wednesday 27 – Saturday 30 November **Tingewick**. Tingewick is turning 80 this year. If you are interested to attend a celebratory event for Tingewick on the last night of the show, please do contact us.

### 2020

Reunions will take place for those who qualified in **1980, 1990, 2000** and **2010**.

If you entered the clinical school in 1969 (March or September), please do contact us about your 50th reunion.

Tickets for the reunions can be purchased through our website:  
[www.medsci.ox.ac.uk/oma](http://www.medsci.ox.ac.uk/oma)

If you qualified in one of these years and would like to offer any suggestions or advice for the organisation of these events, please do contact us.  
Thank you.

## Oxford Medical Lecture Club

The Oxford Medical Lecture Club has been running for many years and has been welcoming fascinating speakers each month to talk about their speciality and the latest developments in clinical and research work. Recent speakers include the neurosurgeon, Mr Henry Marsh; Professor Peter Rothwell, Director of the Centre for the Prevention of Stroke and Dementia and the Forensic Psychiatrist, Dr Susan Iles.

The lecture is held at Osler House on the site of the John Radcliffe Hospital and occurs on the last Monday of the month. The dates of future meetings this academic year are Monday 20 May and Monday 24 June. There are no meetings in July and August.

If you are interested to receive notifications of the meetings, please do contact OMA by phone or email.

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