fusion

THE NEWSLETTER OF THE SIR WILLIAM DUNN SCHOOL OF PATHOLOGY

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UNIVERSITY OF OXFORD

Editorial

It has been a dramatic year in the life of the Dunn School. On the good side, the Department scored first nationally in the recent research assessment exercise, Jordan Raff has joined as the new Milstein Chair of Cancer Molecular Biology, and work has been initiated to replace the former Leslie Martin building with new laboratories to be known as the Oxford Molecular Pathology Institute (OMPI). We have also recently welcomed Prof Bass Hassan who has relocated his laboratories to the Dunn School, so helping establish a critical mass in cancer research within the Department. On the sad side, three of our most senior colleagues (Siamon Gordon, George Brownlee and Gordon Macpherson) have retired, leaving a massive hole in the research and teaching life of the department. The chairs vacated by these retirements cannot be filled until OMPI is completed at the end of 2010.

Our hope is that the new space created will not only enable us to fill our vacant posts with scientists at the highest level, but will also allow us to harbour more joint appointments with the Clinical School. In the past 15 years the Dunn School has undertaken a very high level of rebuilding and refurbishment activity, all aimed at maintaining the Department as a world-leader in biomedical research. Our colleagues have been remarkably patient and accepting of these intrusions, and I am pleased to say that the morale and spirit of the School is as high as ever.

It is very satisfying for us that so many alumni have taken pleasure from receiving past issues of *Fusion*, and we hope that we can continue to keep you updated about our aspirations, developments and achievements as we meet the building and recruitment challenges of the next three years.

Herman Waldmann

Contents

Introducing Jordan Raff

Centrosomes have dominated my scientific life. These tiny organelles were first described more than 100 years ago, and they have always had an air of mystery about them. Through most of the cell cycle, a typical animal cell has a single centrosome, which functions as the major microtubule organising centre. Through these microtubules (MTs), the centrosome plays an important part in organising many aspects of the cell — positioning other organelles (Fig. 1), directing the movement of intracellular vesicles, and helping to establish and maintain cell polarity. But, it is during cell division that centrosomes have their most dramatic role. Before a cell divides, it must replicate its centrosome, and it must do so only once. Each of the two daughter centrosomes then send out radial arrays of hundreds of MTs, which capture the replicated chromosomes and line them up at the centre of the mitotic spindle (Fig. 2); the MTs then separate each of the replicated chromosomes into two daughter chromosomes, pulling the two to opposite poles of the spindle.

Because of their importance in cell division, it has long been thought that centrosome dysfunction might contribute to the development of cancer. Early in the previous century, researchers noted that many types of cancer cells had lost or gained chromosomes or had rearranged their chromosome arms — a phenomenon now called chromosomal instability (CIN) — causing the genome of cancer cells to be in constant flux. Moreover, studies of early embryonic cells revealed that cells that enter mitosis with more than two centrosomes could form multipolar spindles, leading to the missegregation of chromosomes and CIN. In a classic paper in 1914, Theodor Boveri proposed that errors in chromosome segregation are a major driver of cancer and that centrosome amplification (in which cells have too many centrosomes) is likely to be a major cause of these segregation errors. We now know that there is a strong correlation between centrosome amplification and CIN in many cancers, but it has been difficult to test whether these defects are a cause or a consequence of cancer development.

I first became interested in centrosomes largely by accident. After graduating from Bristol University, I initially wanted to work in advertising. At my first job interview in London, however, I was introduced to one of the gods of advertising, as he had come up with the idea for the monkey adverts for *PG Tips* tea. I never liked these adverts, so I decided I should raise my sights and joined David Glover's lab as a PhD student at Imperial College London, who was working on centrosomes and the cell cycle, using Drosophila embryos as a model system. I got off to an unpromising start, announcing at one of the first group meetings I attended that I thought most of the mutants being studied in the lab, which had funny names like Polo and Aurora, probably had nothing to do with the cell cycle. (How wrong I was only became apparent some years later.) Although my scientific instincts clearly needed some fine-tuning, I loved doing experiments, and, especially, working at the microscope, which is still true today.

During this period, I developed methods for following early Drosophila embryos after blocking nuclear division with an injection of a drug that inhibits DNA synthesis. Surprisingly, I found that the centrosomes in these embryos carried on dividing, even though DNA synthesis and nuclear division were blocked. Even more surprising, I noticed that centrosomes were able to induce the formation of the first differentiated cells in the embryo — the pole cells — without the need for nuclei. This was a crucial moment for me: it was my first real discovery, and it indicated that centrosomes had unexpected functions that might be involved in all sorts of developmental processes. I decided to focus on understanding how centrosomes worked at the molecular level.

To this end, I did my post-doc with Bruce Alberts at UCSF. Bruce was most famous for his biochemical work on T4 DNA replication (as well as the popular cell biology textbook), and I realized that I needed to learn more biochemistry if I hoped to understand centrosome function. The Alberts lab had recently started to work on Drosophila and was developing techniques to purify MT-binding proteins, to fluorescently label them, and to follow their behaviour and function after injection into Drosophila embryos. These techniques proved to be crucial for my own future work. I spent nearly five years in the Alberts lab, working on isolating and characterising centrosomal proteins, and I continued with these studies when I set up my own lab in 1994 at the Wellcome/CRC Institute (now the Gurdon Institute) in Cambridge.

Although we and many others have made progress in dissecting the molecular structure and function of centrosomes, our most surprising and, probably, our most important observation to date is that fruit flies can develop into morphologically normal adults even when they have gone through most of development without any centrosomes at all. Having spent most of my scientific life devoted to centrosomes, this finding came as something of a body blow. Although its significance is still hotly disputed in the field, our

subsequent studies have convinced me that most Drosophila cells can survive remarkably well without centrosomes, and I suspect that this will also be true for the cells in more complex eukaryotes.

Luckily for us, however, we found that at least one Drosophila cell type really does not do well without centrosomes — neural stem cells, or neuroblasts. As typical of stem cells, these cells normally divide asymmetrically: the neuroblasts produce another self-renewing stem cell and a smaller cell (called a ganglion mother cell) that divides only a few more times before differentiating into either a neuron or glial cell. In the absence of centrosomes, however, the neuroblasts often fail to divide asymmetrically, leading to the production of too many neuroblasts. Given the general importance of stem cells, we plan to continue our efforts to understand why centrosomes are important for neural stem cells in flies, and we are testing whether they are also important in stem cells and progenitor cells in higher eukaryotic organisms.

We had created flies without centrosomes by mutating a protein that was essential for centrosome replication. We, and others, have now shown that only a relatively few proteins are essential for centrosome replication. Moreover, we found that the over-expression of just one of these proteins can drive extra rounds of centrosome replication and thereby generate flies with too many centrosomes. This allowed us to test directly Boveri's hypothesis that centrosome amplification can drive chromosomal instability and promote the development of cancer. As so often happens in biology, answering this question only raised many more questions. Counter to Boveri's prediction, we found that centrosome amplification did not generate large-scale chromosomal instability, but, consistent with his hypothesis, it did promote the development of tumours. As was the case in flies without centrosomes, flies with extra centrosomes had defects in neuroblast asymmetric divisions, which might help explain how centrosome amplification leads to tumourigenesis without, apparently, causing large-scale chromosomal instability. We are now trying to understand the link between centrosome amplification and tumour formation.

"...I feel fortunate and honoured to be the first holder of the Cesar Milstein Chair in Cancer Cell Biology in the Dunn School"

As a biomedical scientist in Cambridge, I was well aware of Cesar Milstein, and I was lucky enough to meet him briefly on a visit to the LMB several years ago. He was a towering figure in immunology, and I feel fortunate and honoured to be the first holder of the Cesar Milstein Chair in Cancer Cell Biology in the Dunn School. My lab colleagues and I are excited to be moving to Oxford: Alan Wainman and I have already made the transition, while Paul Conduit, Anna Franz, Richard Reschen, Jenny Richens, and Naomi Stevens will be moving from Cambridge in mid-September. We very much look forward to becoming part of the Dunn School community over the coming weeks and months.

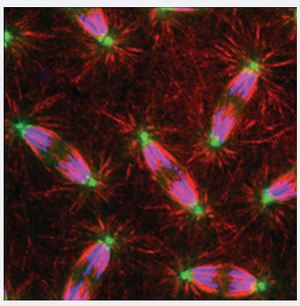

Figure 1. *Mitosis in an early Drosophila embryo. This image shows a field of nuclei synchronously dividing. The centrosomes (green) organise microtubules (red) into a mitotic spindle that ultimately separates the replicated chromosomes (blue).*

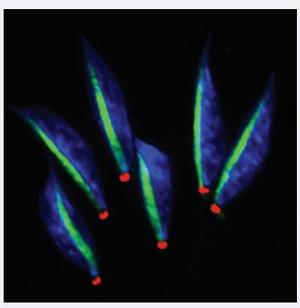

Figure 2. *Centrosomes organise cilia and flagella. This image shows a cluster of sperm heads. A single centrosome (red) sits at the end of the elongated sperm nucleus (blue and green) and organises a motile flagellum (that is not shown in this picture).*

Making a gift to the Dunn School

The Dunn School owes its existence to a philanthropic gift, from the Trustees of Sir William Dunn, and over the years has been the beneficiary of many acts of philanthropy, not least from those who have worked here. Any gift made to the Dunn School helps to further research here, whether it is made to support a specific initiative such as the ones described in this newsletter, or at the discretion of the Head of Department.

If you would like to make a gift to the Department this year, please use the gift form enclosed with this edition of *Fusion.* Please make sure that you have completed a gift aid form so that we can reclaim tax on your gift, and note that if you are a higher rate tax-payer, you can also set your gift against your tax liability for the year. All gifts made to the Dunn School from the USA are also fully tax-deductible, when made through the University's 'giving vehicle' there, the *Americans for Oxford, Inc* organization.

Life and Trypanosomes

Catarina Gadelha

Of the World Health Organisation's list of 10 "neglected diseases", three – African trypanosomiasis, Leishmaniasis, and Chagas disease – are caused by protozoan trypanosomes that kill around 120,000 people per annum. Human African trypanosomiasis, or sleeping sickness, accounts for an estimated 60,000 of those deaths. Along with the impacts on human health, a form of trypanosomiasis also affects cattle and severely limits the use of productive cattle breeds across areas of sub-Saharan Africa.

If untreated, human African trypanosomiasis is invariably fatal and current treatments are unsatisfactory. If we wish to help in combating sleeping sickness, we must understand the biological differences between the parasite and the host that might provide clues for new drug development.

Since joining the Dunn School in 2005, I have worked in two labs, both with interests in novel aspects of trypanosome biology. First in the lab of Keith Gull, I studied trypanosome-specific cell biology and now with Steve Bell, whose lab works mainly on Archaeal DNA replication and cell division, but with an additional interest in trypanosomes.

Trypanosomes and endocytosis

After being transmitted by the bite of a tse-tse fly, African trypanosomes are able to survive extracellularly in the human bloodstream while being fully exposed to the immune system. They accomplish this feat through the expression of a series of immunologically-distinct cell surface coats. Each coat is produced from a single type of variant surface glycoprotein (VSG). Periodic switching of the single expressed VSG gene from a vast silent library enables the parasite to avoid clearance by the host's adaptive immune response. Many invariant surface receptors for endocytosis are concentrated in a protected invagination – the flagellar pocket – at the base of the flagellum. This relatively small region of membrane is the sole site for all endo- and exocytosis performed by the parasite. In fact, the trypanosome flagellar pocket has the highest endocytic capacity ever measured for eukaryotes, and is able to recycle an area of membrane equivalent to the entire cell surface in just 7 minutes!

In spite of its major role in pathogenicity, we were lacking a clear understanding of how the flagellar pocket is organized and compartmentalized to perform its functions. Whilst working in Keith Gull's lab we used electron tomography to construct a detailed 3-dimensional map of the pocket (Fig. 1). Our map enabled us to see a set of cytoskeletal boundaries that demarcate the flagellar pocket membrane domain. This raised the question of how macromolecules, essential to the parasite, cross these barriers and gain access to the pocket lumen, such that they can be internalized by the cell. The answer to this question came when we slowed down the trypanosome endocytic capacity by placing the parasite in the cold. Under these conditions, trypanosomes continue to swim, and macromolecules are able to enter the pocket, but internalization is blocked. We saw that receptor-mediated

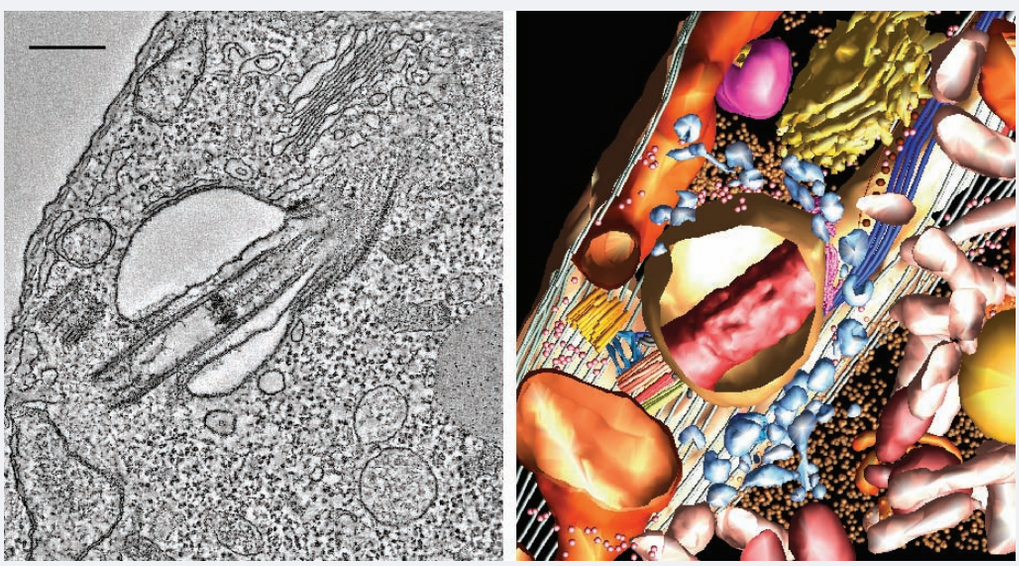

Figure 1 *An invagination of the surface membrane provides a protected environment for endocytosis in trypanosomes. Bar, 250nm.*

and fluid-phase endocytic markers were concentrated in a continuous channel connecting the outside of the cell to the flagellar pocket interior. The channel traverses those boundaries that protect the pocket environment, and thus represents a major route of transport into the lumen.

Our 3-dimensional ultrastructural approach was also used in the study of the architectural arrangement of the cytoskeleton and other organelles in a highly polarised manner around the pocket. Sylvain Lacomble, Sue Vaughan and myself observed that this architectural arrangement is inherited through the trypanosome cell cycle, and our analysis revealed the duplication timings and rotational movements that directed the inheritance of functional flagellar pockets to the next generation of daughter cells. At the start of these analyses, we were acquiring tomograms through collaboration with Prof Dick McIntosh at the University of Colorado. But the Dunn School now has a fully equipped electron tomography suite, and Mike Shaw is assisting other groups in the department with questions that can be addressed via EM tomography.

Trypanosomes and DNA replication

My current post-doctoral position in Steve Bell's lab, which I began in March 2009, involves a different aspect of trypanosome biology: the machinery of genome replication. In the last 4 billion years of life on earth, two distinct sets of DNA replication proteins have evolved: one used by bacteria and a second common to both archaea and eukaryotes. The archaeal system is in many ways a simplified version of that in eukaryotes such as ourselves, and this is one of the reasons for the Bell lab's interest in archaeal replication. Interestingly, DNA replication in trypanosomes turns out to be at an intermediate stage between the minimal machinery of our archaeal ancestor and the complex one seen in vertebrates. By studying these parasites, we may gain insights into how the simple replication structure evolved.

My research focuses on dissecting and understanding the mechanisms by which the parasite replicates its genome. To do this I am using computational methods to analyse the parasite genome, looking for sequences that are plausible candidates for origins of replication. I then take these origin candidates and test their function in replication using 2-dimensional DNA electrophoresis – a technique which can separate DNA fragments on the basis of physical structure. Replicating DNA has a characteristic fork, or – at the origin – bubble shape that migrates on such gels in a manner distinct from linear DNA.

After identifying origins of replication, I intend to look at the proteins that are recruited at these particular DNA regions during replication, their evolutionary distribution and function. Comparative genomic approaches can be used to look at the evolutionary distribution of these components and, thanks to efficient tools for genetic manipulation of trypanosomes (several of which were developed in Keith Gull's laboratory) RNA interference can be used to test for lethality.

Trypanosomes and art

Parasitologists are said to fall in love with their model organisms, and spend a long time admiring their curves and shapes. I confess I'm no exception to this rule – after many hours in Mike Shaw's electron microscopy suite looking at thousands of cells, I decided to take these impressions to my mosaic class. The result is this mosaic representation of a fly-form *Trypanosoma brucei* (as seen by detergent-extraction, negative staining electron microscopy) (Fig. 2). Transforming my research theme into art was such an enjoyable experience that I have since made many more protist mosaics. I am now looking for new sources of inspiration. Perhaps a mosaic of the molecular structure of penicillin? Hmm, that sounds like an idea...

Figure 2. *Mosaic representation of a* Trypanosoma brucei *insect form. The black tile on top right represents 1μm.*

The Dunn School: Out of Africa

Keith Gull

Many associated with the Dunn School will know of its long standing connections with Africa, not least of which are those of our original benefactor Sir William Dunn. More recently Siamon Gordon used his strong connections to assist South African science and scientists. Over recent years I have become increasingly involved in teaching and mentoring of young African scientists. These efforts have drawn on my group's molecular parasitology research and teaching expertise in general and African trypanosomes in particular.

Figure 1. *Dr Eva Gluenz demonstrating image capture and display on the Dunn School fluorescence microscope to Professor Sammy Sacker and students on the course in University of Legon, Ghana.*

The new millennium produced a step change in our knowledge of the vectors and parasites that cause tropical diseases. I and others worked hard in the 1990s to convince funding agencies to include the major tropical disease parasites – *Plasmodium* (malaria), *Trypanosoma brucei* (African trypanosomiasis), *T. cruzi* (Chagas Disease) and *Leishmania major* (Leishmaniasis) in the list of genome projects. These diseases are amongst the most devastating and intractable in the developing world. WHO estimates around one million deaths from malaria per annum with around 110,000 deaths from the other three diseases. The morbidity and social effects of these neglected diseases lead to massive hardship in developing countries. The sequencing of these genomes was achieved in 2005 and immediately made the biology of the parasites open to post-genomic interrogation by scientists around the world. However, it was apparent that although this was a superb opportunity for many young scientists in Africa to engage more productively and collaboratively with research on these diseases, there were intrinsic difficulties. Expertise in bioinformatics, comparative genomics and experimental post-genomic molecular and cell biology techniques was limited, both amongst MSc and PhD students as well as young staff in African Universities and research institutes.

Figure 2. *Dr Bill Wickstead teaching practical classes on the Ghana course.*

I had contributed to biomedical courses in Africa for many years but with the above in mind I used part of a Human Frontiers Science Program grant to design a course in Kampala, Uganda on "Bioinformatics and Post-Genomic Molecular Cell Biology of African Trypanosomes and Malaria". The course involved my laboratory as well as USA, Belgium, Ugandan and Kenyan scientists teaching a mixture of lectures, seminars and computer exercises. We provided an insight to parasite genomes and bioinformatic techniques, but placed that information in the context of how it enables discovery biology for drugs and vaccines in these neglected diseases. Twenty five students from Uganda, Kenya, South Africa, Mali, Nigeria, Cameroon, Malawi and Ethiopia attended the course which was heavily over-subscribed with over 250 applications. I raised funds from many sources to allow all students to attend free of charge and to facilitate all travel,

Figure 3. *Professor Keith Gull shown at the ceremony donating the fluorescence microsope to the Head of Department (Professor Sammy Sacker) at the Biochemistry Department at the University of Legon,, Ghana. Also shown is Dr Jonathan Adjimani a co-organiser of the course and member of the department.*

accommodation and course infrastructure. The quality of the students and their enthusiasm for modern parasitology research and teaching convinced us to raise more funds for future courses. Such partnerships have resulted in myself, together with Eva Gluenz and Bill Wickstead from my laboratory (Figs 1 and 2), helping to organise and teach two further courses: a two week course in the University of Morogoro, Tanzania during 2008 and, in July 2009, a two week course in the University of Ghana, Legon.

We provided lectures and practicals on trypanosomiasis during the course as well as advice to students on experimental design, their own project plans and career opportunities. Eva Gluenz and Bill Wickstead designed both full-day wet bench and virtual interactive practicals. The latter consisted of an MSc-length set of data in raw form that allowed students to move through the identification of an important parasite pathogenicity gene and its analysis by reverse genetics, to phenotyping of the mutant parasite. Students designed the experiments themselves and were then provided with sets of raw results (the data ranging from bioinformatics, to molecular biology, western and northern blots, immunofluorescence and electron microscopy). They interpreted data, planned the next stage and progressively moved through the study over an intense day of interaction with the tutor.

This July in Ghana the wet-bench practical work was designed to teach immunofluorescence diagnosis of parasites in blood and benefitted massively from the donation of an unused fluorescence microscope and colour CCD camera by the Dunn School (Fig 3). My lab set up the microscope in the department, tested it and organised new computer hardware and software to allow image capture and analysis. It was then carefully packed and shipped to Ghana. It worked straight out of the box and 25 West African students from Ghana, Mali, Cameroon, Nigeria and Benin produced superb immunofluorescence images at the end of the practical classes run by Bill and Eva!

"These efforts will continue and an on-going programme of courses, equipment and book donations is planned for both East and West Africa. This takes time and money but all efforts invested by members of the Dunn School are intensely appreciated by colleagues and students in these sub-Saharan African universities."

In addition to courses, I am running a programme of sourcing textbooks for the various departments in Africa where we have these teaching connections. Two years ago we sent a major donation of nearly-new textbooks to the Biochemistry department at the University of Minna, Nigeria where one of my old students is head of department. This summer we are arranging for other books donated from Dunn School staff, students and college libraries in Oxford to be sent to departments in Ghana and Botswana.

These efforts will continue and an on-going programme of courses, equipment and book donations is planned for both East and West Africa. This takes time and money but all efforts invested by members of the Dunn School are intensely appreciated by colleagues and students in these sub-Saharan African universities. In October, I will move to a joint position: while my chair and laboratory will continue within the Dunn School, I shall also become Principal of St Edmund Hall. It is my hope that through the joint fund-raising efforts of both of these successful institutions, I shall be able to assist in building a secure future for molecular pathology, microbiology and medical research within the Dunn School while, at the same time, expanding our efforts to assist in developing the careers of talented young African scientists.

Tales of the Unexpected: The Twists and Turns of a Life in Science

George Brownlee

"My Dear Sir, I was so unwell all yesterday with a bad cough, that I am sorry I shall not be able to dine with you today in Hall. I am afraid your good Downing dinner won't at all suit the influenza." (Charles Darwin to a member of Downing College, Cambridge, 19th January 1837)

Research in Cambridge (1963-1980)

When I started research as a PhD student with Fred Sanger in 1963, I was, like many students starting their research today, unsure what I should do. Sanger had recently joined Max Perutz, Francis Crick and Sydney Brenner in the newly-built Laboratory of Molecular Biology on the outskirts of Cambridge, supported by the Medical Research Council. Would research be a worthwhile career or would medicine be right for me? I had, after all, studied pre-clinical subjects as an undergraduate at Emmanuel College, Cambridge and had a place to continue in clinical medicine at University College, London. But I was attracted to biochemistry in my third year in Cambridge and that is what persuaded me to apply to do a PhD. Sanger already had one Nobel Prize for sequencing insulin: he was to obtain a second in 1980 for his dideoxy method of sequencing DNA.

Apparently, when Fred Sanger asked me at interview whether I wanted to study proteins or nucleic acids, I replied the latter. I was delighted when he agreed to take me, but at that time I did not know how fortunate this was, since I did not know him well. In fact it took me a year to buck up courage to call him Fred. Sanger was a major influence on my career. He had a way of helping, without appearing to be bossy or interfering. In fact he encouraged initiative which, as I learned later, is what all mentors hope will emerge in their students. By seconding me for 9 months to work with Robin Monro in Crick and Brenner's section, I also met my future wife, Susan, who was Robin's research assistant. Susan remembers me then (so she tells me now) as a scatty research student, always losing my notebook and essential protocols!

My research with Robin Monro was unproductive so I returned to the Sanger lab, one floor up, and proposed my own project to Fred. To my surprise, he raised no objection to my studying a small ribosomal RNA, instead of the transfer RNA that I was meant to be purifying. I finally managed to sequence this small RNA, which became known as 5S RNA, in 1967. It took about 4 years, using the then state-of-the-art methods, to deduce its sequence of 120 nucleotides. I needed help from Sanger and his assistant, Bart Barrell, to complete this sequence. Perhaps my main attribute was that I was persistent and did not give up easily.

Thinking back to the 1960s, it is amazing to recollect now how little we then knew. When I started my research there were no DNA or RNA sequences known longer than about 4 nucleotides. The genetic code was unknown. Only a few proteins, such as insulin and ribonuclease had been sequenced. Cloning and PCR had not been thought of. Yet we embarked on sequencing RNA in the Sanger lab with the vision that this would eventually become faster and easier, and that new information would emerge.

What did I learn in this first period of my career, as a student, then a young post-doc and a staff member in Sanger's section of the lab? I learned how to interact with other scientists, to discuss my work openly, to take advice, to work with PhD students and to initiate new lines of research. I also noticed the differences in approach to science by the team leaders. Sanger was very practical, down to earth, not inclined to extensive, theoretical discussion. He always emphasized the experimental approach. His advice was always to "try it out"; if necessary "vary your experimental approach" for a given problem. César Milstein, by contrast, liked long and intensive discussion. But all the senior staff were positive, helpful and encouraging to younger scientists, like me.

I was involved in a number of fundamental discoveries in this period, some with my students e.g. Nick Proudfoot, in 1976 of the AAUAAA polyadenylation signal at the 3′ end of mRNA. Francis Crick once asked me, when I talked about this work, why we bothered to study mRNA sequences when we already knew the genetic code? The answer, of course, was that the non-coding sequences in mRNA were of interest and would have to have some important function. Having said this, it is still unclear to me, even now, why many mRNAs have such long non-coding regions.

The environment I worked in encouraged me to study novel and important questions. The projects were open-ended and novel. We did not know how long the project would take or even if it would succeed at all. One quite novel discovery emerged from my interest in sequencing immunoglobulin mRNA. With César Milstein, Mike Matthews and my first PhD student, Tim Harrison in 1972, we discovered an N-terminal signal sequence responsible for the secretion of an immunoglobulin light chain from the cell. This was the first time that anyone had provided experimental evidence for how proteins were secreted from the cell. Another discovery, somewhat later in 1976, with Claude Jacq and another student, Ross Miller, was the presence of pseudogenes in DNA. We invented this term to describe, apparently, non-functional, near-repeat DNA lying adjacent to the 5S genes of *Xenopus laevis*. Pseudogenes are now known to be widely distributed in the human genome. These discoveries, both surprising and unpredicted, will remain with me as one of the joys of science – finding out something quite new and unexpected. Whether others fully recognized this contribution or not is immaterial – one always remembers the excitement of an important discovery.

Cambridge to Oxford (1980–2008)

When I was contacted by Sir Henry Harris with the news that the Dunn School of Pathology wanted to appoint me to a new Chair (the Edward Abraham Chair) in Chemical Pathology, in association with Lincoln College, I accepted. It was just too good an offer to miss, giving me about ten times the lab space I had in Cambridge, the chance to run my own section in Pathology, to build up molecular biology in Oxford and to meet other Fellows in Lincoln. Moreover, I had tremendous support from Henry Harris. The late Rodney Porter, then Head of Biochemistry and, like me, a student of Fred Sanger, encouraged me as well. It did not seem to worry Henry that I was not really working on any aspect of Pathology (although I had very recently in Cambridge started to work on the flu virus), that I had little teaching experience and had never examined formally!

"Make sure you have access to research students" and "send your profuse apologies to statutory committees that you are obliged to attend", Max Perutz, head of the Laboratory of Molecular Biology in Cambridge, advised me. I took both to heart. Even more important was the appointment of Barbara Paxman, MBE as my PA. Her input into the smooth running of the Unit, continued by Joanne Collett after she left, were essential to the success of the Chemical Pathology Unit. Following Max Perutz' advice and with my PA's help, I set about applying for our own quota of research studentships from the Medical Research Council, the BBSRC and the Wellcome Trust. Over the period 1981–1998, after which we amalgamated with the Dunn School as a whole, we were awarded more than 20 studentships in total.

It was important to me that I was able to attract Francesco (Tito) Baralle and Nick Proudfoot to the Dunn School from Cambridge, because initially we were quite isolated from other research groups. Both Tito and Nick quickly established their own vibrant research groups and were also successful Tutorial Fellows — Tito at Magdalene and Nick at Brasenose College. Tito was interested in genes controlling blood lipid and cholesterol levels and with his student, Carol Shoulders, isolated a number of genes for the first time, such as the apolipoprotein A genes. With Alberto Kornblihtt, a post-doc from Argentina, he also cloned fibronectin, which occurs in different protein isoforms. Tito's group was one of the first to recognize alternative splicing in the human genome as the mechanism for generating protein isoforms. The only problem at that time was that the UK was at war with Argentina and Alberto, as an Argentinian citizen supported by his government, was required to return home from enemy country (the UK). Other strategies had to be devised to ensure he was able to continue working at the Dunn School during this challenging period. Nick Proudfoot continued the work he had initiated with me in Cambridge on polyadenylation and started to study termination of transcription, initially of the α and β globin gene cluster with Tim Humphrey and other DPhil students, and subsequently with Emma Whitelaw and others, who came as post-docs.

The quota research studentship positions were vital for Tito, Nick, Jeff Errington (who joined us later on Tito's departure) and me in establishing our research groups. I also set up shared facilities in the Unit so that we all shared commonly used radiochemicals, enzymes and consumables within the Unit. This saved us all costs on our research grants and ultimately helped us jointly fund new purchases when this became necessary. I remember one year, however, when we were over budget, that we banned the use of disposable gloves because of their excessive cost!

Figure 1. *Barbara Paxman's leaving party. Left to right: George Brownlee, Nick Proudfoot, Jeff Errington (background), Barbara Paxman, Pippa Murray, Penny Handford, Mick Boulger.*

Figure 2. *The Haemophilia B team. Left to right: Peter Winship, Penny Handford, Paul Hughes, George Brownlee, Merlin Crossley, George Petersen (sabbatical visitor).*

I have been asked to say what I did in Oxford that would not have happened had I remained in Cambridge. It is unlikely I would have cloned the factor IX cDNA. Moreover the collaboration with Alain Townsend and Sir Andrew McMichael leading to several papers concerning the mechanism of antigen presentation, would not have happened. On starting a new job in Oxford, I definitely took the view that I should start something new and chose to try and clone the clotting factor IX cDNA, after some initial discussion with Peter Esnouf. This was an ambitious project, far from routine then, since only a few cDNAs had been cloned by the late 1970s, and then only when the mRNA was in good yield. It was also a fortunate choice as I was unaware, at the time, of the existence of the Haemophilia Centre in Oxford and that I would get so much help from its Director, Charles Rizza. My initial interest was in the nature of the genetic mutations in the factor IX gene causing haemophilia B. Indeed we went on to study many interesting mutations later. However, it was only when, with Andy Choo, Jasper Rees and Keith Gould that we were successful in obtaining the first short fragment of the bovine factor IX cDNA sequence in 1982 that I realized that, if we could express factor IX in cells, this could be the basis of a procedure for producing therapeutic recombinant factor IX for haemophilia B patients. This we did in 1985.

As the first holder of a new Chair, that had been established from funds generated by Sir Edward Abraham from a successful antibiotic (cephalosporin) patent, I had resolved to patent anything that could potentially yield a novel therapeutic product. This did not interfere with our ability to publish our work in Nature, as the patents could be filed while a paper was under the confidential review process. Fortunately I did this, with Andy Choo for the first factor IX gene patent and later with Don Anson and Ian Jones on the factor IX protein patent. These patents were licensed to British Technology Group (BTG) directly at a time when Oxford University and the MRC (our sponsors) took no interest in discoveries in Universities. BTG sublicensed the patents to Genetics Institute in Boston, who, in 1999, eventually manufactured recombinant factor IX for haemophilia B patients, thus by-passing the need to isolate factor IX from blood donors. It has been extremely interesting for me to observe how an academic discovery can be translated into a wealth-creating and useful medical treatment. Oxford University has also benefitted from royalties received on these patents, because they helped to permanently endow a new Chair in Molecular Biology within the Dunn School. It is fitting that the first holder of this Chair is Nick Proudfoot, in recognition of his outstanding contributions to molecular biology and gene regulation.

Our main initial contacts in Oxford were actually from Rodney Porter's MRC Unit in the Biochemistry Department. Keith Gould and I had set up oligonucleotide synthesis in-house, as oligonucleotides were key to the factor IX, apolipoprotein and fibronectin cloning. Oligonucleotides synthesized under Keith Gould's direction also helped many others in cloning of genes of for example the complement cascade (Porter group) and later on in cloning lymphocyte surface antigens such as OX2 (now called CD200) by Melanie Clark with Neil Barclay in the Dunn School. In the mid-1980s, Keith Gould and I actively collaborated with Alain Townsend and Sir Andrew McMichael at the Weatherall Institute of Molecular Medicine in elucidating aspects of the then rapidly evolving knowledge of peptide processing and antigen presentation to cytotoxic T cells. T cell epitopes of the influenza haemagglutinin and nucleoprotein served as model epitopes in this study. It was very satisfying to have been able to help others with their isolation of novel clones, and to have contributed to advances in antigen presentation.

I continued my research on influenza virus up to my official retirement in 2008, although I ceased working on the factor IX gene, its promoter and the possibility of gene therapy for factor IX almost 10 years ago, because of difficulties in funding. It is a truism that scientists do their best research work in the earlier years. Later on, if they are lucky, they are joined by talented staff, who carry on the work. As I have got older, I have been fortunate to have worked with Ervin Fodor, initially as a DPhil student, later as a post-doc, and now running his own independent lab. Together, we have intensively studied the process of transcription and replication by the influenza polymerase. Tao Deng, one of my last DPhil students, and Frank Vreede, who joined me latterly as a post-doc, have also made major contributions to our knowledge of replication in influenza virus. We found, to our surprise, that initiation of replication occurs internally on one of the influenza RNA (the cRNA) templates. Also we elucidated one mechanism by which newly-synthesized polymerase subunits are imported into the nucleus.

A very significant advance was made 10 years ago when Ervin Fodor discovered a new method for isolating

influenza virus in the laboratory. The work had started when Ervin took a post-doctoral position in Peter Palese's lab at Mount Sinai School of Medicine, New York University, but only succeeded more than 2 years later after his return to Oxford. With this method, we could introduce 12 expression plasmids into mammalian cells and within 1 week or so isolate influenza virus, or a desired mutation in such a virus, at will. This was a very useful method for fundamental research into the function of the influenza promoter (which we were studying), and for investigating the function of individual influenza proteins. It has been used by Palese and colleagues to regenerate the devastating 1918 Spanish flu. This method — this time patented through Oxford University — also has practical applications in human medicine, e.g. to engineer safe influenza vaccine virus strains in case an H5N1 bird flu pandemic emerges. The method can be used to generate a swine flu vaccine that should be available this Autumn against the current H1N1 Mexican swine flu pandemic.

Finally, I would like to thank all students, post-docs, colleagues and collaborators who have worked with me and made my career so enjoyable both here in the Dunn School in Oxford and earlier in Cambridge. In this short account I cannot mention all their contributions. I have omitted many fascinating stories, e.g. the shot-gun cloning of the influenza virus genome (Stan Fields and Sir Greg Winter); the haemophilia B patients with promoter mutations who recovered spontaneously at puberty (Merlin Crossley, Peter Winship); and the intensive study of the calcium-binding epidermal growth factor domain of factor IX (Penny Handford, Paul Hughes).

A special thanks goes to my research assistants, the late Elma Cartwright in Cambridge, Joyce Huddleston, Vroni Knott and Jane Sharps in Oxford. Joyce Huddleston, who had previously worked with Sir Edward Abraham, deserves special mention because, through her immaculate lab notebooks in 1980, she "shamed" me into improving my own lab records!

The Foibles of Flow Cytometry:
An Interview with Nigel Rust

Could you tell us a little about your background and how you first became involved in flow cytometry?

While working with Andrew McMichael and Judy Bastin to find a marker for human T cells, we generated an anti-platelet antibody (AN51). This was the result of the early techniques of cell separation and the poor discrimination available with radioimmuno assay. At this time, Peter Morris from the Nuffield Department of Surgery, decided to purchase a new instrument called an Ortho Cytoflurograph to phase out the use of the radio assay. He employed Nigel Carter to be responsible for the instrument and help its development in the unit. Andrew proposed that I should learn how to use the instrument for his group: at that stage it was just a single parameter machine.

An upgrade became available in the form of a micro computer that enabled 3 parameter work to be carried out and so we were then able to distinguish different cell types and establish which cells were labelled with fluorescence.

In April 1988, Nigel Carter was offered a post in Cambridge which he accepted, giving 4 week's notice, but as he was on holiday for the final 2 weeks, an immediate replacement was required. I knew how to use the instrument but not how to switch it on or set it up. As I had worked for Peter Morris and had transferred at short notice to Andrew's group, I was asked if I would take responsibility for running the machine, my previous research study having just been completed and published.

Could you explain the basis of flow cytometry for those who have not previously encountered the technique?

Flow cytometry is a technique for studying individual cells in suspension as they flow past a light source (blue laser light), the results being collected by light detectors. The cell acts like an optical lens, changing the angle of the light as it passes through: this blue light is collected as so-called 'Forward Scatter' and gives an indication of the size of the cell. The organelles within the cell reflect the blue light, this is referred to as 'Side Scatter' and gives an indication of granularity. Human white blood cells can be divided into at least four distinct cell populations (platelets, lymphocytes, monocytes and granulocytes) on the basis of these two parameters alone. With fluorescent dyes (which are excited by the lasers in use) we can further define these cells, either by the absorption of dyes that bind internal components or by using monoclonal antibodies (bound to different fluorchromes) to stain antigens expressed on the surface of the cell. Flow cytometers can be divided into two distinct types,

analytical — for giving information about the proportions of cell types found in a sample — and sorters that can separate out these different cell types for further investigation.

How has flow cytometry evolved during the time you have been involved in the field?

When I first started, we used one laser to excite a single fluorochrome. Nigel Carter had just started looking into the reported use of a new reagent called phycoerythrin, isolated from red seaweed. We had a small amount of success, but not a good response from what is now one of the best fluorochromes available.

Due to the instability of the cytometer and the development of more fluorochromes, we purchased two new instruments in December 1995, both capable of 3–5 colour work. One was an analyser that researchers could use to carry out their own experiments and the second was a sorter for the isolation of cells. Since the sorter had two lasers, we were able, for the first time, to extend our studies to the analysis of five colours. The computers also changed to Apple Macintosh in May 1996, allowing further interrogation of the signals given and their manipulation for presentation.

When I moved to the Dunn School, I was able to purchase a state-of-the-art sorter that could use 3 lasers and yield 8 colour data. Earlier this year, I went to a presentation by one of the manufacturers who anticipates the release, in late 2009, of an instrument capable of interfacing with 7 lasers for the analysis of no less than 36 colours, so things continue to evolved rapidly!

Figure 1. *Evolution of the flow cytometer: the Ortho Cytofluorograph.*

Figure 2. *Evolution of the flow cytometer: the Becton Dickinson Vantage 2.*

What has been the most challenging task you have been given during the years you have spent at the Dunn School?

Ironically, the most challenging work was not for a member of the Dunn School, but was to separate coccoliths from clay for Ros Rickaby from the Department of Earth Sciences. Within the Department, it was a challenge to develop the isolation of dendritic cells for Gordon MacPherson's group, and to persuade members of his group that there were more populations than they wished to observe, as they improved their isolation and preparation techniques. The work with Fiona Powrie has always been a challenge as we seem to be constantly moving forward in cellular populations that may influence the autoimmune responses in inflammatory bowel disease.

Which aspects of the service you provide do you find most frustrating and which the most rewarding?

Instabilities in the machine give both of these feelings as they can appear to defy logic and behave irrationally, which for an inert collection of electronic and optical components seems impossible. The most rewarding parts are the ability to surprise people by presenting them with a reasonable number of pure cells at the end of the day, and the acknowledgements I receive at presentations and publications.

What would be your advice to those contemplating using flow cytometry for the first time to purify their favourite cell type?

Come and talk to me first, as well as others who study the same cells and may have already tried flow cytometry, in order to maximize your understanding both of the instrumentation capability and the properties of your cell type. Learn all you can about flow cytometry before you start, either through books, tuition or from online resources. However, by far the best option is always to talk with someone who has more knowledge than you.

Some Reminiscences of the Dunn School

Alvin Volkman, M.D., D.Phil.

Time has fragmented and blurred most of my memories of my stay in Jim Gowans's laboratory at the Sir William Dunn School of Pathology in the early 1960s leaving me with what I think of as a disordered collection of mental flotsam. These debris, nevertheless, seem to remain on perpetual standby ready to pop up at the first evocative word or sight. They are for the most part pleasant memories sometimes uncomfortably so. Resolving to keep a lid on sentiment I did not place the Dunn School on my "must" list when planning a visit to England last year. This omission was not done without recriminations. I had not been back for several years and once in Oxford my interest in seeing the new buildings and progress at the Dunn School eventually overrode personal concerns.

Although I arrived without prior notice Siamon Gordon was gracious enough to receive me and my son, Nicholas, and to give us an update of activities and a tour of the newer facilities plus an outline of plans for the future. The three of us later wandered into the hallowed older corridors, scanned the rogues' gallery for familiar faces, and continued our chat whilst walking slowly along the hallway past the closed doors. Of course we opened the door to the laboratory in which Jim Gowans had worked and I was pleased to see that it was crowded and that the people within seemed appropriately busy.

When we paused for a moment near one of those cater-cornered doors near the stairs I asked Siamon, "Wasn't that Nat Smith's office?" But Siamon had arrived at the Dunn School after Smith had left and didn't recognize his name. I mentioned that Nat Smith was in fact the father of Dame Maggie Smith, the distinguished actress. Siamon commented on how quickly people can be forgotten and suggested that perhaps I ought to write a few words about Nat Smith.

I think of the Dunn School as it was in the early Sixties as an absorbing and unique place to work. Many of the senior scientists had distinguished themselves and had achieved national and international recognition. Several members of the penicillin team of the forties were still working at the laboratory bench. Professor Florey was, of course, a Nobel Laureate. There were, in addition, younger investigators whose stars were rising rapidly. And there were other individuals whose presence and personalities added a special spirit.

But back to Nat Smith. I met him on my first day of work but not immediately. This is how it went. At about 8:15 am on a deceptively fine and balmy summer morning in 1961, I climbed the front steps, grasped one of the shiny brass handles and swung the door open. There before me were several white-coated men and women, all wearing rubber gloves, busily waxing wood and polishing brass. I tried to navigate around them to reach the stairs but a rather small middle aged woman stepped forward nimbly and with the assurance of a fullback folded her arms and blocked my path. She smiled and asked how she could help me. "I am on my way up to Dr. Gowans' laboratory." I said. "It's too early," she replied firmly as she shook her head. "Too early," confirmed the others, like a Greek chorus. "No one comes to work this early," she added, "They would get in our way, don't you see?" I opened my mouth in a preliminary effort to say that I did not see at all, but no words emerged. She seemed to sense victory and suggested that I first go to George's Café in the Covered Market for a "nice English breakfast". She led the way to the door, all the while giving me directions and soon I was headed down the steps, an early bird in full retreat with no worm to show for the effort.

I found George's and ate my first ever "Full English Breakfast," which proved to be a confrontation with cholesterol presented in three or four different forms. I recovered rapidly, however, during the pleasant walk back to the Dunn School. As I approached I noticed a very elegant looking man in his late fifties or early sixties at the bottom of the steps. The white lab coat he wore was heavily starched, thoroughly pressed and exceptionally white. He was about to ascend the steps but paused when he noticed me crossing South Parks Road. As I drew near he smiled and extended his right hand in a cordial manner. "Ah," he said, "You must be new here. I am Nathaniel Smith. Welcome."

This, I thought, is much more the kind of greeting I expected and introduced myself. As we shook hands I noticed that under his lab coat, Nat Smith, as I came to know him, wore a waistcoat spanned by a gold watch chain; his trousers were pressed to a knife-edge; a tasteful silk tie and a crisply starched collar topped his white shirt. Smith had an engaging smile, and an impressive shock of straight white hair brushed backwards. To my surprise he invited me to join him for a cup of tea in his office and I accepted. He presided over tea while telling me about his work. He said that he had assisted the late A.Q. Wells in studies on the acid-fast Vole bacillus as a possible basis for a vaccine against human tuberculosis. Smith's name appears on several of Wells' publications. Wells had worked on this problem for a number of years but eventually vaccines prepared elsewhere from BCG

became the choice internationally. Wells had died a few years earlier and Professor Florey had let Smith stay on.

Smith paused before pouring a second cup of tea; spout poised a few inches above the rim of my cup and asked, "Is my daughter, Margaret…Maggie, well regarded in America?" I was lost for a moment. Why on earth should I know anything about his daughter? I asked myself. Maggie Smith? Then the penny dropped: I remembered from conversations with theatre-going friends that they had been impressed with an English actress named Maggie Smith and that she had received excellent reviews in her first appearance on Broadway in 1956. I myself did not follow theatre closely in those days and was unaware of her recent stage appearances. In 1961 most of the future Dame Maggie's great triumphs of stage and screen were yet to be. My skimpy knowledge about Maggie's standing in America seemed to disappoint Nat but not too many years would pass before he would no longer need to ask anyone about Maggie's accomplishments. Tea and conversation continued but I soon excused myself remembering that my own future lay behind another door in the Dunn School and it was late enough so that my arrival would not mark me as either compulsive or American.

Since that cup of tea with her father, I have seen Maggie Smith in films many times but unfortunately never on stage. When a close-up of Dame Maggie appears on-screen, however, I see something of her father in her face; a few memories flash by and then, in some mystical way, her performance, invariably good, becomes even better.

There were others in addition to Nat Smith who added to the unique character of the Dunn School. I will mention only two. Someone I remember very well is Jim Kent. Prof Florey, I believe, told me that one day, in 1927, while working in a laboratory at Cambridge, he needed assistance. Florey noticed a small, teenage boy sweeping the floor and called him over. James Kent was the young man's name and he was only about fourteen years old. Florey virtually recruited Kent on the spot thus beginning a remarkable relationship that lasted until Florey's death forty years later. By the time I arrived in Oxford Mr. Kent, a short, cheerful and friendly man, seemed to be working as an overseer of technical services and a facilitator for the investigators. Kent, as Florey's technician, had been involved in animal testing during the early assessment of the antibiotic potential of penicillin.He clearly enjoyed telling and retelling stories about his role in these experiments. His favourite and mine, too, was about the day when eight experimental mice were infected with virulent streptococci; half the mice received penicillin and half did not. Detailed accounts of this key experiment have appeared in print many times with appropriate tribute to Florey and to Norman Heatley, a pivotal figure in the penicillin studies, but listening to Kent's eyewitness version gave me a sense of, "You are there." He related it with fitting facial expressions ranging from doubt to wonder and with attempts to imitate Florey's voice and demeanour. Kent said that Florey had slept in the laboratory that night, checking the mice at intervals, and by about 3:00 am the four mice that had not received penicillin were dead; the four protected mice had survived. Kent, who had been sent home at about six in the evening, returned the next morning, (Sunday, May 26, 1940). As he continued, Kent would drop his voice an octave or so: "So the Old Man says to me," he would say, "Kent, I think we've got something here." Biographies and other accounts of what Florey said on this historic occasion quote him as having used the word,"Miraculous." Maybe so, hyperbole was certainly justified but I like to believe that Jim Kent quoted Florey correctly; a few understated and unpretentious words and the antibiotic era began.

One of the most distinguished elder members of the Dunn School during my stay there was Sir Paul Fildes. Sir Paul celebrated his 80th birthday in 1962. He was the son of Sir Luke Fildes, a well-regarded artist and illustrator, who is represented in the Tate. The elder Fildes is remembered in particular for a painting in which he captured the essence of a physician practicing medicine as it was once so admirably done: at the bedside of a sick child in its home. (A copy of this painting stands at the top of the main stairs. One of your editors takes pleasure in showing it to medical students and challenging them to think about its message.)

Early in his career Sir Paul spent some time in the laboratory of the great Paul Ehrlich. Directives to a young Fildes, scribbled by Ehrlich were hanging in frames in the Dunn School library. In World War II Sir Paul achieved distinction as the head the Biological Warfare Laboratory at Porton Down.

To an American, Sir Paul seemed to represent an England of the past at least as portrayed in cinema. By chance, I sometimes was in or near the entry hall just as Sir Paul arrived. He bore himself well and walked a little stiffly but jauntily. Upon arriving at the Dunn School, hat tilted at a rakish angle, he would pause and slowly work his tightly fitting leather gloves off, one finger at a time. He would then slap the gloves into the palm of his left hand straighten his back and ascend the steps. In mild weather when he wore no overcoat I sometimes saw him "shoot" his shirt cuffs before mounting the steps. Cuff shooting is now a lost art but Sir Paul was a master who executed the manoeuvre with flair. The fit of his clothes testified

to the quality of English tailoring and their older styles to the durability of British wool.

Sir Paul was an accomplished raconteur and clearly enjoyed having a circle of listeners gathered about him. His stories were often witty and entertaining despite his reserved demeanour. My favourite story was about an event in World War I, 1915 or 1916, when Sir Paul was in service at the Royal Naval Hospital. The tale, as I remember, went very much like this: "I was in London one night, dining at the Athenaeum with two friends when we heard a strange noise, a waiter was sent to investigate. He returned promptly, highly excited and said, "Sir, it's a German Zeppelin!" My friends and I immediately asked for our coats and hats, ran into the street and looked up to the sky where we saw an airship moving off. We crowded into a taxi and I said to the driver (at this point Sir Paul's eyes twinkled and he smiled ever so slightly as he raised his head and pointed upward) "Follow that Zeppelin!" And off they went, three bon vivants in a taxi careering through the darkened streets of London on the trail of fleeting history.

As I close, I have to confess that I was unable to suppress a surge of distressing nostalgia during my visit to the Dunn School but it was mercifully short lived and no resuscitation was needed. I thank Siamon Gordon for having generously given up his morning and for patiently listening to stories of the days when dinosaurs roamed the Earth or at least South Parks Road.

News, Honours, Prizes

August 2008
Distinction titles: our congratulations to **Marion Brown, Ervin Fodor, Thomas Harder** and **David Vaux** who were awarded the title of Reader and to **Susan Lea** who has gained the title of Professor in the 2008 Recognition of Distinction exercise.

October 2008
Many congratulations to **Stephen Bell** who has been selected as an Alexander M Cruikshank Award Lecturer by Gordon Research Conferences. Stephen gave his lecture at the Waterville Valley Resort, July 09

December 2008
Congratulations to **Keith Gull** on being elected Principal of St Edmund's Hall. This joint appointment between a department and a college is a first for Oxford.

February 2009
Susan Vaughan (Gull lab) has been awarded the title of University Research Lecturer.

June 2009
Fiona Powrie has been elected to the Sidney Truelove Chair in Gastroenterology which will be located in the clinical and preclinical departments of the medical school here at Oxford.

July 2009
Teaching Excellence: our congratulations go to – **Anton van der Merwe** who receives an award in the Major Educator category for his work on embedding graduate studies within the Dunn School. Also to **Chris Norbury** who has received an Excellent Teacher award; the selection panel was particularly impressed by his innovative approach to introducing FHS Molecular Medicine students to cancer biology.
Duncan Howie who also received an Excellent Teacher Award and was nominated for the award by a group of students here at the Dunn School.

Congratulations to **Catarina Gadelha** (Bell Lab) who has been elected Lecturer in Pathology at Trinity College, and awarded the status of Associate of the Higher Education Academy in recognition of her training and contributions to teaching at Oxford.

Sept 2009
Fiona Powrie has been awarded the first **EFIS-EJC Ita Askonas Prize** in recognition of the new insights her work has provided into the disturbed immunological regulation in Inflammatory Bowel Disease. The prize was awarded at the European Congess of Immunology on Sept 13th.

Champions: A History of the Dunn School Cricket Club .

Two recent e-mails from Adrian Gray, acting captain of the Dunn School cricket club, spurred me on to investigate the history of cricket in the Dunn School. Adrian joyfully announced on 25/9/09 that the club had again won the Jack Cox trophy by defeating "Stats/Medawar" in the final (winning team details below). His earlier e-mail, celebrating a win over Biochemistry mentioned his own unusual (unique?) bowling figures of 0.1 (overs) 0 (maidens) 1 (wicket) 0 (runs); this means, of course, that Adrian bowled only the last ball of the match, which captured the opposition's last wicket. The story brought back personal memories of an evening in 1978 against Charlbury 2nd XI where my own figures were 6, 2, 6, 12 and it spurred me on to write down my findings for Fusion.

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1953	2, Prs. Batting Gloves	18/3	1	16	6
18th. Apl.	1, Cricket Bat		3	3	9
	1, do		3	7	0
	1,Pr. Wicket K.Gauntlets		3	4	8
	1, Abdo.Protector			15	9
	1, Cricket Ball		1	5	6
	2, Prs. Pads	51/9	5	3	6
	1, Score Book.			7	6
	1,Pr. Pads. S.H.		1	10	0
	Repairs to 1 Bat.			2	0
			20	16	2
	Discount		1	10	0
			19	6	2

Our earliest cricket club records date from 1953, which, in view of the invoice above for the supply of equipment, looks likely to be date of foundation of the club. A glance in the same shop window last week revealed that a cricket bat now costs £130, an interesting index of inflation. It is also interesting to note that the Professor (Florey), agreed to be club President and together with other academic and technical staff, donated 'subscriptions' ranging from a guinea (£1.1.0.) to 2/6d to help establish the new club.

Only one score book has survived from the 'early days'; the most remarkable bowling figures in that are 2. 2. 0. 3. Yes, 3 wickets for no runs in 2 overs by Jerrome in 1956 against Forestry. A close second (or even better?) is 2.2. 0. 3. 5. by Taylor in 1957 against the Clarendon! Worthy of mention also is a spell of 4.0.8.4 by Jim (now Sir James) Gowans as opening bowler which helped ensure a win against South Oxford CC in 1956. The match against Forestry in 1961 must have been played on a 'bowler's wicket': it was certainly brief. The Dunn School were dismissed for 26 in 14 overs and Forestry reached 27 for 7 in 6 overs.

The earliest known photograph (of the 1954 team) was supplied by Ian Lockwood, (back row 2nd L) who studied for a DPhil with EP Abraham and subsequently worked in the pharmaceutical industry. Other identified figures are Donald Robinson (front row R), who became Professor of Biochemistry at Leeds, the Captain Glass, the departmental photographer, on his left the Secretary. Jerome, an electron microscopist who moved to the hospital pathology department, Arthur Glanville, the department carpenter and storekeeper (top row 3rd R) and the Jackson family, (umpire, scorer and player front row L).

The balance sheet from that year shows a subscription income of £8.1.0 and a balance carried forward of £1.11.7½d. (I wonder how many players in today's team even understand that notation?)

Sir William Dunn School of Pathology
Cricket Club
Season 1954

STATEMENT OF INCOME AND EXPENDITURE

INCOME	£. s. d.	EXPENDITURE	£. s. d.
Balance b/fwd from 1953.	11. 0½	Cord and tarred hemp (mending nets)	18. 6.
Subscriptions as per receipt book.	8. 1. 0.	Ground match fees Steeple Aston	14. 0.
		St. John's	6. 0.
		Batting gloves.	16. 11.
		Cricket bat rebladed.	1. 5. 0.
		Hire of ground and nets.	3. 0. 0.
		Balance in hand, c/fwd to 1955	1. 11. 7½.
	£8. 12. 0½.		£8. 12. 0½.

1955
January 1st. Balance in hand b/fwd. £1. 11. 7½.

The nature of departmental cricket changed in 1977 with the introduction of the Jack Cox trophy, a cup awarded to the winners of a 20 over league and knock out competition between university departments.

Before that time, fixtures were with a mixture of village teams such as Minster Lovell, Charlbury, Chalgrove, Wootton, and Great Tew (where Mike Bramwell remembers with pleasure his 'hat trick') and departmental teams. The village matches were often played on very picturesque grounds and the local pub was never far away! With the advent of the Jack Cox trophy these fixtures were dropped.

The Dunn School has made its mark on this competition by winning four times; in 1983, 1993 (see photo) 1999 (see menu for celebration dinner held in Oriel College) and this year. We were also runners up in a close match last year.

SIR WILLIAM DUNN SCHOOL OF PATHOLOGY C.C.
JACK COX TROPHY WINNERS 1993.
Mike Bramwell, Gareth Morgan, Ian Fraser, Steve Twigg, Wim de Villiers
Anthony Doyle, Simon Davis, Gordon McPherson
Mark O'Dell, Mark Wright, Mike Tomlinson, Geof Smith [not present]

Over the years the team has included a Nobel prize winner (John Walker), a cricket blue (Alan Ezekowitz), FRS's (Jim Gowans, George Brownlee).

But mention must be made of the two cricketers who have done more for Dunn School cricket over the years than any others; they are Mike Bramwell and Gordon Macpherson – appropriately placed at the ends of the back row on the 1993 winning team photo.

Below is what might be regarded as a more typical team photograph (from 1980!)

The 2009 Winning team was as follows:

Adrian Gray (captain)
James Harper
Clive Metcalfe
Gus Stock
Senthil Natesan
Ben Hodgson
Hugo Garcia-Rueda
Simon Cherry
Mark Hawkes
Andy Johnson
Mudassar ? (guest).

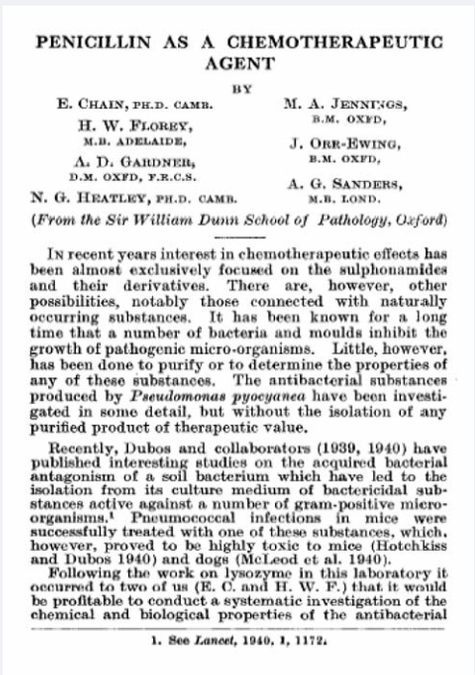
Eric Sidebottom

Cultural Transmission:
How Information about Penicillin Spread throughout Europe during World War II

Gilbert Shama

Before beginning to write this article, I conducted a small experiment: seated at my desk in front of my computer I attempted to obtain a copy of a scientific article through one of the powerful electronic databases, to which I have access. The article I wanted appeared in *The Lancet* in 1940 and it took me about 20 seconds to access and view it on the screen and then another 30 seconds to print it out. In less than a minute, without having had to get out of my chair, I actually had the document in my hand. Nothing so miraculous in that, but it hadn't always been so easy to get hold of that particular article.

The article I had downloaded was entitled 'Penicillin as a Chemotherapeutic Agent,' and the authors were a group of researchers from the Sir William Dunn School of Pathology, led by Howard Florey. The article presented the dramatic results obtained when purified penicillin was administered to mice infected with lethal staphylococci. This was followed about a year later by a second *Lancet* paper giving highly detailed descriptions of the methods for the production, isolation and purification of penicillin.



PENICILLIN AS A CHEMOTHERAPEUTIC AGENT

BY

E. CHAIN, PH.D. CAMB.
H. W. FLOREY, M.B. ADELAIDE,
A. D. GARDNER, D.M. OXFD, F.R.C.S.
N. G. HEATLEY, PH.D. CAMB.
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IN recent years interest in chemotherapeutic effects has been almost exclusively focused on the sulphonamides and their derivatives. There are, however, other possibilities, notably those connected with naturally occurring substances. It has been known for a long time that a number of bacteria and moulds inhibit the growth of pathogenic micro-organisms. Little, however, has been done to purify or to determine the properties of any of these substances. The antibacterial substances produced by *Pseudomonas pyocyanea* have been investigated in some detail, but without the isolation of any purified product of therapeutic value.

Recently, Dubos and collaborators (1939, 1940) have published interesting studies on the acquired bacterial antagonism of a soil bacterium which have led to the isolation from its culture medium of bactericidal substances active against a number of gram-positive micro-organisms.[1] Pneumococcal infections in mice were successfully treated with one of these substances, which, however, proved to be highly toxic to mice (Hotchkiss and Dubos 1940) and dogs (McLeod et al. 1940).

Following the work on lysozyme in this laboratory it occurred to two of us (E. C. and H. W. F.) that it would be profitable to conduct a systematic investigation of the chemical and biological properties of the antibacterial

1. See *Lancet*, 1940, I, 1172.

These were the first papers to appear on the subject since Alexander Fleming's first description of penicillin in 1929. Florey's articles had appeared at a time when Britain was at war and when the normal channels by which journals were distributed came to be severely disrupted. Journal subscriptions to enemy states were immediately cancelled, and as Germany invaded European countries postal services from Britain became suspended. Neutral states were relatively unaffected and in the spring of 1941 the Swiss pharmaceutical company Ciba wrote to Florey requesting a *Penicillium* culture. In normal times Florey would probably have obliged them, but these were not normal times. He saw the possibility that if he supplied Ciba with a culture it might be passed on by Swiss researchers to their German counterparts – something he was determined not to let happen. Florey had evidently recognised the strategic advantage in a time of war of an effective antibacterial agent. He wrote to Fleming asking him not to send cultures overseas, and Fleming assured him that *as far as he could remember*, he had not sent any to Germany.

In fact German scientists had heard about penicillin. Quite how is difficult to know with certainty, but a system for acquiring first British, and, later when the United States entered the conflict, American technical publications had been put in place. This was centred on German embassies in neutral countries such as Portugal and Sweden. Once in Germany, books and journals were copied and could be distributed anywhere within the country.

Interestingly, the Germans shared their information with their Japanese allies; accumulated penicillin articles were transported to Japan by submarine, and for submarine spotters it can be revealed that vessel I-8 left the French port of Brest on 5th October 1943 and arrived in Kure near Hiroshima on 21st December.

Of course, reading about the miraculous effects of penicillin was one thing, but making it was something else entirely. In the 1940s this required the Fleming strain of *P. notatum*. Fleming's recollections about not having sent cultures to Germany were incorrect: Dr H Schmidt at the IG Farben works at Marburg had a culture that he may have received directly from Fleming. Since obtaining the culture he had never attempted to grow it. He must have read or been told about the *Lancet* articles, and for a brief period of time Schmidt was in possession of the most valuable mould culture in the whole of Germany and was ready to perform his patriotic duty. Chauvenistically, it refused to grow. It was passed on to microbiologists at the Berlin firm of Schering but they too failed: it seems the culture had become non-viable through prolonged storage.

The realisation was made that if Fleming had sent a culture to Schmidt, then he must have sent them out to researchers in other countries too. One obvious repository was the great mould culture collection at Baarn in the Netherlands. The archives there contain scores of 'requests' from German companies asking for various species of penicillia. Whether the culture collection actually possessed the Fleming strain is not known. But if they did, they did not supply it to anyone in Germany.

Actually there had been at least one other person in Germany with a culture of *P. notatum*: Julius Hirsch was expelled from his post at the University of Berlin in 1933 for the simple reason that he was Jewish. He managed to establish himself in Istanbul and became a Professor in the Institute of Hygiene. Hirsch had worked for some time in London and it seems that, whilst there, he had acquired the Fleming strain. In Turkey he had freer access to British and American publications than he would have had in Germany and he commenced studies with *P. notatum* which he eventually published. Possibly aware of the huge Anglo-American effort to mass produce penicillin, he seems to have concentrated his efforts on studying a bacteriostatic enzyme produced by the mould. One is left wondering how different the story of German penicillin might have been had Hirsch left his culture of *P. notatum* behind in Germany!

German microbiologists eventually began to isolate their own antibiotic-producing organisms and even published their results in learned journals. Some of the strains they isolated may well have produced clinically-useful antibiotics, however the research was never properly co-ordinated and in the end only very small quantities of penicillin were ever produced in Germany.

The letters received at Baarn from German agencies must have alerted the microbiologists there to the latest research on penicillin. However, Dutch scientists were literally starved of foreign journals. But then a chance event happened. Andries Querido, a Jewish scientist, came to be interred in 1943 in a transit camp at Westerbork. Because of his scientific expertise he was allowed periodically to visit the company where he was a consultant at the Gist en Spiritusfabriek in Delft – his family were effectively hostages to ensure his return to Westerbork. On one such journey, he happened to be passing through Amsterdam railway station where he encountered an acquaintance, Professor van Crefeld, who actually had about him a Swiss review article on penicillin that cited Florey's articles. He lent it to Querido who took it to Gist where it was copied. Researchers at Gist soon set about isolating their own strains of penicillia and eventually established a small production process.

News about penicillin passed into the public domain through reports in newspapers and through BBC radio broadcasts. Indeed, Bernard Sureau, a doctor attached to the Pasteur Institute claimed that his boss, Federico Nitti, heard a BBC foreign language broadcast and that it spurred him to commence research on penicillin. The rather less romantic truth is that researchers at the Institute probably first heard from the French pharmaceutical company Rhône-Poulenc who had possibly obtained their information from Switzerland. Crucially, the Institute possessed the Fleming strain – Fleming had personally given Andre Lwoff a culture. They only ever succeeded in making small quantities of penicillin – enough to treat some 30 persons. This did not stop the researchers publishing their results in French medical journals. In peacetime the Institute would have been at the heart of research into understanding the mechanism of penicillin antibiosis. The fact that they were able, in a time of war, to succeed in producing any penicillin at all represented a significant achievement.

When Florey saw the startling results of his first experiments with penicillin his instincts as a scientist must have driven him to publish them immediately notwithstanding the war. He may even have felt a moral imperative to do so – here, after all, was a novel compound with near miraculous curative properties. He soon came to see penicillin as offering the Allies a strategic wartime advantage and became a pivotal figure in establishing its mass production. Florey sought to deny penicillin to Germany and was kept abreast of German initiatives to produce penicillin through intelligence briefings: he could never have guessed at the efforts which were taken to obtain and transmit copies of his first publications on penicillin.

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Illustration courtesy of the University Picture Library

OMPI: a new building for the Dunn School

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"The Dunn School", more properly known as the University Department of Pathology, is to have a new building. It will be called the Oxford Molecular Pathology Institute (OMPI) and is due to be completed by the end of next year.

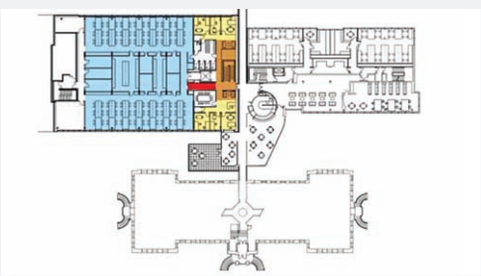
The original Department of Pathology was opened in 1901 in front of the Department of Human Anatomy. It was handed over to Pharmacology in 1927 when the present Sir William Dunn School building was completed, and was only recently demolished.

The much unloved concrete Sir Leslie Martin building, completed in the late 60's, at the same time as the Zoology/Psychology building opposite, was the first expansion of the pathology department. However for a number of years, it has become clear that this building was reaching the end of its useful life. It was planned at the end of Howard Florey's tenure of the Chair of Pathology, and completed in the early years of Henry Harris' leadership. The ground floor was financed by the MRC to house James Gowans' Cellular Immunology Unit (later led by Alan Williams and then Neil Barclay), and the top floor by the Wellcome Trust, to house the Chemical Pathology Unit, led by Edward Abraham (and later by George Brownlee). The middle floor was built with funds provided by the University Grants Committee (now HEFCE) to accommodate University Lecturers and research staff. At its peak, the building housed about 120 staff, and was the site of many important breakthroughs, including the cloning and expression of recombinant Factor IX, the discovery of the immunoglobulin superfamily, and the elucidation of the functions of the dendritic cell, to name just three.

However, the building was riddled with the bluest of asbestos, making refurbishment difficult, had collapsing mechanical services, was intrinsically cramped and awkwardly laid out. We had plans to strip the second floor back to the concrete frame and refurbish it for the next Abraham Professor of Chemical Pathology. However, it transpired that this was not only technically challenging, but the resultant planned accommodation was not seen as enticing by at least two potential candidates for the position. Following a feasibility study reviewing the options, it became clear that the best solution was to demolish and replace the building in its entirety.

Accordingly, the Oxford Molecular Pathology Institute will be on the site of the obsolescent Leslie Martin Building, and will be functionally integrated into the School of Pathology. The Institute will house strong existing Wellcome Trust-funded programmes in immunology, molecular developmental biology and microbiology and MRC-funded programmes in immunology. It will also house a new generation of career development and senior research fellows, and new appointees to the vacant chairs of Chemical Pathology (EPA, vice George Brownlee), Experimental Pathology (Glaxo, vice Siamon Gordon), and Cellular Pathology (vice Gillian Griffiths). Each of these chairs will be given the opportunity to build substantial new research programmes in the molecular and cellular biology underlying disease processes and the prevention and treatment of disease.

The building will comprise five floors, of which the basement is largely assigned to support services. The four above-ground floors each comprise approximately 11,000 sq ft (1,100 m) of office, primary and secondary laboratory space suitable for up to six research groups, to a maximum capacity of 56 laboratory staff per floor. The design incorporates open-plan, multi-group primary labs that include write-up desks for laboratory staff, and substantial secondary laboratories that can be configured for a variety of specialist purposes. A cluster of PI and support offices and meeting rooms around the main stairway form the interface between each laboratory floor and the School's shared café, common room, library and seminar rooms.



We believe the design will reinforce the existing collegial culture, while providing first rate, flexible research accommodation. You can follow the week-by-week development of the building project at **http://picasaweb.google.co.uk/wsjames**.

William James

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