PHARMACOLOGY MATTERS

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Today's science, tomorrow's medicines

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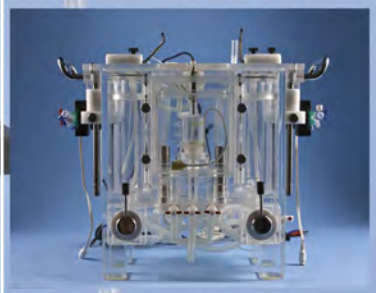

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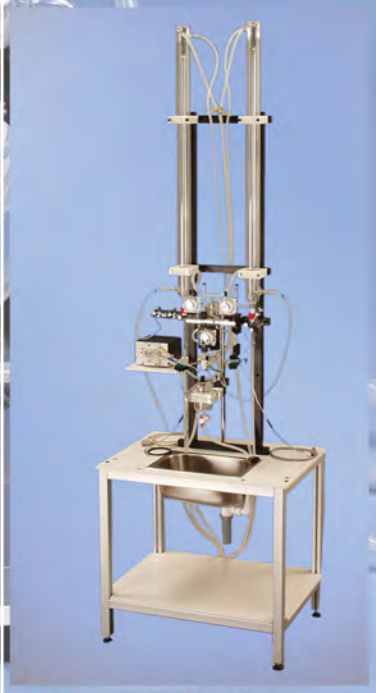

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BPS celebrates a landmark anniversary year

Tim Atkinson FSB FRSC
Editor-in-Chief,
Pharmacology Matters

Tim Atkinson has an MSc in Health and Disease from Birkbeck College, University of London and a doctorate in pharmaceutical and healthcare research from Middlesex University, London. He trained in clinical biochemistry, haematology and neonatal screening in the NHS at Birmingham Children's Hospital and North Middlesex Hospital, London prior to entering clinical development where he currently works on global oncology trials for the pharmaceutical industry. He is also an experienced medical publications professional having worked for pharmaceutical companies, contract research organisations and scientific publishers in medical communications and regulatory roles.

In this special August issue of *Pharmacology Matters* we invite you to celebrate the truly inspiring, dedicated and remarkable work of both individuals and institutions who fundamentally changed our understanding of biology, created the foundations of an unrivalled modern healthcare system, and who devised what was perhaps the most ambitious scientific project of all time to decode human life at the molecular level. As we honour and marvel at 60 years since the publication of the structure of DNA by James Watson and Francis Crick in *Nature* in 1953; 65 years since the birth of the NHS in 1948; and the 10 years since the Human Genome Project was completed in 2003, we reflect and pay tribute to key individuals who trail-blazed and innovated, ultimately leading to greater understanding of disease and engineering of new treatments with patient care at its heart. We are indebted to the pioneering work of the many scientists who progressed pharmacology to its status as an important translational discipline that holds promise of future treatments over next generations.

In their introductory article, Jane Mitchell, Maria Fernandes and Jenny Koenig (page 5) present a unique insight into Rosalind Franklin based on a review of the book by her sister, Jennifer Glynn. Rosalind Franklin's X-ray diffraction photographs showed the structure of DNA that was used by Watson and Crick in their seminal paper, yet Franklin remained unacknowledged in the discovery until after her death. The historical context to Franklin's life through the eyes of her sister reveal her true personality in addition to those challenges in working life she encountered.

Being an alumnus of Birkbeck College, University of London, where Franklin worked as a Fellow in the Birkbeck Crystallography Laboratory in the 1950s, I am delighted that Christine Slingsby and Tracey Barrett from the Institute of Structural and Molecular Biology at Birkbeck have provided an overview (page 7) of Franklin's studies on X-ray diffraction and analysis, and how this early work inspired current research on molecular biophysics. Clearly, Franklin's immense academic talent helped to establish Birkbeck as a leading research institution in crystallography and structural biology.

Hannah Watson and Fraz Mir (page 10) explore the future of the NHS over the next 65 years set against the introduction of novel biologics and biosimilars. The highly topical and controversial challenges to the NHS are discussed in light of economic constraints and a burgeoning healthcare system. Debate about funding the NHS is much needed to ensure the NHS is secure for future generations.

In his retrospective look at pharmacology in the early NHS, Brian Callingham examines the content of the 8th British Pharmacopoeia in 1953 (page 12). His article provides a fascinating insight into what was considered important over 60 years ago and how pharmacotherapy has changed drastically from bygone days when mercury was used in medicinal preparations!

Bridging a link between early pharmaceuticals that were used in the NHS, perhaps without the extensive preclinical research and rigorous regulatory clinical trial framework that today is absolutely critical for all drug development, is Will Redfern's article on safety pharmacology (page 14). In it, he describes the evolution of safety pharmacology and its translational importance when developing new medicines, particularly for detecting side effects early in the drug discovery process.

Finally, in this tripartite anniversary issue we also praise the outstanding accomplishments of leading scientists and collaborators who initiated, developed and worked on the 13-year long Human Genome Project that was completed in 2003. Scientific endeavour and technological advancements using genomic data are now enabling a new era of therapeutics ranging from stem cell therapies to personalized medicines, which we explore in the next issue of *Pharmacology Matters*.

We hope you enjoy this special anniversary edition of the BPS magazine.

Cover credit: i stock

Your BPS

Jonathan Brüün
BPS Chief Executive

A very warm welcome to this NHS and DNA themed edition of *Pharmacology Matters*.

Pharmacology and, of course, clinical pharmacology continues to play a significant role in the health of the nation – we often talk about our members working 'from bench to bedside' – so it is appropriate to take stock of that unique contribution to the development, regulation and prescription of new, safe and effective drugs.

In my time at BPS I have been privileged to work with our members on a variety of projects that will have a direct impact on the quality of care patients receive through the NHS. Perhaps the most significant example is the Prescribing Skills Assessment (PSA – www.prescribe.ac.uk/psa), and its companion project Prescribe (www.prescribe.ac.uk), which provides UK undergraduates with free-to-access e-learning resources in the principles of pharmacology and clinical pharmacology.

BPS is at the helm of the PSA, alongside our partners the Medical Schools Council, and is supported by a broad stakeholder group including the General Medical Council, British Medical Association and NHS Employers. It aims to create a single, national assessment of the prescribing skills of UK medical students, including their understanding of the pharmacological principles which underpin those skills. In my opinion, its potential to positively impact on the safe prescription of medicines in UK hospitals cannot be overstated.

The PSA team is led by Professor Simon Maxwell and supported at The Schild Plot by our Head of Education Jess Strangward. Already in 2013 this team, along with our partners, has delivered an online pilot assessment to around 5,000 medical students, generating excellent feedback. As I write, we are awaiting the results of the psychometric analysis that will more rigorously evaluate the quality of the assessment, and inform our decision on its future implementation. Given this valuable opportunity to reinforce the role of pharmacology and clinical pharmacology at the heart of the NHS, I look forward to updating you in 2014 and beyond.

BPS has also been active on another critically important issue to the NHS: medicines pricing. As many of those reading this article will be aware, by 2014, a Value-Based Pricing system will complement the existing Pharmaceutical Price Regulation Scheme (PPRS), with the aim of directly linking the price of a medicine to the benefit it has been shown to deliver. Through our Clinical Section and with the support of BPS Policy Manager Ruth Meyer, we have produced a statement highlighting the vital role of for clinical pharmacology expertise in evaluating the clinical- and cost-effectiveness of medicines. I would encourage you to read the full statement at bit.ly/12NYLXk.

Aside from these developments, we've been busy across the organisation since my last update. In April, BPS held a joint meeting with the American Society for Pharmacology and Experimental Therapeutics (ASPET) in Boston. The meeting had a packed and high quality scientific programme, to which BPS contributed symposia and keynote speakers, and a busy exhibition hall that provided opportunities for our staff and officers to meet existing and future members, and to showcase the work of the Society.

We were expertly and generously hosted by ASPET Executive Officer Christie Carrico and her team, and we were grateful to them for making our stay so productive and enjoyable. Christie recently announced that she will be retiring from her post so I thought I would take this opportunity to say how much I have enjoyed working with her in recent years and to wish her all the best for the years ahead. I also look forward to working closely with Christie's successor in due course.

One significant item on the agenda for the Boston meeting was the launch of our new open access journal, *Pharmacology Research & Perspectives* (PRP). The journal, which boasts Dr Mike Curtis as Editor-in-Chief with Dr Darrell Abernethy as Deputy Editor, is a joint initiative with ASPET and our publishers Wiley-Blackwell that seeks to publish original research, reviews and perspectives in all areas of preclinical and clinical pharmacology, therapeutics, education and related research areas. I am delighted that Mike has written an article on page 18 of this magazine to highlight our new journal, and would highly recommend it to you.

Also underway is a member engagement survey, a formal governance review reporting to Council in late summer, and the specification of a new member database (a critical tool for all organisations like ours) among other initiatives. As a result, we will enjoy a busy summer and are well underway to delivering our strategic objectives bit.ly/ZMtVrD.

In the midst of this activity, we have created an important new position in the Society: Finance and Commercial Director. I'm delighted to say that the post, which will support our core financial, governance, legal and facilities needs, while providing an increasingly important 'business partnering' service, will be taken up by Mike Poole from 29 July.

Mike is an ACA-qualified Chartered Accountant with a wealth of financial and business expertise. His priority is to support the Society's 5-year strategy with robust financial and business disciplines that protect, diversify and grow income while increasing efficiency. Mike succeeded in a similar role at the Royal College of Paediatrics and Child Health where he supported a period of fourfold income growth that included a significant income from publishing. He joins BPS from Leukaemia & Lymphoma Research where he recently updated their financial strategy and enabled them to safely commit their highest-ever annual sum towards research. The BPS team, including our Honorary Treasurer Dr Robin Hiley, are all looking forward to working with Mike in the years ahead.

I hope you enjoy this edition of *Pharmacology Matters*.

My Sister, Rosalind Franklin – Jenifer Glynn: A Discussion

Maria Fernandes
King's College London

Jenny Koenig
Editor, Pharmacology Matters

Jane Mitchell
Imperial College London

Maria graduated from King's College London in 2009 with a BSc (Hons) in Pharmacology with an Extra Mural Year. She went on to complete an MRes in Integrative Biomedicine in 2010. She is now in the final year of her PhD at the Institute of Pharmaceutical Sciences, King's College London, where her research concerns the role of TRP channels in pain and thermoregulation. Maria also has an interest in pharmacology outreach, especially in schools.

Jenny is a Fellow at Lucy Cavendish College, University of Cambridge, where she teaches Pharmacology and Maths for Biologists. Jenny particularly enjoys bringing maths and pharmacology together. She also has her own science education and communication consultancy, Science ETC, and is an editor of Pharmacology Matters.

Jane is the Head of the Section of Pharmacology and Toxicology and head of the group of Cardiothoracic Pharmacology at National Heart and Lung Institute (NHLI) Imperial College. She is also Chair of the postgraduate student committee for NHLI. Jane completed her PhD under Professor Sir John R Vane and has also worked with Professor Ferid Murad (NAS US, Nobel Laureate) on the biochemistry of nitric oxide synthase. Professor Mitchell won the AstraZeneca Women in Pharmacology Prize in 2012.

Outside the building I (Maria) enter every morning, there's a blurry, unassuming photo known as 'Photo 51', an image that King's College London has said is 'possibly the most important photograph in the world'. You might have guessed that I work at Franklin-Wilkins Building, King's College London – a building named after Rosalind Franklin and Maurice Wilkins, two scientists involved in the story of the discovery of the structure of DNA.

Photo 51 was taken by Rosalind Franklin and was the spark that set off the discovery of the structure of DNA by Watson and Crick – published in *Nature* in April 1953. One of the most famous discoveries in biology, the work is infamous for the lack of acknowledgement of the seminal work of Rosalind Franklin,

Photo 51: .Franklin-Wilkins Building

at least until well after her death in 1958. It is well documented that Franklin was unaware of the fact that Wilkins had shown Watson and Crick the photo that essentially led to their award of the Nobel Prize in Physiology or Medicine in 1962. Even then, it was only after James Watson presented a thoroughly unflattering view of Franklin in his book, *The Double Helix*, that her friends and family – including Franklin's good friend Anne Sayre and the biographer Brenda Maddox – set the story straight with their own books about her life.

To mark the 60th anniversary of the *Nature* papers, Dr Jenny Koenig, Professor Jane Mitchell and I met to discuss a book written by the historian Jennifer Glynn - *My Sister, Rosalind Franklin*. It is an account of Franklin's life through the eyes of her younger sister, including excerpts from letters between Franklin and her family, throughout her short life. It's a fascinating account of one of the most famous female scientists in history, showing the human side to a prodigious scientific talent. In this painting of an intrepid explorer who often got herself into precarious mountaineering situations, the woman behind the somewhat intimidating name emerges. Although she didn't suffer fools gladly, by Glynn's account, Franklin was warm and loyal to her friends – quite the opposite of the stubborn woman depicted by James Watson.

So, what did we learn from this account, and is the story of Franklin's short life still relevant today? We discussed many themes and the relevance of Rosalind's experience to our lives today.

Mentors and role models

Franklin grew up in a nurturing family with a strong intellectual and political history. She was encouraged to think for herself: in the letters shared in Glynn's book, we see her arguing the morality of the war, and religion, and standing up for herself and her beliefs against her parents. Whilst some have suggested that her father did not approve of women in science, Glynn testifies that he was more concerned that Franklin and her siblings were doing something to help the war effort.

Female role models did exist in the late 1930s: Professor Dorothy Garrod was an esteemed Newnham alumna, a palaeontology professor involved in the excavation of Saxon skeletons during Franklin's first year. Although Franklin didn't know her well, she provided an example of a successful woman in science and highlighted the changing shape of the academic landscape. A much closer female mentor was Adrienne Weill, a "French Jewish refugee scientist" who brought her young daughter Marianne with her. Weill was welcomed at Cambridge, a former pupil of Madame Marie Curie and living proof that a successful mother and successful scientist could be one and the same person. In addition to this, Weill proved to be a helpful contact later in Franklin's life.

Working environment

A good working environment is not only important for the production of good work, but also the preservation of one's sanity! Franklin experienced both constructive and destructive working environments through her career. Immediately after completing her undergraduate degree, Franklin worked under Professor Norrish, a future Nobel Prize winner. He also happened to have a fairly disagreeable reputation, an excerpt from a letter from Franklin stated that he was:

> *"the sort of person who likes you all right as long as you… agree to all his mis-statements, and I always refuse to do that."*

She had a terrible time:

> *"I am intensely bored with my work, I despise my professor. I dislike the men who work in my lab, and they resent and generally ignore my presence".*

Franklin's answer to 'the Norrish problem' was to move to a different lab, the British Coal Utilisation Research Association (BCURA) where she completed her PhD studies whilst contributing to the war effort, investigating permeability of different coals and the principles of molecular sieves. From there, she moved to Paris, to the Laboratoire Central des Services Chimiques de l'Etat - a position she obtained through Weill. Here, according to Glynn, Franklin had four happy years. She worked under Jacques Mering, and made great friends including Vittorio Luzzati, whilst honing her X-ray diffraction skills - contributing to the development of carbon fibres.

After Paris, she moved to King's College London. Unfortunately the atmosphere at King's was worse than when she had worked under Norrish. According to Maddox, the labs were filled with "Barracks-room beer-drinking camaraderie"; female scientists were not allowed in the men's common room to eat lunch or talk to colleagues. Her relationship with Maurice Wilkins was notoriously poor. On joining the lab, Professor John Randall, the director of the biophysics research unit, asked Franklin to use her X-ray diffraction skills to investigate 'biological fibres' including DNA, despite the project belonging to Wilkins, who was away on holiday. Wilkins had thought Franklin would be his assistant and not take over his own work. It was not the best start to a pivotal relationship.

Franklin's experience highlights the importance of doing your research before joining a lab. It's becoming the norm to visit the lab you planto work in before you join. Simply knowing that you want to be a scientist isn't enough and just falling into a group is not the best way to start your scientific career. The sexism that Franklin encountered at King's should be a thing of the past, but it is an open question to what extent unconscious bias remains. With proper management training and awards like the Athena SWAN, equality in science now receives greater attention.

Collaboration

The story behind the discovery of DNA is associated with a lot of conflict. If everyone had collaborated ,would they have discovered the structure of DNA much earlier? There are so many unanswered questions, not least the question of why Franklin was excluded in the first place. Was it simply because she was a woman, or was it just that Wilkins and Franklin did not get along? Watson had concerns that Linus Pauling would get to the structure of DNA before them. Whatever the reasons, we can only speculate now, and learn the importance of good collaboration.

Networking

In a similar vein, networking can be as invaluable as collaboration with regard to our studies and careers. Franklin would not have moved to Paris were it not for her mentor, Weill's networks. Later, JD Bernal (who was so impressed with her work in x-ray diffraction that he invited her to join the group) recruited Franklin to her final position, at Birkbeck College. Her visibility through attendance at conferences and her publications led to a new job. As it happened, Rosalind saw out the end of her career whilst working on the tobacco mosaic virus, determining its structural arrangement including the location of its RNA, having published about 18 papers, according to Glynn, whilst in the grip of ovarian cancer.

In our discussion of Rosalind Franklin's life through the eyes of her baby sister, we've covered many subjects that are still relevant today. I've learned that Franklin was an incredibly driven, strong person. She suffered from anxiety and self-doubt all the way through her life: a line that struck a chord with me was from a letter whilst she was writing up her thesis:

> *"The more I write, the more I realise how incredibly dull it all is, and I'm not very optimistic about the result."*

Knowing that someone who turned out to be such a prodigious talent felt the same way as so many other PhD students is a huge inspiration. Whatever the portrayal of Franklin – "bad-tempered, arrogant bluestocking" or kind older sister, one thing is certain: Franklin did Franklin to perfection. She didn't let anything de-rail or distract her. She was a combination of academic genius, hard worker, and intrepid explorer. She faced many setbacks: not being taken seriously, being excluded completely and dealing with her fair share of stubborn colleagues. Despite not receiving the full recognition that she deserved for her DNA work, Franklin is finally being recognized for the phenomenal scientist that she was.

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Franklin's Legacy to Birkbeck

Christine Slingsby & Tracey E. Barrett
Birkbeck College, Institute of Structural & Molecular Biology

Christine (right) graduated in Biochemistry at the University of Liverpool and gained her D. Phil at Oxford University in the Nuffield Laboratory of Ophthalmology. She brought the study of eye lens transparency to the X-ray Crystallography Department at Birkbeck in the seventies, with financial support from the Medical Research Council. She is now Professor of Structural Biology at Birkbeck.

Tracey (left) graduated in Molecular Biophysics from Leeds University and obtained a D. Phil at the University of York in Crystallography in the nineties. After postdoctoral research at both the National Institute for Medical Research and UCL, she was awarded a BBSRC David Phillips career development Fellowship to continue her studies on the Structural Biology of DNA repair at the Institute for Cancer Research and Birkbeck. She is currently a Senior Lecturer in the Department of Biological Sciences at Birkbeck.

In May 1952 Rosalind Franklin took her famous X-ray diffraction photograph of the hydrated 'B-form' of DNA, nicknamed Photo 51, which revealed critical parameters of its helical structure [1]. The model of the anti-parallel DNA double helix published by Watson & Crick in *Nature* in April 1953 was based on their prior access to her measurements, but this was not acknowledged at the time. In that same month, JD Bernal invited Franklin to bring the third year of her fellowship to Birkbeck, to continue to study the structure of biological substances by means of X-ray diffraction.

Bernal, the outstanding intellectual of his generation [2], came to Birkbeck in 1937, having previously taken the first X-ray diffraction pattern of a 'wet' protein crystal with Dorothy Hodgkin in Cambridge in 1934. As vividly recounted by Brenda Maddox [3], Franklin moved from King's College London, leaving behind JT Randall's well funded 'palace' in the Strand to the war-damaged Georgian 'slums' on the east side of Torrington Square in Bloomsbury, which was then the Birkbeck Crystallography Laboratory in the Department of Physics.

Bernal asked her to follow up his pre-war studies (carried out with Isadore Fankuchen) of the rod shaped tobacco mosaic virus (TMV). Using her skills to control the hydration state of biological samples, and her expertise in modifying X-ray cameras, combined with access to sealed fine-focus X-ray tubes developed at Birkbeck by Werner Ehrenberg, she was able to take information-rich X-ray diffraction photographs of oriented gels of TMV. With these pictures she enticed Aaron Klug from Cambridge to Birkbeck in early 1954, and in the following year recruited John Finch and Ken Holmes as PhD students.

Franklin was an enthusiastic traveller. She enhanced the output of her stellar Birkbeck team: collaborating with Don Casper from Yale; collecting virus samples from Nobel laureate Wendell Stanley, head of the Berkeley virus laboratory; and networking with her former "rivals" Crick, Watson, Linus Pauling and Laurence Bragg, all Nobel laureates.

Franklin's funding situation was always dire, not having an academic appointment and her conclusions as to the dimensions of the TMV particles were in conflict with Norman Pirie, the most powerful virologist in the UK. Unfortunately, he carried enormous weight with her funder, the Agricultural Research Council.

The key question concerning the structure of TMV was the location of its nucleic acid, RNA. Franklin compared side-by-side X-ray fibre diagrams of oriented gels of intact TMV virus and the reassembled isolated protein: the overall similarity of the patterns showed that they must form very similar structures but differences in the distribution of equatorial intensities indicated a structural change along the length of the core [4]. She published in *Nature* [5] back-to-back with a paper from Don Caspar (which Maddox claims Franklin wrote herself as he was too laid back then to complete paperwork), where she deduced that the RNA is inside the helical protein shell, but some distance from the central axis being embedded in the protein subunits. Thus began the structural biology of nucleoprotein.

From X-ray photographs of crystals of turnip yellow mosaic spherical virus, her team concluded that in addition to the cubic symmetry of the crystal, the particles showed higher icosahedral pseudo-symmetry and were made up of multiples of twelve subunits [6]. They deduced that virus assembly requires "the occurrence of particles in more than one orientation", consolidating the role of quasi-assembly in biological systems, an idea articulated in depth in 1962 by Caspar and Klug [7].

In 1956, Franklin was asked by the Royal Institution to exhibit giant models of helical TMV and spherical poliomyelitis virus at the 1958 Brussels World Fair. Her work was interrupted when she was stricken by the first symptoms of ovarian cancer. She died in April 1958, aged 37, before the exhibition took place and before she could take up an academic position that autumn at Birkbeck.

Franklin in a very short period of time established Birkbeck as a world leader in the X-ray analysis of biological materials.

Inspiring Christine Slingsby:

A major lens protein component is alpha-crystallin which is notorious for its polydispersity. Although this attribute is a nuisance in a crystallography setting, it is a useful adaptation for a disordered system to prevent phase separation and crystallization that would lead to light scattering and cataract. By tracing the evolutionary lineage of this class of proteins to ancient family members, a distant relative was found in wheat that formed a monodiserse globular assembly. The crystal structure showed how a single protein chain can occur in more than one orientation by employing alternative configurations of tail regions to build the symmetric assembly, similar to a virus [8].

After her death, her team continued the work at Birkbeck and then in 1962 moved to Cambridge to join Max Perutz at the Medical Research Council Laboratory. After many battles, Bernal established a Crystallography Department in 1965 to ensure the tenure of crystallographic research after he retired in 1968. In 1974 the Department was under threat of closure, but the strong international reputations of Bernal and Franklin swayed the College into appointing Tom Blundell to the Bernal Chair (1978-1996). In addition to expanding protein crystallography, Blundell pioneered the use of building models of human proteins involved in disease based on atomic coordinates from related templates.

The 1980s and 90s saw the emergence of protein engineering and crystallography as tools for drug design and established the importance of structural biology to the pharmaceutical industry. In 1997 Aaron Klug returned to Birkbeck to open a new molecular biology lab "The Rosalind Franklin Laboratory". The Bernal Chair was subsequently held by Janet Thornton (1996-2001), reflecting the rise in computational methods in macromolecular science due to the overwhelming increase in depositions to public databases of protein and nucleic acid sequences and their atomic coordinates of their 3D structures.

Franklin's achievements at King's College and Birkbeck College showed the importance of applying the most powerful biophysical methods available to the most appropriate biological sample to answer a biological question that often crossed established disciplines. In recognition of the importance of combining single particle image analysis by electron microscopy with X-ray diffraction to visualize increasingly large and complex nanomachines, the Bernal Chair was taken up in 2001 by Helen Saibil. The drive to investigate cellular biological processes by whatever means has led to the dissolution of the borders of the original Crystallography Department to be replaced by a Birkbeck-University College London "Institute of Structural and Molecular Biology" led by Gabriel Waksman. The current estate on the west side of Torrington Square, while not exactly a palace, is equipped to a very high level.

Imaging of the simple, self-assembling helical TMV has returned to Birkbeck, but now as a test object to assess quality of electron microscopy equipment. An appreciation of the level of macromolecular complexity that can be encoded in a small viral genome can be seen in modern images of the infectious bacteriophage icosahedral capsids packed with DNA under high pressure [9]. The ability to take a series of Cryo-electron microscopy snapshots of a nanomachine, such as the GroEL chaperone powered by ATP, together with flexible fitting of X-ray derived atomic coordinates, has led to the proposal of reaction pathways to explain how force might be used to disentangle wrongly assembled proteins [10]. Waksman has obtained atomic resolution snapshots of the complex machinery caught in the act of assembly, transportation and secretion of adhesive filaments through a gram-negative bacterial membrane [11].

Acknowledgements

The authors are grateful for the financial support of the Medical Research Council, UK (grant numbers G0801846 and G0701236, respectively), and TEB to the Wellcome Trust.

Inspiring Tracey E. Barrett:

Franklin's work on the X-ray diffraction of DNA directly inspired me during my first year as a Molecular Biophysics undergraduate student. Recently I have focused on how Kaposi's Sarcoma-associated herpes virus (KSHV) subverts its host by producing proteins that specifically target cellular antiviral defenses and promote replication. One such protein is KSHV SOX, an enzyme capable of hydrolyzing DNA and RNA that is required for both packaging of viral DNA inside its capsid and degradation of host mRNA. This enzyme is a potential drug target for patients in the advanced stages of Kaposi's Sarcoma, a malignancy that effects AIDS patients and other immuno-compromised individuals, for which there are currently no effective therapeutics. To elucidate the mechanism by which the KSHV SOX recognizes and processes DNA substrates, I have used X-ray crystallography to reveal the structure of the enzyme bound to a double helix of DNA [12].

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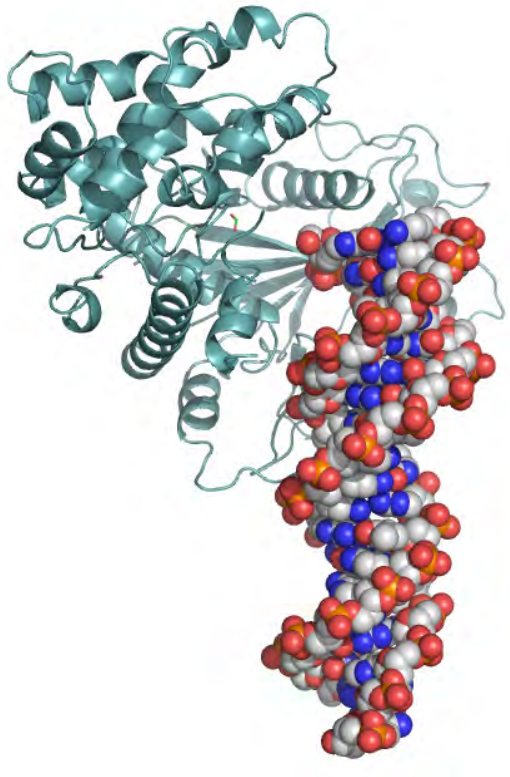
Fig 1.



The KSHV SOX enzyme (ribbon coloured in teal) bound to a double helix of DNA (in space fill) showing the phosphate atoms (red) in the polynucleotide backbone on the outside of the helix.

Chasing biologic shadows: casting light on an aspect of the next 65 years of the NHS

Hannah Watson
Editor, Pharmacology Matters

Fraz Mir
Editor, Pharmacology Matters

"We shall never have all we need…expectations will always exceed capacity. The service must be changing, growing and improving – it must always appear inadequate."

Aneurin Bevan, Minister of Health 1945-1951 (1)

For most United Kingdom (UK) citizens, the National Health Service (NHS) is one of the foundations of British society and without a doubt has helped to mould the UK into the nation we see today. The Welfare State was envisioned during wartime and created in the aftermath of World War II, with the NHS reportedly being a temporary component. However, a scientific, media-rich, cosmopolitan society has now replaced that austere, stoical, broadly cohesive 1940s Britain. Over the years the NHS has had many triumphs and successes as well as its fair share of problems; despite all the challenges the NHS is very much still fighting fit. It faces a number of ongoing hurdles i.e. maintaining and improving quality, public trust, intense media scrutiny and balancing finances. These hurdles have been overcome in the past but for how long can the NHS continue to do so before reaching "breaking point"?

Expectations of the NHS continue to grow exponentially and in the current media-driven world, the public are ever more aware of the new but often prohibitively expensive treatments available to them. This puts healthcare providers in the precarious position of funding new advances whilst continuing to support current methods, all whilst trying to balance the finance books.

Of current modern interventions, the availability of biological agents or "biologics" is perhaps one of the most publicly controversial. Biologics are innovator products derived via a complex process from living organisms and provide significant advances over traditional medicines. They offer potentially life changing advances to patients by offering novel therapeutic options for countless pathologies, including cancers, inflammatory bowel and joint diseases and other immunological conditions to name a few. Trials suggest significant benefits in relative terms when compared to "best current therapy". However, it has been argued that absolute benefits in terms of hard clinical outcomes are possibly less convincing; this will likely become clearer with time, as more trial data becomes available.

Bar the debate about actual clinical efficacy, their other major downside is cost. Biologics are expensive to research, develop and trial. Naturally, there is a spectrum. However, a fair majority of biologics cost on average £9500 per patient per year compared with around £450 per year for more traditional therapies. The same data was used to estimate that in the financial year 2007–08, each acute NHS trust spent up to £3.5 million on biologics for the treatment of rheumatoid arthritis alone (2).

Therefore the potential cost projections of treating a dozen or so other conditions with biological therapies is truly astounding.

Until these costs can be minimised, their availability to UK citizens will remain limited. The controversy surrounding Herceptin (trastuzumab), a biologic used in the treatment of breast cancer, made headlines a few years ago. It sparked the 'postcode lottery' debate in the public media that led to intense angst within the non-funded regions of the UK. Interestingly, the European patent for Herceptin expires in July 2014, which should lead to a reduction in costs. Other monoclonal antibodies, including Humira (adalimumab), Remicade (infliximab) and Rituxan/Mabthera (rituximab) (3) have patents that will not expire in Europe for a few years yet.

A potential solution is the creation of "biosimilar" drugs. These are developed to be virtual identical shadows of their original biologic counterparts. However, they are still limited by patenting of the original biologic and the issues surrounding 'data exclusivity'. To be licensed for use the biosimilar product must be a near on replica of the original. Importantly, the pharmacological properties must be equal to the original reference biologic. There are already many pharmaceutical companies across the world working on biosimilars for some of the most successful biologics in current use. With sales of biologics in the billions per drug it is a vastly profitable competitive marketplace and with the impending expiration of current patents there is the possibility that a competitive market in the realm of biosimilars will widen potential clinical usage by improving cost-effectiveness.

NICE is pivotal in the agreement of funding of new interventions; as such they will be very influential in how the biopharmaceutical industry will grow. Importantly, 2010 marked a critical turning point when NICE recommended a biosimilar medication for childhood growth failure (Omnitrope) for use in the NHS for the very first time (4, 5). Of note, Omnitrope has been shown to be clinically equal to that of the original biologic Genotropin, not just less costly (6).

Furthermore, it has been suggested that biosimilars will not only be less costly but may in fact sometimes be pharmacologically superior to the biologics, which they shadow. Biosimilars utilise minor interior structural differences that lead to the same exterior finish. However, these alterations may lead to a positive clinical enhancement with potentially fewer side effects, so called "biobetters". Either way, it is important to note that biosimilars are by definition not 'bioidenticals' with some arguing that they should be thought of as different drugs but in the same "class".

The NHS and its finances will inevitably continue to be a focus of political discussion in the coming years. Debate surrounding the

cost-effectiveness of treatments like biologics is likely to continue in health circles. However, despite the need for an open and frank engagement with the public about how we fund the NHS in general, the major political parties continue to lack the courage to embark on such a dialogue for fear of retribution at the ballot box. This reluctance, in turn, may perversely hasten the implosion of one of the nation's most prized institutions rather than preserving it for future generations.

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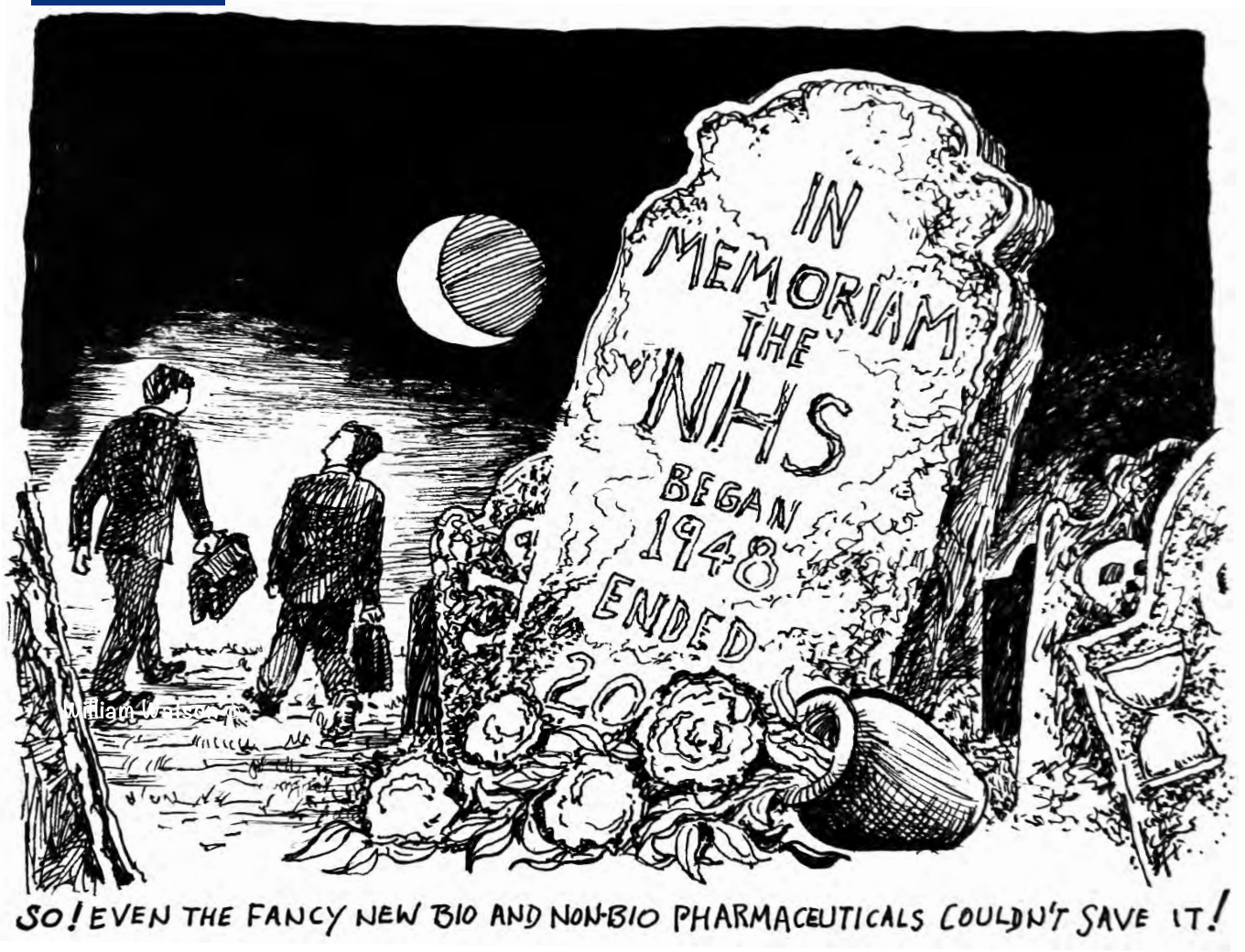

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Pharmacology in the early NHS: A Personal Reflection on The British Pharmacopœia of 1953

Dr Brian Callingham
University of Cambridge

Brian read pharmacy at Brighton Tech. but 'found' pharmacology. 'Deported' to the London School of Pharmacy for final undergraduate year. He undertook a PhD, supervised by Monica Mann, on reserpine and the rat adrenal gland. In 1964, deserted a secure lectureship in London for a three year demonstrator's post at Cambridge in Arnold Burgen's Pharmacology Department and a Fellowship at Queens' and am still there, such is 'temporary' in the Fen. Worked on catecholamine uptake followed by MAO and SSAO but in 'retirement', the cardiovascular actions of NSAIDs are very rewarding and beat basket weaving at the 'Derby and Joan Club'.

Back in the 1960s, our colleague Bill Grundy was often heard to exclaim, almost wistfully and in a broad Lancastrian accent,

> *"I remember when morphine wa' king!"*

Bill, as a survivor from the *"Ancien Regime"* of E.B. Verney at Cambridge, was pointing out that not long before there were very few therapeutic agents of proven effectiveness and safety available to clinicians that could be contenders for morphine's throne. The world was changing from the days where *Materia medica* ruled and one of the ways of change was the publication of the eighth *British Pharmacopœia* in 1953. For the first time it was published with the names of drugs and preparations in English with their Latin names relegated to second place.

Even though most official abbreviations remained based on Latin names, we soon recognized this change from the Latin of the 1948 Pharmacopœia marked a crucial step into 20th Century practice, five years after the beginning of the National Health Service. Also the enclosure of imperial measures in brackets, where formally they had equal standing with metric was a small but significant step on the path to the modern world.

The fact that seven years of Latin at school was no longer needed for this first year pharmacy student and his contemporaries was a mixed blessing as part of the mystique had gone, as it would be only a matter of time when prescriptions would also be written in English. How quaint to us now, was the then current view that patients really did not need to know what they had been given!

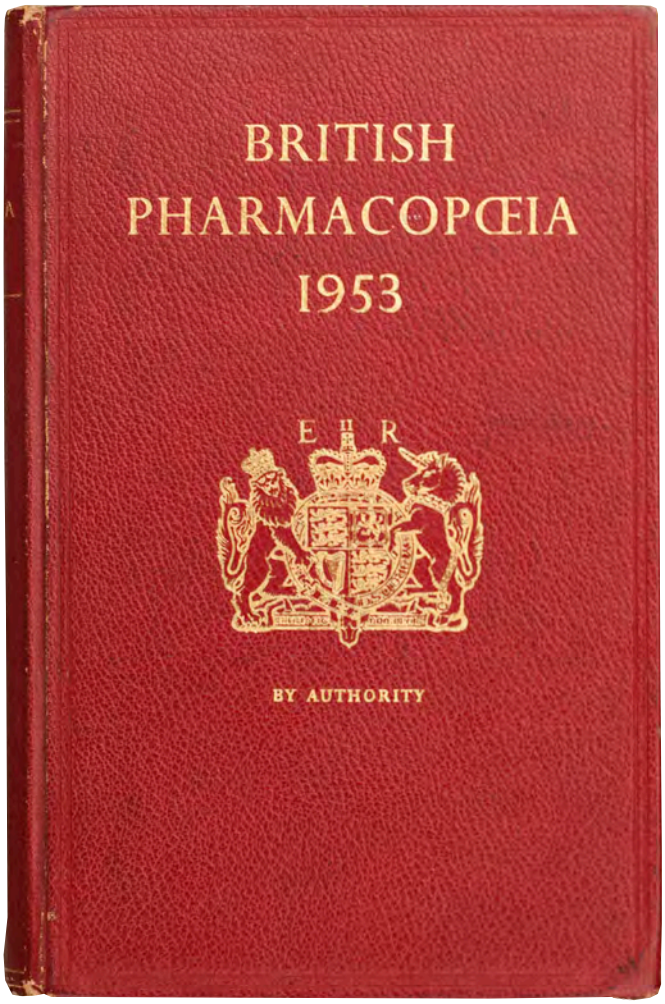
Bearing in mind that the 1953 Pharmacopœia was not a pharmacology textbook but the official compendium of those drugs and preparations that had made it into the 'Premier League' of current medicine, what was its function? In its monographs, it defined standards of purity and stability and set out how one ensured that samples of drugs and other agents met those standards. Only rarely was any serious pharmacology or clinical use ever mentioned but it did give the ranges of adult doses of the drug, which the authors were at pains to point out, were for general guidance only. However, pharmacy students were subjected to a formal examination to determine how many maximum doses they knew. Such knowledge, learned by rote, must have saved many disasters when perhaps prescribers' handwriting could be the source of confusion!

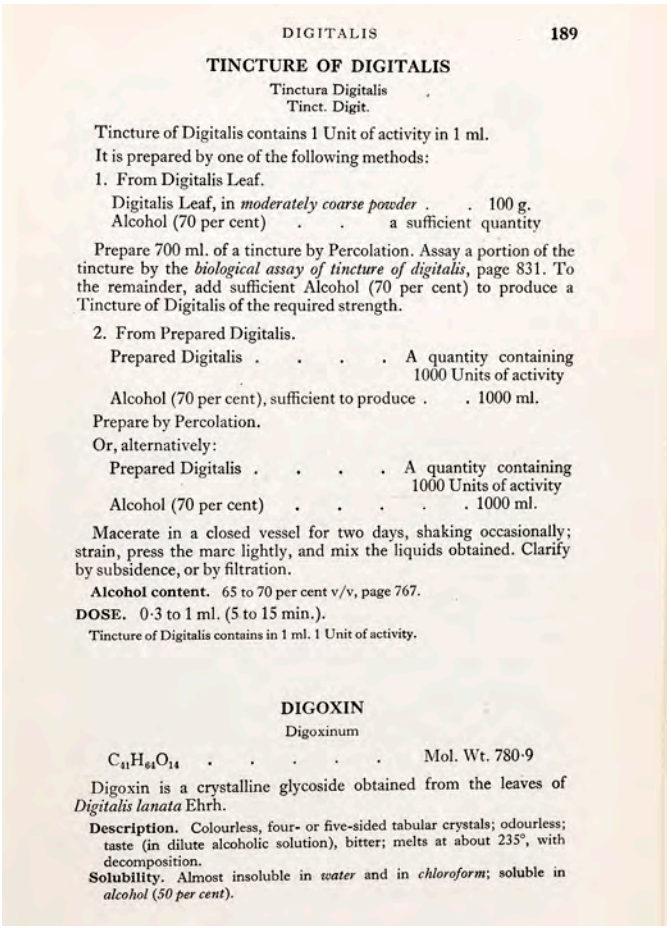
The main body of the book is made up of 732 monographs, arranged alphabetically, concerning not only drugs and vaccines, officially considered to be the most important, but also other essential materials, such as solvents, emulsifying and suspending agents. Aspirin, as acetylsalicylic acid (as it could only legally be called aspirin in the United Kingdom), is found near the beginning and as tablets (0.3g or 5 grains each) alone or as tablets with phenacetin or with ipecacuanha and opium, while at the other end, zinc oxide and its preparations make up no less than ten monographs.

This snapshot in time makes for fascinating reading and is a fairly stark reminder of what was considered important sixty years ago and how much has changed since then. Take for example anti-hypertensive agents; there were none we would recognize as such today. Even hexamethonium did not feature. Diuretics were represented by mersalyl, administered as an injection with theophylline, with about twenty monographs concerned with mercury in one form or another. Times have changed dramatically and now Cambridge Water Company are forever accusing the department of leaking mercury into the drains at concentrations that must be miniscule compared with times past!

The presence of monographs on penicillin cream, ointment, tablets and lozenges shows that much was to be learned about the proper use of antibiotics. A concern for a particularly common ailment of the time is apparent from the four monographs on senna and it preparations. No assay methods for potency are suggested and the possible presence of adulterants was determined by the application of classical pharmacognosy.

Many drugs described were not pure synthetic agents but natural products containing mixtures of active ingredients, such as digitalis leaf (*Digitalis purpurea L.*) and its official preparations, which merited four monographs. Digoxin, a single glycoside from *Digitalis lanata*, had three (see photo). These monographs, in particular, quite dramatically illustrate the fact that the Pharmacopœia was at a turning point in the discovery and development of therapeutic agents. The prescribed assay methods for digitalis were biological (bio-assays) and measured 'pharmacological effect' or 'potency' a term used in some monographs, which was expressed in 'units' by comparison with 'standard preparations' of known potency. Digoxin was measured chemically, as it was a single glycoside, so the assay was not concerned with potency but only with purity.





DIGITALIS 189

TINCTURE OF DIGITALIS

Tinctura Digitalis
Tinct. Digit.

Tincture of Digitalis contains 1 Unit of activity in 1 ml.

It is prepared by one of the following methods:

1. From Digitalis Leaf.

Digitalis Leaf, in *moderately coarse powder* . . . 100 g.
Alcohol (70 per cent) . . . a sufficient quantity

Prepare 700 ml. of a tincture by Percolation. Assay a portion of the tincture by the *biological assay of tincture of digitalis*, page 831. To the remainder, add sufficient Alcohol (70 per cent) to produce a Tincture of Digitalis of the required strength.

2. From Prepared Digitalis.

Prepared Digitalis . . . . A quantity containing 1000 Units of activity
Alcohol (70 per cent), sufficient to produce . . 1000 ml.

Prepare by Percolation.

Or, alternatively:

Prepared Digitalis . . . . A quantity containing 1000 Units of activity
Alcohol (70 per cent) . . . . . 1000 ml.

Macerate in a closed vessel for two days, shaking occasionally; strain, press the marc lightly, and mix the liquids obtained. Clarify by subsidence, or by filtration.

Alcohol content. 65 to 70 per cent v/v, page 767.

DOSE. 0·3 to 1 ml. (5 to 15 min.).

Tincture of Digitalis contains in 1 ml. 1 Unit of activity.

DIGOXIN

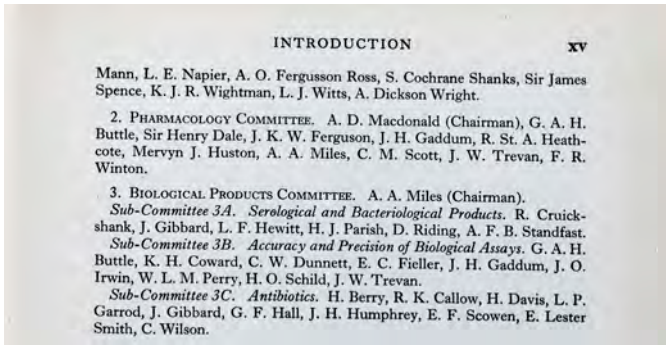
Digoxinum

$C_{41}H_{64}O_{14}$ . . . . . Mol. Wt. 780·9

Digoxin is a crystalline glycoside obtained from the leaves of *Digitalis lanata* Ehrh.

Description. Colourless, four- or five-sided tabular crystals; odourless; taste (in dilute alcoholic solution), bitter; melts at about 235°, with decomposition.

Solubility. Almost insoluble in *water* and in *chloroform*; soluble in *alcohol (50 per cent)*.



INTRODUCTION xv

Mann, L. E. Napier, A. O. Fergusson Ross, S. Cochrane Shanks, Sir James Spence, K. J. R. Wightman, L. J. Witts, A. Dickson Wright.

2. PHARMACOLOGY COMMITTEE. A. D. Macdonald (Chairman), G. A. H. Buttle, Sir Henry Dale, J. K. W. Ferguson, J. H. Gaddum, R. St. A. Heathcote, Mervyn J. Huston, A. A. Miles, C. M. Scott, J. W. Trevan, F. R. Winton.

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Sub-Committee 3B. Accuracy and Precision of Biological Assays. G. A. H. Buttle, K. H. Coward, C. W. Dunnett, E. C. Fieller, J. H. Gaddum, J. O. Irwin, W. L. M. Perry, H. O. Schild, J. W. Trevan.
Sub-Committee 3C. Antibiotics. H. Berry, R. K. Callow, H. Davis, L. P. Garrod, J. Gibbard, G. F. Hall, J. H. Humphrey, E. F. Scowen, E. Lester Smith, C. Wilson.

Pages from the eighth *British Pharmacopoeia*

Gradually the need for these bio-assays, so beautifully described by Burn, Finney and Goodwin only a year earlier in the second edition of their 'Biological Standardization', would diminish with time and be almost forgotten in the present day. It would, of course, be a mistake to think that bio-assays have no role in the modern world, since the principles established sixty years ago still underlie much of quantitative pharmacology, even if a 'Latin Square' is only a hazy memory!

In the 1953 Pharmacopœia, Appendix XV (biological assays and tests) takes up fifty-five pages, illustrating the importance of these methods. It begins with a summary of the essential statistics involved as well as explaining the nature of standard preparations and what 'units' meant. Biological assays are described for aureomycin, penicillin and streptomycin as well as for toxins, including diphtheria antitoxin, gas-gangrene antitoxin and tetanus antitoxin.

Products from mammals where chemical assays were either unsatisfactory or unknown were also assayed biologically and included insulin, heparin, gonadotrophins, oxytocin and vasopressin. Tubocurarine, although a supposedly single entity was still assayed biologically because it was extracted from members of the genus *Chondrodendron* with the associated risk of contamination by chemically-related products with different or no activity. Even though the suggested assay methods were the rat phrenic nerve-diaphragm or rabbit head-drop method the student's patience was sorely tested by other bioassay methods such as the acetylcholine-stimulated frog *Rectus abdominis* muscle. These assay methods clearly required a great deal of skill and dexterity as well as patience, something that today's students may be grateful to have avoided, a trade-off perhaps for having to learn so many more drug names.

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Safety pharmacology – pharmacology's dark side

Will Redfern
AstraZeneca

Will Redfern is an experienced safety pharmacologist based at AstraZeneca in the UK. He has worked for AstraZeneca for 15 years (in Loughborough then at Alderley Park), before which he was at Syntex and Quintiles in Edinburgh. He is a BPS Fellow and is currently Secretary of the Safety Pharmacology Society (www.safetypharmacology.org). Will is also co-organizer of a two-day meeting on drug-induced cardiovascular toxicity at Alderley Park this November (www.bstp.org).

Much of research pharmacology is about discovering new receptors, new endogenous transmitters and mediators, new pathways, and new mechanisms, and applying this knowledge to discover and develop new therapies for old diseases. However, pharmacology does have a dark side: safety pharmacology.

Safety pharmacology is a preclinical discipline focusing on the undesirable pharmacodynamic effects (adverse effects; side effects) of new drugs on physiological functions at therapeutic exposures and above (Redfern *et al*, 2002). Basically, it's all about the stuff you really don't want your drug to do. But given that drug-induced adverse effects are reckoned to be just behind the 'Big Three' (heart disease, cancer and stroke) in the league table of causes of death in the USA (Lazarou *et al*, 1998), there is clearly no room for ostrich-like behaviour. And reflecting a theme of this issue of *Pharmacology Matters*, the burden on the NHS may run to nearly £500m annually as a result (Pirmohamed *et al*, 2004). So, clearly, getting safety pharmacology right is extremely important.

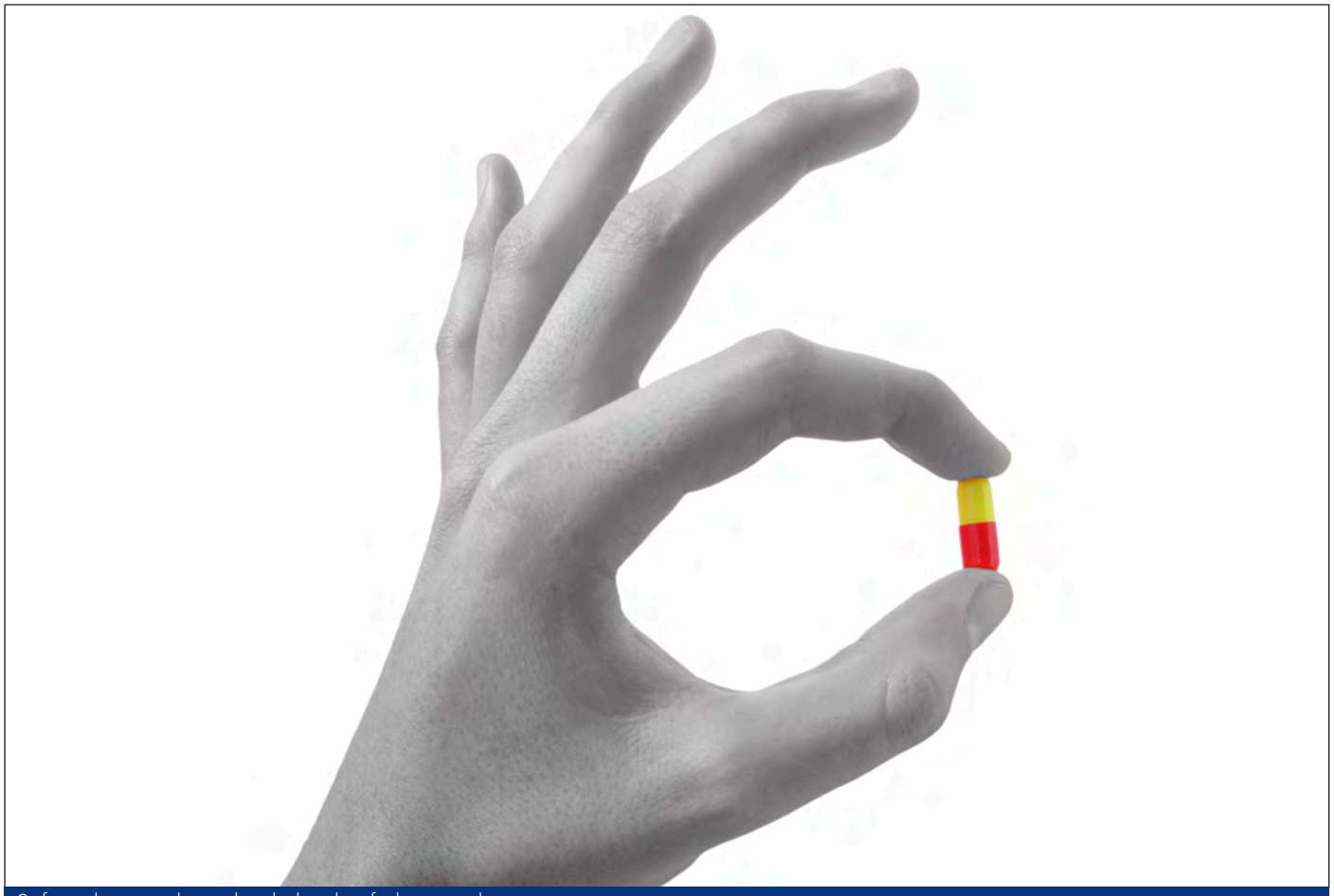
I've worked in academic research, drug discovery (efficacy) and safety pharmacology. The best way I can describe the difference between working on a drug project (say) to treat stroke and evaluating the safety pharmacology of compounds within the same project is as follows. When you achieve a breakthrough in efficacy in preclinical *in vitro* assays or *in vivo* models predictive of human efficacy, you may indulge in cartwheeling, whooping, fist pumping or high-fiving, depending on your cultural origins and on who's looking. If on the other hand, you're a safety pharmacologist, and the same compound is found to prolong QT interval (more of that later) or cause convulsions, you can't really go in for that sort of behaviour – even if you'd told the project team it would, and they wouldn't listen. And achieving an unequivocal 'no effect' can rarely be described as breathtaking either. So, fewer 'Eureka!' moments in safety pharmacology. Doesn't mean it isn't enjoyable and rewarding, as I hope to illustrate.

Like most safety pharmacologists, I didn't embark on my pharmacology journey thinking "I want to investigate the side effects of drugs". I originally graduated with a pharmacology degree at Sunderland, followed by a PhD (combining physiology and pharmacology) at Manchester, followed by a post-doc at Birmingham (again, combining the two disciplines).

At a time when the terms 'biochemical pharmacologist' and 'molecular pharmacologist' were in vogue (yes, around the time of the 30th anniversary of the discovery of the structure of DNA!), I would have described myself as a 'physiological pharmacologist'. Sadly, that term didn't catch on (too much alliteration, probably), but by the time I joined the pharmaceutical industry in Mike Spedding's department at Syntex in Edinburgh in the late 1980s I had received a very good grounding in integrated *in vivo* physiology to go with my pharmacology knowledge. This was to serve me well.

Right from the off at Syntex, I became 'hands-on' involved in the weird and wonderful world of behavioural pharmacology. In addition, by talking to *in vitro* colleagues, watching them at work, and seeing them present their data and interpret it, I also absorbed some of the key principles of *in vitro* electrophysiology, radioligand binding, and various isolated organs and other 'black box' *in vitro* assays, without actually doing any of them.

I was largely doing *in vivo* 'general pharmacology', but it was only years later that I figured out what that term meant. It meant 'off-target pharmacology', where 'off-target' referred either to the primary molecular target or to the physiological system being targeted. So, for example, we investigated whether the effects of one of our compounds selected for clinical development would cause anxiety as a side effect, via its primary molecular target. This was delequamine (RS-15385-197), a potent, selective α_2-adrenoceptor antagonist. Available evidence in the published literature strongly suggested that blocking these receptors would be anxiogenic. Yohimbine infusions precipitated panic attacks in humans, and yohimbine was anxiogenic in rodent tests of anxiety. We confirmed this anxiogenic effect of yohimbine in rats using an elevated plus maze. However, delequamine (and another selective α_2-adrenoceptor antagonist, idazoxan) were clearly not anxiogenic in the same test (Redfern & Williams, 1995). Yohimbine has promiscuous activity at several receptors. Selective antagonism at the α_2-adrenoceptor didn't mimic its anxiogenic effects. This is a cautionary tale about presumed implication of a particular receptor in a particular adverse effect, based on the effects of 'old' compounds. However, it can be very difficult to shake off the collective consciousness of 'class effects' when a more selective compound arrives on the scene, devoid of this adverse effect



Safety pharmacology, the dark side of pharmacology

Together with these 'general pharmacology' findings, submission of a candidate drug to regulatory authorities before human exposure required a standard package of safety pharmacology studies, assessing effects (at therapeutic doses and above) on multiple organ functions. In 2000, the 'general pharmacology' and 'safety pharmacology' studies were consolidated by a consensus of regulatory authorities in the three major territories (Europe, US and Japan), under the umbrella of the International Conference on Harmonisation (ICH), into a regulatory guidance document on safety pharmacology known as 'ICH S7A'.

Adverse effects of drugs can occur by augmented effects at the primary molecular target in the target tissue of interest, when the dose is increased. Alternatively, they can arise due to effects on the primary molecular target in other tissues, or on secondary pharmacological targets, or as a result of metabolites, or drug-drug interactions, or secondary to changes to homeostasis, or nonspecific effects. Detecting these side effects early in drug discovery, deconvoluting the mechanism and assessing the risk (in terms of safety margin and intended patient population) is the role of the safety pharmacologist (Redfern & Valentin, 2011).

Safety pharmacologists may have specialist skills and knowledge in one area or technique (e.g. cardiovascular system), or a broad overview across all organ systems. Generally the former can be found in large pharmaceutical companies and contract research organizations (working in teams), whereas the latter are generally found in small pharma companies (wearing multiple hats).

One key consideration has become increasingly important to the safety pharmacology community over recent years: preclinical to clinical translation. Safety pharmacologists deploy cutting-edge techniques, but what do the data they generate actually mean for humans? For example, what does a 20% reduction in locomotor activity in a rat translate to in human at the same exposure level? And surely, this will be pharmacology-specific (e.g. we can't reliably extrapolate from knowledge around the translation for, say, benzodiazepines to a novel drug mechanism)?

Without confidence in translation it is difficult to make decisions on whether or not to progress a compound in light of an adverse safety pharmacology finding. This is especially difficult with a novel pharmacological target which, for a pharmaceutical company, means most of the time.

Then there is the issue of safety margins. They are often applied based on opinion and judgment, and according to the severity of the disease being treated. Clearly a two-fold margin to an adverse effect is insufficient (it's easy for a patient to accidentally take a second tablet absentmindedly). A three-fold margin is too close to this to suddenly consider as acceptable. What about a 10-fold margin? This is generally held to be acceptable for some safety margins (e.g. occurrence of seizures), but very few therapeutic margins have been studied systematically. Ten years ago we analyzed relationships between nonclinical cardiac electrophysiology data (hERG IC_{50}; cardiac action potential duration; QT interval) and the risk of *torsade de pointes*,

a potentially lethal cardiac arrhythmia. We found a strong relationship between the margin from free therapeutic exposure to hERG IC_{50}, with a 30-fold margin providing a safe and optimal cut-off point (Redfern et al, 2003). This was based on published data; published data does not exist to the same extent for other adverse effects, so this has required inter-company collaborations using anonymised in-house data (Valentin et al, 2009).

What led to our work on 'QT risk'? By the mid-1990s, regulatory authorities had become increasingly concerned about sudden cardiac deaths in otherwise healthy patients due to drug-induced *torsade de pointes*. A European regulatory document was issued that required evaluation of *in vitro* and *in vivo* cardiac electrophysiology parameters (including potency at the hERG potassium channel). The large pore of the hERG channel continued to be extremely accommodating to large swathes of the output of the industry. Fourteen drugs have been withdrawn from sale as a result, approval for product registration has been denied for numerous others and untold numbers of candidate drugs have been stopped by companies long before they ever reached the point of registration.

The invention of automated ion channel screening devices using a multiwell plate format enabled chemists to adjust their molecular structures to move away from hERG blocking activity. Nowadays safety pharmacologists screen at a range of cardiac ion channels (as part of early off-target pharmacology profiling; Bowes et al, 2013), and apply action potential simulation to the readout, so that only relatively clean compounds go on to be tested *in vivo* for effects on QT interval (Pollard et al, 2010).

It is probably true to say that 'QT Pharmageddon' reinvigorated safety pharmacology as a key scientific discipline within the pharmaceutical industry, but surely we've now got that covered? What's important for the future is that we go about our work in safety pharmacology effectively so that we don't stumble into another crisis involving something we should have detected preclinically. Continued recruitment of high quality pharmacologists into safety pharmacology roles is the key to success, and raising awareness of safety pharmacology within the wider BPS community helps with this. There have been two well-attended symposia on safety pharmacology at BPS Winter Meetings since 2006, and hopefully there will be more to come.

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Aspects of pharmacology education: flashcards

Jenny Koenig
Editor, *Pharmacology Matters*

Two weeks before the second year medics' exams, a student arrives in my office; she's clearly upset and fearing that's she's going to fail: "Pharmacology is impossible!" she cried, "All the drug names sound the same, I can't pronounce them, let alone spell them and there's just far too many to learn. Should I buy those flash cards? Will that help?" she howled with an edge of desperation in her voice. I suppressed the urge to suggest that it might be a bit late for that now but it raised these questions:

1. Do flashcards help?
2. Is there any educational research to support their use?
3. How can they be used effectively?

One of the most effective revision techniques is practice testing and a number of studies have demonstrated that the process of trying to recall information helps to embed it (Dunlowsky *et al*, 2013). Flashcards are one good way of doing this. Another effective revision technique is to spread out your study over time. This is important: a common mistake in the use of flashcards occurs when students take a very large number of flashcards and try to learn too many drugs in one sitting.

However the devil is in the detail: how successful flashcards are really depends upon how they are used. Students often use flashcards in a very limited way, simply to memorize a set of facts. Weaker students tend to buy commercially-available flashcards or copy from others and this is an indicator of poor exam performance due to less time-on-task and less time on study activities that promote conceptual learning. Sleight and Mavis (2006) found that those students in the top third of the class prepared their own study aids and used a variety of revision methods.

The advantages of making your own flashcards are that it makes the student search out the information and evaluate it, prioritising relevant information. It is often a good idea to start with just the basic information and to write just keywords rather than sentences. If written from the top to the bottom of the card, then the information can be covered and revealed to further extend the idea of testing retrieval. Colour and imagery can also be used to make the cards more visually appealing and, for some people, more memorable. The main disadvantage for home-made flashcards is accuracy – there needs to be some mechanism for identifying mistakes

Flashcards are used best when combined with other revision techniques. Mind-maps or concept maps, for example, provide a method for prioritizing, summarizing and visualising information, and can be combined with flashcards to help put the drug names into context. Senchina (2011) outlines a number of other "card game" approaches in a medical microbiology course.

There are an increasing number of free online tools for creating quizzes and flashcards. One of these is www.quizlet.com, which is very easy to use – you'll find yourself creating flashcards in no time. It can import from a spreadsheet file provided the name and definition are given in a particular format. In addition to creating flashcards, Quizlet can use the same information to create other types of quiz, including multiple choice, matching and true-false.

There are several free flashcard apps available. They are generally pretty easy to use and you can be up and running very quickly. I tried out the Study Blue app having been taken with the idea that students could study using their smartphone (compatible with both Android and iPhone) or the web application. However I'm not sure I think it's a good idea. I created some flashcards using the web application then tested myself using my smartphone. When creating flashcards, I typed in "atropine" and then was shown 30 flashcards which already contained that drug. All the cards contained slightly different information, presumably because the information those students had put in had come from different courses.

I find that students worry a lot about learning just what they need to know and no more, but they often struggle to decide what they really need to know. The stronger students have the confidence to decide for themselves what they need to know and go with that but the weaker ones could easily be distracted by all the information presented to them and possibly even try to learn all of it. It was interesting that of my 40 tutorial students this year, only a few used electronic flashcard apps with most of them preferring the old-fashioned handwritten cards.

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Open access publishing and the BPS

Mike Curtis
Editor-in-Chief,
Pharmacology Research & Perspectives

The BPS recently launched an 'open access' journal called *Pharmacology Research & Perspectives* with its partners at American Society for Pharmacology & Experimental Therapeutics (ASPET) and Wiley-Blackwell. (www.pharmacolesresperspect.com/).

This is a brief guide to open access publication, designed to explain its relevance to you and its importance to the BPS.

'Open access' is jargon for 'free content'. By 'free' I mean that the 'content' (the paper) can be viewed for no charge by anyone with access to the internet. As an author, open access means that the whole world gets to read your paper for free.

There has been pressure from organized groups of taxpayers (who view themselves as the funders of research) to have instant open access to the products of their patronage. This means that they consider that *any publication arising from work funded by public bodies* such as the US National Institutes of Health (NIH), British Medical Research Council (MRC), or indeed even any work carried out in a publicly funded institution (such as, in the UK, a university or hospital) *should be made immediately available to read*.

Research papers have traditionally been published in research journals that operate in a capitalist economy, in which the publisher funds its operation and publication costs, and generates an income, from sale of content. This is true irrespective of whether the publisher is a 'for profit' organization with shareholders, or an in-house operation run by a research charity. There are innumerable examples of each. Most, if not all, journals with a high Impact Factor, have been carefully developed over many years by highly professional publishers, with professional (remunerated) editorial staff. All journals have a requirement for income to pay for processing and publication. Publishers are not charities. Few if any journals are run at the expense of a wealthy benefactor who simply gifts all the necessary expenses.

If authors are required by their funders to publish 'open access', a simple solution would be to lodge the research outputs on an accessible web page. Unfortunately, the research funding model requires that we investigators publish in high Impact Factor journals. These journals are the ones with kudos. Indeed, kudos and Impact Factor appear to go hand in hand. If we researchers acquire no kudos we get no grants.

Another solution to the need to publish 'open access' would be for authors to pay high Impact Factor journals to make their accepted papers 'open access'. In fact, this is already happening, and increasingly so. This option has existed for many journals for many years. However this option was rarely taken up in the past because there was no need. Our fellow scientists have instant access to most publications, paid for by their institutions. This is especially the case in 'richer' countries and institutions – exactly the places where we would like our papers to be read. So there has been no self-generated pressure in the past from authors to opt to pay for 'open access'.

Things are changing. At the highly-funded end of the research spectrum, state-owned funding bodies have accepted that the public that ultimately funds the research via taxes should be given instant open access. Consequently, such funding groups have formed consortia to provide the fees required by high Impact Factor journals to obtain instant 'open access'.

That, however, is not the end of matters. The move towards a higher demand by authors to publish work instantly 'open access' affects the publishers of journals. Currently all journals obtain their necessary income from a mixture of private subscription, advertisements and (the largest segment) institutional library subscriptions. If authors (via their funding bodies) pay for instant 'open access' then the content (the paper) is instantly 'free' to readers. In which case, why should the library or the subscriber pay for the journal? All the while that only a minority of papers are published as instant 'open access' content, the market and the publishers can live with the situation. For example, several journals with which we are very familiar publisher less than 1% of papers as instant 'open access' content. However, imagine a situation where all papers are published by authors whose funding bodies insist on instant 'open access'? Libraries would cancel subscriptions. From whence, then, would the publisher derive its necessary income?

The reason this is important is because the income publishers currently obtain from institutional libraries needs to match the feasible income obtainable from authors via their funding bodies. Let us imagine a journal that publishes 1,000 papers a year and charges authors £2,000 for instant 'open access'. With 100% of papers paid for by authors, this would provide an income of £2,000,000 per annum. I have no idea whether this would match the typical income obtained presently for a journal publishing 1000 papers a year. Such information is difficult to obtain. Let us imagine the amount is half the amount currently earned by the subscription model of funding. Clearly the shift to 'open access' publication has the potential to generate a significant loss of income, if not properly managed. Thus the publisher must work out how much it *needs* to charge to maintain income versus how much it *dare* charge in a market that will become highly competitive. Regardless of one's views about the merits of Impact Factor as a measure of 'standing', Impact Factor determines kudos (see above) and will therefore set the upper limit to the charges the publisher will seek.

Over time a journal's income stream will transition from institution library subscription to fully author-funded 'open access'. This presents an interesting separate challenge. At some point the

institutional libraries will decide a threshold of free content has been reached and will cancel the subscription. Moreover there comes a point where so much content is instant 'open access' that it no longer becomes viable for the publisher to publish anything in that journal that is *not* instant 'open access'. Any such paper (one for which the author has no desire nor need to pay for instant 'open access') would be effectively embargoed to all but those individuals willing to make a one-off payment to access the article. This is not a manageable publishing model, so the publisher will have to navigate between two funding models in a more piecemeal fashion. This is inescapable and could lead to income turbulence. Publishers will have been modelling this turbulence. I cannot comment on what they have determined. However the most likely long term outcome will be that journals currently offering a mixed model (of instant 'open access' for authors wishing to pay for it, plus an embargo for those unwilling) will eventually switch to a model where authors will be given only *one option* – to pay for instant 'open access'. The other unknown here is the duration of the interlude to the change to instant 'open access' *only*.

Given all this, and being scientists, what would be the first best plan to interrogate the pathology and seek means of intervention? I am a big fan of animal models. BPS (together with ASPET) has invented an animal model of 'open access' publication. It is called Pharmacology Research & Perspectives. It has two aims. One is to iron out the crinkles of 'open access' publication that we have not yet anticipated, with a view to learning how to manage *British Journal of Pharmacology (BJP)* and *British Journal of Clinical Pharmacology (BJCP)* in the event they transition to exclusively instant 'open access' format. The second goal is entirely separate and represents the opportunity to make a virtue of necessity and create a great new journal for BPS, which provides novel content, some of which is different in type from that normally published by *BJP* (and *BJCP*). Additionally it lends a wonderful opportunity to build a bridge with our sister society, ASPET. Finally, it offers the opportunity to provide an entirely new editor training scheme, creating editors, early in their careers, who may later be invited to become editors of our established journals. You can read about these initiatives in separate articles to appear in *Pharmacology Matters*, and soon also on the journal web pages www.pharmacolesresperspect.com/.

Pharmacology Research & Perspectives

Open Access

Quantitative Pharmacology: An introduction to integrative pharmacokinetic-pharmacodynamic analysis: book review

Reviewed by Arvid Carlsson, Nobel Laureate
Gothenburg University

Authors: Johan Gabrielsson and Stephan Hjorth
Apotekarsocieteten, Swedish Academy of Pharmaceutical Sciences, 2012

264pp., hardcover - ISBN-978-91-979452-3-3

Dedicated textbooks in the area of integrative pharmacology are very scarce, notwithstanding the true need for educational narratives on the subject. It is therefore very gratifying that Johan Gabrielsson and Stephan Hjorth, both of whom carry a substantial track record (30yrs+) of industrial experience and academic research in pharmacokinetics and pharmacology, have taken the task on to fill this longstanding void.

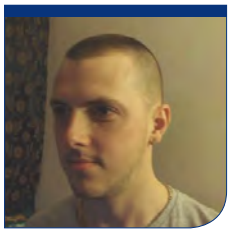
The book focuses on why integration of pharmacokinetics (PK; what the body does to the drug) and pharmaco-dynamics (PD; what the drug does to the body) is so important in drug discovery and development. Gabrielsson & Hjorth embrace the subject matter both thoroughly and enthusiastically, with several illustrative real-world examples. Topics covered demonstrate well how an integrated approach may avoid the problems and pitfalls related to design of studies, analysis and interpretation of data. Practice examples for the reader are also, commendably, included. Divided into seven Chapters, the book instructively states the holistic approach intended by the authors. Given their affiliations in the Pharma environment it is logical that much emphasis is put on biomarkers, translational aspects and scaling from animal species to man. In my view, Gabrielsson & Hjorth have successfully achieved their stated purpose with the book.

The first chapter sets the stage through a general introduction into the field of quantitative pharmacology and some of the terminology commonly encountered. A useful framework is described, on how to link drug and system-specific properties using biomarkers as navigational tools, through a translational chain of events from geno/phenotype to clinical response in disease, and from animals to man. The book then goes on to examine the impact of PK upon our understanding of a pharmacological response. Chapter 2 sheds light on factors, confounders and challenges involved in connecting PK and PD for any given drug in vivo and points to complexities translating in vitro findings to *in vivo*. Chapter 3 focuses on various aspects of plasma protein binding and when it matters. A thought-provoking and illuminating example is the notably changed predictions of drug safety margins based on comparisons of total instead of free unbound plasma concentrations across animal models (e.g., Fig 3.10). Throughout Chapters 2-3 the authors emphasize unbound (free) plasma concentrations for comparisons of results across species, compound and studies. This theme is echoed also in later Chapters (cf., e.g., Fig. 5.28), further stressing the importance of relating PD responses to drug levels actually encountered by the target biophase. Non-linearities commonly observed in drug discovery, and which sometimes confound the interpretation of pharmacological data, are discussed in Chapter 4, whereas Chapter 5 concisely presents rapid concentration-response equilibria. In the latter context, Fig. 5.26 illustrates a far from unknown, but often neglected, relation between receptor occupancy and response magnitude for some targets and drugs. Do comparisons of IC50/EC50 values between different agents and across exposures always represent the most relevant measure in a given drug benefit/risk efficacy comparison?

Chapter 6 addresses the temporal disconnect sometimes found between plasma concentrations and target binding and physiological or disease biomarkers. In this context, the concept and usefulness of hysteresis analysis is described by the authors in a very didactic fashion. They effectively explain the merits of this approach to re-connect two or more otherwise seemingly separate biomarkers; several Case Studies are also included – intended as potential practice examples for the interested reader. In the final chapter the reader's attention is then focused upon the prospects of inter-species scaling of PK/PD properties from animals to humans – a task of utmost importance in the drug development perspective.

Taken together, the book emphasizes the importance of utilizing *in vivo* data and thereby distances itself quite a bit from the commonly reductionistic use of *in vitro* data as a substitute for whole animal systems. I find this a very sympathetic approach that does a good job in uncovering the power of integrating PK and PD findings to optimize drug discovery and development. Mathematical equations and derivations are perhaps unavoidable in a book carrying integral PK content. However, the authors have strived to limit these and to maintain a high transparency in the understanding of complex and abstract relations using a nicely graphics-supported style throughout the presentation. Background acquaintance with PK and PD concepts is useful but not a prerequisite for the presumptive reader. To summarize, this book by Gabrielsson & Hjorth should provide very attractive and comprehensive reading for a broad audience – inside as well as outside Pharma – with interest in integrating PK and PD observations for greater understanding of how to connect drug fate and treatment consequences *in vivo*.

Fire in the Blood: film review



James Buckley
Imperial College London

James graduated from the University of Southampton with a BSc in Pharmacology. He then obtained his PhD in Respiratory Pharmacology from Imperial College London in 2013. James is currently researching childhood asthma in the Leukocyte Biology group, based at the National Heart and Lung Institute, Imperial College London. James is also a member of Scientists for Labour, a political action group involved in lobbying and advising politicians on science policy issues

Do giant, multinational pharmaceutical companies have moral responsibilities? If so, how and to what extent should they be forced to balance them with their financial and business priorities? These are the questions that lie at the heart of director Dylan Mohan Gray's film chronicling the struggle to improve access to AIDS medicines in developing countries in the late 1990s. Although the film becomes a solid documentary, it ultimately lends its focus too often to the human tragedy, with too little examination of the economic and political systems that lie at the heart of the problem. The film therefore ends up with plenty of pathos, but is naive in its analysis and gives too few practical solutions that might prevent this problem happening again.

By the late 1990s, infection with HIV was no longer the quick and painful death sentence that it had been in the 1980s. With the discovery and subsequent introduction of antiretroviral drugs, both the life expectancy and quality of life of somebody undergoing treatment for HIV infection increased dramatically.

However the fruits of this scientific and pharmacological success were not shared equitably throughout the world. Whilst the citizens of Western countries with well-funded government or insurance-based healthcare systems, such as USA and Europe, could benefit from these new and expensive patented drugs, those from developing countries, without the means to pay for them, went without. *Fire in the Blood* tells the story of the patients and doctors who found themselves at the heart of this problem and the subsequent campaign to get pharmaceutical companies to allow developing countries cheaper access to HIV medicines. The film tells their story well, graphically relaying the reality of untreated AIDS prognosis through the perspectives of doctors who were forced to watch as their patients suffered.

Unfortunately, by choosing to document the story anecdotally using multiple individuals with similar stories, the film became needlessly repetitive – personally, I didn't need convincing that this is a less than optimal arrangement. This repetitive element grew to be especially accentuated as, whilst the overall story progressed, the director kept returning to these anecdotes – breaking up the pace, and distracting from the political and economic story that led to these personal tragedies.

Whilst the message of the film is not as simplistic as "Big Pharma is evil", its investigation into the underlying political circumstances is limited and at times the film wants to have it both ways: at times criticising pharmaceutical ethics and then conceding that they are must operate as businesses. Admittedly on occasion, the pharmaceutical companies do little to help themselves, with excuses given for why their medicines are unsuitable for developing countries including *"Timed interval dosing would be impossible as Africans can't read clocks…they use the sun to tell the time"*.

However the problem with the film's analysis is that (as even noted in the film) pharmaceutical companies are ultimately revenue maximising entities whose *raison d'etre* is economic, not humanitarian. Both UK and US company law states that the responsibility of the board of directors of a company is to the shareholders, and it is by maximizing shareholder value that the directors remain in their positions. In contrast to the films logic, it is simply unrealistic to expect altruism from a system that rewards, and indeed is based upon, self interest.

In addition, the filmmakers seem surprised that extremely powerful multinational corporations might use their power and resources to influence government policy to favour them. By shedding this naivety, what appears to be a problem with the morality of pharmaceutical companies can easily be viewed as an inevitable consequence of the current political system, where lobbying is permitted, and the current economic system, where drug development is typically delivered by private enterprise..

One hope is that the current system can still result in wildly different behaviour by pharmaceutical companies, as reflected in the different policies introduced by GlaxoSmithKline and Novartis on access to their medicines in developing countries. Novartis is trying to block access to generic anticancer drugs in India (perhaps a reputational risk worth taking financially?), while GSK has donated a billion anthelmintic drugs to treat intestinal worm infections in developing countries and banking that the positive publicity will in the long run be financially beneficial. As pharmacologists, we should consider whether it is our duty to ensure that the fruits of our scientific research are to be spread in an ethical and moral way. One method of promoting this might be the adoption by individuals and institutions of ethical frameworks and guidelines for selling intellectual property that include developing market access to any drugs eventual developed. This viewer is however cynical about the likelihood that pharmacology could bring about real change to the wider system in which we work.

If you watched *Fire in the Blood* or want to comment about any of the issues raised, please contact Hazel O'Mullan (hom@bps.ac.uk).

Shakespeare's Medicine Cabinet at the Cheltenham Science Festival, 2013

Jeffrey K Aronson
President Emeritus, BPS

What was the "cursèd hebenon" that Claudius used to kill Hamlet Snr? Could *Carduus benedictus* have cured Beatrice's cold, or was it much ado about nothing? What was in the death-mimicking potion that Friar Laurence gave Juliet? What poison did Cymbeline's dastardly Queen seek to give to her step-daughter Imogen? And how did the juice of a flower make Titania fall in love with an ass?

BPS has been participating in the Cheltenham Science Festival for several years and has sponsored crowd-pleasing presentations on topics such as the pharmacology of cannabis, coffee, curry, and chocolate, organized by Clive Page and his colleagues; this year tea took its turn. Last year a session on self-experimentation involving Nobel Prize winner Barry Marshall was also popular [1], and this year Rod Flower tried to answer Shakespearean pharmacological conundrums. The hundred-strong audience in Cheltenham's Parabola Arts Centre was enthralled and appreciative.

Rod started by pointing out the many references in Shakespeare's plays to flowers, trees, shrubs, spices and herbs, including many different poisons and herbs for inducing lust or sleep or mimicking death. He suggested that Shakespeare may have obtained his medicinal knowledge from herbals of the time, by William Langham and Richard Bankes, and specifically from his contemporary John Gerarde (1545–1612), who examined candidates for admission to the Barber-Surgeons' Company in Barber-Surgeons' Hall, near the corner of Mugwell and Silver Streets, where Shakespeare lived during his time in London [2]. Gerarde's 1597 *Herball or Generall Historie of Plantes* was derived principally from that of the Flemish herbalist Rembert Dodoens, *A Niewe Herball*, with which Shakespeare would already have been familiar from Lyte's English translation of 1578, itself a translation of Clusius's French version [3].

Seeking the answers to Shakespeare's medicinal conundrums is no easy task, particularly since pharmacological knowledge of the time was rudimentary and depended largely on old wives' tales and dubious mechanistic theories such as the four humours of Hippocratic medicine and the doctrines of similars, signatures, analogy, and contagion [4]. According to the doctrine of similars, objects or circumstances similar in shape, colour, or sequence of events to those preceding or resulting from a disease would be therapeutic (e.g. stewed raven to treat greying hair). The doctrine of signatures proposed that plants and animals have distinctive marks that suggest medicinal properties (e.g. the root of bryony, which resembled a swollen foot, for dropsy and walnut shells for head injuries). The doctrine of analogy accorded therapeutic powers to the measures taken by sick animals, such as the food they took and their methods of resting. And the doctrine of contagion was that anything associated with the supposed cause of a disease would be therapeutic (e.g. moonstone for lunacy).

Add to all this the dramatic licence that Shakespeare would undoubtedly have exercised, and we can see how difficult Rod's task was. Nevertheless, hypotheses are possible.

Could hebenon have been henbane, metathetically mistaken for ebony, which hebenon originally was [5]? Other possibilities, such as hemlock and yew (German eibenbaum) seemed less likely. And *Carduus benedictus* was an equally unlikely cure for Beatrice's cold, when what she really needed was a good dose of Benedict! Was Juliet lulled to death-like sleep by one of the Solanaceae, mandrake or nightshade, or by opium? The latter was Rod's sensible (or insensible) choice. On the other hand, although Cymbeline's Queen may have thought that she had obtained aconite from her doctor, Cornelius, intending to poison Imogen, what he actually gave her ("a certain stuff") could not be properly identified, although leopard's bane was a possible candidate. Perhaps the stuff was again opium, since Imogen, having received it from Pisanio, takes it and falls into a death-like trance from which she eventually recovers.

But the most interesting hypothesis of the evening was that love-in-idleness, which in Shakespeare's day was a common name for the wild pansy, *Viola tricolor,* had aphrodisiac properties that might be exerted through systemic absorption after its juice had been squeezed into the eyes, as described in *A Midsummer Night's Dream*. Rod tested the hypothesis in the interval by offering the audience cups of pansy tea accompanied by another supposed aphrodisiac, honeyed almonds [6]. Was it my imagination, or were amorous looks soon being exchanged around the auditorium? It must be admitted, however, that the experiment was not placebo-controlled. Perhaps it would have been more interesting to have tried to substantiate Ogden Nash's pharmacological hypothesis that while candy is dandy, liquor is quicker. Although Rod did remind us of another Shakespearean pharmacological dictum, from Macbeth's porter, that alcohol "provokes the desire but takes away the performance".

Rod, on the other hand, had clearly not been indulging—his performance was as impeccable as ever. The entertainment was enlivened by performances of the relevant extracts from the plays by drama students from Imperial College under the direction of Sílvia Ayguadé.

So what next? How about Holmes's herbs or Poirot's poisons?

Rod Flower's performance was as impeccable as ever

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Meetings: an update

Professor David Webb
Director, Wellcome Trust STMTI
and Vice President - Meetings, BPS

Translational Medicine and Therapeutics Meeting

On 1 March 2013, Edinburgh University hosted a UK-wide meeting on translational medicine and therapeutics (TMAT) at the Queen's Medical Research Institute on the Royal Infirmary site at Little France.

The meeting, supported by BPS, was a joint venture between organizers of the Medical Research Council's (MRC's) Scottish Clinical Pharmacology and Pathology Programme (SCP3; director Professor Iain McInnes, University of Glasgow), the MRC's North West England programme in Clinical Pharmacology and Therapeutics (NWE MRC; director Professor Munir Pirmohamed, University of Liverpool) and the Wellcome Trust's (WT's) Scottish Translational Medicine and Therapeutics Initiative (STMTI; director Professor David Webb, University of Edinburgh). Each of the programmes offers clinical PhD fellowships to outstanding young clinicians training in the UK, and concentrates on translational approaches to disorders of high clinical priority with significant unmet clinical need where there is compelling opportunity for 'bench to bedside' transition. This key strength of clinical pharmacology has become increasingly complex with the development of powerful assay, imaging and 'omics technologies [1]. The focus of these programmes is primarily on translational and clinical pharmacology, but in the case of SCP3, extends to the important links between clinical pharmacology and pathology, through recognition of the central importance in novel therapeutics of targeting and exploiting pathogenic mechanisms.

The meeting was a one-day event, open to all interested parties, and attracted around 100 attendees, including medical students, clinicians in training, senior clinicians and academics, and representatives from the pharmaceutical industry. As well as providing financial support for the meeting, Jono Brüün, Chief Executive of BPS, was available to lend his, and the Society's, support to this important field of pharmacology. The purpose of the meeting was to showcase the UK's strengths in translational medicine, and hear about the work of the TMAT fellows supported by the initiatives, who presented innovative and exciting work from their translational PhD projects as oral and poster presentations over much of the day. It was clear that some of the work had the potential to rapidly influence clinical practice and patient care.

Professor Sir John Savill, Chief Executive of the MRC, and Head of the College of Medicine and Veterinary Medicine and a Vice Principal of the University of Edinburgh, opened the meeting and gave a keynote lecture on the collaboration between the MRC and the pharmaceutical industry. This was followed by a broad-ranging lecture from Professor Paul-Peter Tak of GSK, who spoke about the innovative and evolving world of drug development and clinical trials. The programme leads then gave brief introductions to each of the initiatives (NWE MRC, SCP3 and STMTI). There was a very lively poster and networking session over lunch followed by impressive talks from two fellows from each programme (Dr Jagtar Nijjar – SCP3 Glasgow, Dr John Reynolds – NWE MRC Manchester, Mr Ben Stutchfield – STMTI Edinburgh, Dr Sarah Minnis-Lyons – SCP3 Edinburgh, Dr Lauren Walker – NWE MRC Liverpool and Dr Hannah Bayes – STMTI Glasgow). The Chief Scientist for Scotland, Professor Andrew Morris, closed the meeting, summarising the value of focusing on early-stage researchers and giving an excellent overview of translational research as it stands in the UK, and indicating its substantial potential in the future.

The meeting was deemed a great success, with feedback suggesting the delegates found it interesting, informative and motivational. Indeed, the feedback from this year's meeting indicates that the Fellows feel they benefitted greatly from the meeting and would very much like to repeat the event on an annual basis. Particular mention was made of the benefits of meeting as a TMAT cohort and of the networking opportunities available on the day. We are fully committed to facilitating such events to allow UK TMAT Fellows to have regular contact with each other and aim to extend the meeting to allow for a keynote talk and informal dinner on the evening before the meeting. We look forward to repeating the event next year. The final details have yet to be decided, but the meeting will be widely advertised, including through the BPS website, once the arrangements have been made.

We are delighted with the success of this year's meeting and very grateful to Melanie Salton, STMTI Administrator, who made all the arrangements, and to BPS for their support.

EACPT Summer School

In early July 2013, in fantastic summer weather, and with considerable enthusiasm, around 120 clinical pharmacologists from five continents and 21 countries gathered in Edinburgh for the 10th European Association for Clinical Pharmacology and Therapeutics (EACPT) Summer School. Around half of the delegates were from the UK, with the rest from Europe and beyond – including delegates from Australia, China and Nigeria, and four from the newest member state of the European Union, Croatia. We were delighted to have attracted such broad-ranging participation, which gave the meeting a truly international flavour,

and an excellent buzz. EACPT has as its aim the promotion and development of clinical pharmacology and therapeutics in Europe, and the Edinburgh meeting provided an excellent chance to hear from a number of international leaders in clinical pharmacology. The format of the meeting was designed to provide lots of opportunities for interactions between delegates and speakers.

The meeting was held at the Royal College of Physicians of Edinburgh, a beautiful Georgian building with excellent facilities set within the New Town of Edinburgh, and hosted by Professor Simon Maxwell and myself. Representing BPS, we were ably supported by Karen Schlaegel (Head of Meetings and Events) and Helen To (Events Officer). Ivor Williams was kindly available to capture highlights of the event on camera. We were also delighted to be generously provided with educational support and bursaries to assist with travel and accommodation costs from EACPT, GlaxoSmithKline and Takeda Pharmaceuticals. Additional bursary support for UK delegates was provided by BPS. The UK Federation of Royal Colleges of Physicians approved the meeting for 12 CPD credits and the Society of Biology 41 credits.

The theme of the meeting was translational pharmacology, toxicology and therapeutics, and the programme consisted of around 20 keynote presentations by invited experts, workshops, 40 poster presentations, and linked social events.

The first day focused on drug development. Professor Munir Pirmohamed (University of Liverpool) gave the first keynote lecture on stratified medicines, followed by further keynote lectures from Professor Ingolf Cascorbi (University of Kiel) on genomics and 'personalised' therapy, and Professor Adam Cohen (University of Leiden, and Centre for Human Drug Research) on 'dream-driven' drug development.

On the second day, the focus shifted to drug regulation, clinical toxicology and cardiovascular disease. Here, keynotes were provided by Professor Sir Kent Woods, on innovation, regulation and the public health, and Professor Sir Michael Rawlins on the National Institute for Health and Clinical Excellence (NICE); the first 14 years.

We were privileged to have the first opportunity to hear the GlaxoSmithKline Prize lecture from Professor Amrita Ahluwalia (Barts and the London School of Medicine and Dentistry) on a 'green' approach to cardiovascular disease: recycling inorganic nitrate and nitrite. Not only is Amrita the first woman to win this prize, she is also the first basic pharmacologist to do so, through achieving a very successful translation of her lab-based research into the clinic, which she ably described in her lecture. There were also demonstrations/workshops on prescribing assessment (Professor Simon Maxwell, University of Edinburgh), and on new forms of communication in science (Professor Donald Singer, University of Warwick), and a practical session on getting research into print (Professor Kim Brøsen, University of Southern Denmark).

The meeting ended on Saturday lunchtime, after a session on new developments in hypertension, stroke and pulmonary hypertension. The delegates stepped out into the hottest and the sunniest day of the year by far, either to head home or to relax and enjoy the pleasures of Edinburgh city centre. To cap it all, a Scot, Andy Murray, even won Wimbledon that weekend!

Professor Ingolf Cascorbi

Professor Adam Cohen

EACPT Summer School conference dinner

Professor Sir Kent Woods

Professor Sir Michael Rawlins

Professor Ingolf Cascorbi, previous Chairman of EACPT, had this to say: "Thanks a lot, and congratulations for this remarkable high quality summer school, which was well attended and perfectly organized".

There was a strong interactive element to the meeting and many opportunities for delegates to network with the speakers, not least over the posters, during the workshops, and over dinner. We were delighted with the success of the meeting and hope that it proved valuable for all those who participated. The feedback received has been extremely positive, and views can be found on an EACPT blog [2]. I was extremely impressed by the high quality of the work on research and prescribing presented at the meeting, and it gives me considerable confidence that this will allow clinical pharmacology to continue to attract the brightest academic trainees into our specialty.

We look forward to the main biennial EACPT Congress, to be held in Geneva between 28 and 31 August 2013.

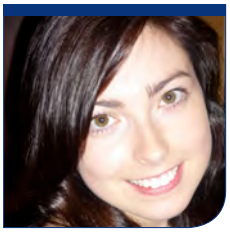
David

References

[1] FitzGerald GA. Anticipating change in drug development: the emerging era of translational medicine and therapeutics. Nature Reviews Drug Discovery 2005;4:815-

[2] eacpt.blogspot.co.uk/2013/07/young-pharmacologists-notes-from.html?m=1

Young Pharmacologists: an update



Hannah Watson
Editor, Pharmacology Matters

EACPT Summer School 2013, Edinburgh

At the time of writing there is just a month until the 10th EACPT Summer School in Edinburgh. I am looking forward to hearing from the keynote speakers and the social agenda looks equally inviting! If you are not planning to attend, look out for a full account of my experience in December's issue.

Pharmacology 2013, London

The Young Pharmacologists are busy finalizing their contributions to *Pharmacology 2013*. Planning for the much anticipated informal Welcome Reception on the first night of the conference (Tuesday 17 December 2013) is well underway. It will again be held at Sixty One Whitehall, London. For those of you not familiar with the venue, it is a historic site identified as the original site of Henry VIII's private bed chamber in the Tudor wing of Whitehall Palace. Online registration for *Pharmacology 2013* is open bit.ly/V8FLy1.

A reminder: Undergraduate and postgraduate membership

Undergraduate BPS membership is free and offers excellent benefits for pharmacology and medical students with an interest in pharmacology. BPS postgraduate membership is only £20 a year and is applicable all postgraduates, including clinicians with specific interests in pharmacology.

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