Pharmacology Matters

BPS BRITISH PHARMACOLOGICAL SOCIETY
Today's science, tomorrow's medicines

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pharma futures

open innovation | personalized medicines | losing the plot? | policy & media | young scientists

BPS BRITISH PHARMACOLOGICAL SOCIETY

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The Twelfth International Conference on Endothelin

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Editorial

We welcome contributions from our readers, all suggestions should be e-mailed to the Managing Editor: hom@bps.ac.uk

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The state of UK science is rarely out of the headlines these days, and several seismic events have shaken the pharmaceutical industry to its foundations. The closure of Pfizer's Research and Development site in Sandwich was a shock, and a stark reminder (if we needed it) of the effects of a shrinking global economy on Pharma. But it is not all doom and gloom: the government's Comprehensive Spending Review protected the sector from the worst of the cuts; a month after the Pfizer announcement another industry 'giant', GlaxoSmithKline, became the first major UK employer to announce that it will pay university tuition fees for graduate trainees, a move that will ensure 50-100 trainees are trained and retained within the pharma industry; and science researchers were prioritized in the government's much maligned immigration cap.

The articles in this issue stress the value of long term commitment and investment in the future of UK Pharma, and argue that the UK can maintain its strong position in world science if it evolves successfully. Articles from Helen Dowden and Martin Todd discuss forging a closer working relationship between pharma and the wider scientific community, encouraging a shared scientific dialogue ultimately leading to the discovery of new innovative drugs. Imran Khan, Chief Executive of Campaign for Science and Engineering (CaSE) reviews the changes that have taken place in science policy campaigning over the last year, and how online resources will influence future campaigns to secure the future of the sector.

The BPS Young Pharmacologists' committee have for the first time written an article collectively (pg 17) about the future of pharmacology and therapeutics, reminding us all that the importance of pharmacological research should not be forgotten amongst the politics, policies and profits.

This issue also looks back through time, featuring the first of a five part retrospective look at the greatest drugs of the last century - the first installment showcases the contraceptive Pill - and for the historians amongst you, there is a review of the pharmacological uses of honey and beeswax in Egyptian medicine (pg 20).

Finally I would like to thank Sara Barnes and Adam Smith for their work on Pharmacology Matters over the years, and extend a warm welcome to Hannah Watson who replaces Sara as Younger Members Editor.

Enjoy
Hazel O'Mullan
Managing Editor

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View from Angel Gate

Kate Baillie
Chief Executive, BPS

The Society ended 2010 on a high note, with 809 registrants for our Winter Meeting, London 2010 – the highest figure in recent years. In addition to an excellent scientific programme with a series of symposia organized in conjunction with the British Hypertension Society, the Association of Hospital Pharmaceutical Physicians in Industry (AHPPI) and the British Toxicology Society, we were pleased to welcome members of the public to the first BPS Public Lecture from Professor Les Iversen.

The Young Pharmacologists also had cause to celebrate, with high levels of demand for their "I love Pharmacology" T-shirts, Proceeds from the sale of the T-shirts will be put towards a bursary to enable an African scientist to attend World Pharma 2014 in Cape Town.

Two successful workshops were held alongside the Winter Meeting on Stem Cells and General and Advanced Receptor Theory (GART). The GART workshop proved so popular that a second workshop has been arranged for July 2011, which also sold out quickly!

The meeting also provided a forum for representatives from a variety of different organizations and institutions to discuss the development of greater co-ordination between activities relating to *in vivo* education and training, animal welfare and integrative pharmacology/physiology. This is now being followed through by Nick Goulding and Annie Geraghty, who would be delighted to hear from you whether you work in academia, industry, CRO's or bio-tech. If you wish to get involved contact arg@bps.ac.uk.

Plans are already underway for the next Winter Meeting, so save the date of 13-15 December 2011 now! We were delighted to receive 27 proposals for the nine symposia slots available for this Meeting which has also enabled us to submit proposals for BPS symposia to the major EPHAR Congress next year as well as the Physiological Society's 2012 meeting. At the Winter Meeting, London 2011, we will welcome delegates from the Chinese Pharmacological Society to a joint symposium on *Clinical pharmacology of drug development and clinical research in China* and will also host the Editorial Board meetings for both the BJP and BJCP.

We have recently been informed by Cheltenham Science Festival, that in addition to our next session in the popular "Science of.." series, which this year will focus on the Science of Cannabis, the proposal to hold a pharmacological examination of the treatment of cardiac arrest has also been approved. In *Heart Attack!* pharmacologist Mark Christie and clinician Emma Baker discuss the treatment of cardiac issues in a fascinating analysis of molecules and medicines, risks and benefits, life and death.

The Women in Pharmacology Committee is hosting two events in March, both of which will be held at the new meeting facilities at Angel Gate. On 3 March, we hosted a training day for the mentoring scheme and a Leadership Skills workshop took place on 8 March. This year we attracted 30 applicants for the mentoring scheme (12 mentors and 18 mentees) and now have 67 mentors on our database. The Women in Pharmacology committee will be offering grants towards the costs of childcare from this year, to enable BPS members to attend meetings. For more information, contact Annie Geraghty at arg@bps.ac.uk

BPS members were also involved in the RCP Medicines Forum: *Physicians and the Pharmaceutical Industry* on 3 February as part of the follow-up to the Renaissance of Clinical Pharmacology Working Party chaired by Jeff Aronson.

The conference covered a broad range of subjects, including sessions on the UK as a destination of choice for pharmaceutical trials, NHS clinical trials networks, translational research, and discussion of the Academy of Medical Sciences recently published report 'A new pathway for the regulation and governance of health research which the BPS has agreed to endorse. The next step will be to support the AMS in its efforts to get the NHS to adopt the recommendations in the report in order to improve the UK environment for clinical trials and embed a culture that values research within the NHS.

Also at this meeting, an address given by Earl Howe, Parliamentary Under-Secretary of State for Quality (Lords), at the Department of Health, stressed the support of the Coalition Government for a strong Pharma industry in the UK, and for medical research in general.

Sadly, this meeting came close on the heels of the announcement of the closure of Pfizer's R&D facility at Sandwich. BPS released a position paper setting out some initial views on the closure, and its impact on R&D in the UK, and we have been working to offer help and support to members, as well as reaching out to non-members affected by this decision. We are also arranging for members of the Industry and Diploma Committees to meet with representatives from Pfizer to discuss in more detail how we can provide practical support and services.

We have been using the BPS's new Connected Community to discuss this situation via the Industrial Pharmacology discussion group,[1] if you are interested in contributing to the debate, joining the BPS consultancy network, or wish to find out more about the enhanced website functionality available to members, please contact Jonathan Bruun at jb@bps.ac.uk

Kate Baillie BA MA MBA, Chief Executive BPS

1 To access the Connected Community, you will need to input your usual BPS username and password.

Pharma Futures: Can Open Innovation Revive the Pharma Industry?

Helen M Dowden

Helen M Dowden, AstraZeneca Pharmaceuticals, USA

Helen Dowden is a Strategic Intelligence Leader within the Research & Development organization of AstraZeneca. She has worked in the pharmaceutical industry for more than 20 years, providing commentary and analysis to worldwide research and commercial functions. Helen holds a BSc in Biochemistry from Imperial College of Science and Technology and a PhD in Neuropharmacology from the Institute of Psychiatry, both at the University of London.

A closer working relationship between Pharma and the wider scientific and clinical communities is a logical evolution in the quest to advance pharmacological medicine. The question is, can it help stem the tide of rising R&D costs and boost the number of innovative new medicines reaching the market?

Secrecy, confidentiality, and intellectual property (IP) have been cornerstones of the pharmaceutical industry since its inception. Only regulatory agencies have been privy to the data generated in drug development programs, and the information remains under lock and key unless the company chooses to release it. Preventing competitors from gaining a competitive advance has been a key priority for almost all profit driven pharmaceutical corporations.

This is beginning to change. Over the last decade, as the science of drug discovery has become increasingly complex and Big Pharma increasingly unproductive, some industry observers are wondering if the risk of not sharing data may actually be greater than the risk of sharing. Companies are looking for ways to change the economic equation underlying drug development; specifically to increase the likelihood of success for development candidates while minimizing infrastructure expense. As a result, we've seen a string of research site closures, the latest example being Pfizer's planned exit from its Sandwich, Kent, facility, concurrent with an increased focus on collaboration.

A push for more open collaboration with the industry is also coming from government-funded research institutions and universities who are used to open information flow and who are increasingly mandated to help find practical uses for basic research - especially if it leads to local economic development.

Collaboration between industry and the external world is of course nothing new. However, in the past these relationships have often been structured as service or consultancy agreements with little sharing, other than fiduciary, on the part of Pharma. What we are beginning to see is a greater willingness on behalf of both parties to step outside their comfort zones, experiment with new business models and relax their traditional ideas about IP and academic freedom. This move to a freer flow of IP, ideas and people into and *out of* organizations has been termed "open innovation" (Chesbrough H, 2003).

Lilly has arguably been the most creative in terms of opening the channels between its internal labs and the outside science community. Back in 2001, it launched InnoCentive, a global web-based community matching scientists to R&D challenges posed by companies. Client companies post their problems on the InnoCentive web site and offer registered experts significant financial awards for the best solutions. Lilly also uses open source platform technology in its latest Phenotypic Drug Discovery (PD2) initiative, which provides external researchers free, confidential access to Lilly's phenotypic drug discovery assays (for Alzheimer's, diabetes, cancer, and osteoporosis) in return for first rights to exclusively negotiate a collaboration or licensing agreement with submitters of those compounds. A secure web portal provides global external researchers access to Lilly's drug discovery and development process while, at least initially, retaining all their IP rights.

Much has been made of the recent uptick in collaborations between pharma companies and academic institutions. In

the first six months of 2008, Pfizer announced at least four multi-year deals with leading academic institutions exceeding a total of $60 million in committed funding. Most major Pharmas have entered similar arrangements with at least one leading research institution. The majority of these involve a sum of $10-25 million to be distributed among projects selected through a joint committee. However, a few, such as Genentech in its partnership with University of California San Francisco (UCSF)'s Small Molecule Discovery Center for neurodegenerative disease, and AstraZeneca in its partnership with University of Pennsylvania for Alzheimer's disease, have taken collaboration to a new level. In these cases the university effectively becomes the research end of the pharma company's drug discovery effort in a specific area, providing biological and/or chemical expertise to guide selection and development of drug candidates. Rather than being a service provider, the university becomes a true partner in the R&D process, with milestones and royalties negotiated in advance much as would be the case in a pharma-biotech collaboration. Key to such arrangements is the selection of a focused area of research that is of mutual interest to both parties, and a healthy respect for the partner's business needs or scientific freedom. Some of the cultural barriers that have hindered close working relations in the past might be eased through pharmas' recent restructuring, which breaks their research organization into smaller, more autonomous units designed to imitate an academic environment.

Other efforts Pharma is making to foster early-stage discovery innovation include venture funding and the sponsorship of incubators. Most of the major pharmaceutical companies, and several mid-sized and biotech companies, have their own venture capital organizations designed to supply seed funding to early-stage research programs in areas likely to be of future interest to them. In 2009, GlaxoSmithKline announced the creation of an Open Innovation Bioscience campus at its research site in Stevenage, UK, in collaboration with the UK government and the Wellcome Trust. The company is contributing land, facilities and investment totaling almost one third of the £38 million project. The park will provide facilities for about 1,500 outside scientists to conduct early stage research and a financing vehicle to run the program. Earlier experimenters with the incubator concept include Pfizer and Biogen Idec, but both had very few projects and most have since completed term without being productive.

Full open access for a pharma company's targets, compound collections and/or IP, except for diseases such as malaria and tuberculosis where commercial return is already limited, remains unlikely given the industry's reliance on patents to protect its research investments and the need to satisfy shareholders. However, even in these areas we are seeing the genesis of a new way of working; for instance, Pfizer's proposed Knowledge Bank would put all preclinical drug targets in the public domain.

There are also numerous examples of more open collaboration further along in the drug development chain. Here the challenge of integrating and analyzing vast amounts of clinical data is beyond the scope of any single corporation and groups of pharma companies have united to form pre-competitive consortia. In 2004, the US Food & Drug Association (FDA) launched its Critical Path Initiative in an attempt to boost the number of new drug submissions, and this has spawned a number of such consortia, predominantly focused on predicting safety and translational medicine (identification of biomarkers that will determine a drug's efficacy or guide treatment decisions). Europe's Innovative Medicines Initiative (IMI) has a similar remit, and AstraZeneca is the coordinator for one of its programs: Europain brings together 21 industry and academic partners to explore the best translational models and biomarkers for neuropathic pain. The IMI also has a program aimed at knowledge management, attempting to standardize data sources so that the increasing amount of drug discovery information in the public domain can be more effectively integrated.

Some of these efforts have recently expanded into traditionally more sensitive areas. As part of the Critical Path's Biomarkers Consortium, a large-scale breast cancer study, known as I-SPY 2, is ongoing. This first-of-its-kind precompetitive public-private partnership enables the testing of multiple experimental drugs from multiple pharma companies under one "master" investigational new drug application (12 drugs over five years). The data from the trial will be stored in a database at UCSF and the University of Texas M.D. Anderson Cancer Center and will be made available to drug companies and other investigators who register on the study's website.

In another first, Merck & Co., Pfizer and Eli Lilly have teamed up to form the independent, non-profit Asian Cancer Research Group. The Group will create a database of pharmacogenomic information from Asian cancer patients, with the ultimate goal of providing better diagnostics and treatment options to this population. Collaborative relationships will be established throughout Asia to collect the tissue samples and data and, over time, the database will be further populated with clinical data. Lilly will use its open source technology to make the data publicly available to academic researchers.

The lack of progress in developing effective therapies against intractable diseases such as Alzheimer's has led to calls for the sharing of early clinical trial data so that the whole industry might learn from individual companies' failures. A step in this direction was taken in June when, under the auspices of the Critical Path's Coalition against Major Diseases, five pharmas including AstraZeneca agreed to pool the data from the placebo arms of their failed Alzheimer's trials into a publicly available database. Initially data from 4,000 patients across 11 clinical trials will be shared in order to create a more robust cohort for determining disease progression and the identification of potential biomarkers.

The above examples attempt to indicate the deepening relationships that are burgeoning between industry, government and academia. Although fragmented at present, as participants become more comfortable with these new ways of working the goal will be to integrate these efforts. Only by working together can we hope to close the gulf between basic and clinical research and give rise to a new era of pharmaceutical innovation.

Reference

Chesbrough H, "Open Innovation: The New Imperative for Creating and Profiting from Technology", Harvard Business School Press, 2003

A unique alliance from three cultures: industry, publishers and academia working together to share costs and risks

Martin Todd

Martin Todd
AstraZeneca
Pharmaceuticals, UK

Martin Todd is a member of the Strategy Portfolio and Performance Group at AstraZeneca Pharmaceuticals in Alderley Park, Cheshire UK. He has been involved in managing R&D projects in cardiovascular pharmacology, establishing a global high throughput screening facility for the company and more recently in developing options and planning new R&D initiatives.

He is a member of the BPS Executive Committee, the BPS Membership and Awards Committee, and Chairman of the newly formed BPS Industry Committee which is developing initiatives to promote scientific dialogue, skills and training between academia and industry and to explore and facilitate new ways of working.

Pharmaceutical companies share with the film industry the search for blockbusters through a high attrition process where many good ideas fall by the wayside on the way to a marketable product. Since the heyday of the big film studios in the 1930s, the film industry has become expert at managing costs through sharing rather than owning the relevant technology, distribution channels and film stars. The Pharmaceutical industry is set on a similar journey where an industry once fiercely independent in controlling all of its assets and facilities, has been moving to share aspects of its work with third parties to reduce costs, increase efficiency and reduce the time taken from concept to blockbuster. Spin-offs and 'open innovation' have become attractive options as Pharma reshapes R&D activities so that more work takes place in academia and in small start-ups, and the risks of product failure are shared.

As a result, a market is being created for projects and products, some of which were originally owned by large Pharma, others which have arisen from biotech companies or from academia. These projects are being pursued through the enthusiasm and energy of third parties which often include managers and scientists displaced through Pharma reorganizations. In addition there are academic groups keen to identify new targets, compounds and technologies to create spin-offs and value for their organizations. Those with experience in the Pharma industry know that risk management of a project portfolio is a key activity with potential medicines coming from either home grown, acquisition from other companies, or from collaborators in universities. In addition there are important opportunities to re-profile or reposition compounds which have already progressed down the R&D road and can be relatively quickly taken into man for new indications. Understanding the value of these different types of projects at all stages in the R&D process, in this Pharma marketplace, is a challenge for the owners of the projects, as well as potential buyers and sellers. This situation is compounded by a lack of clarity around definitions of biological activity and the potential for misinterpretation of data.

In evaluating a potential drug candidate you might ask yourself a range of questions: what value does this have to a potential purchaser? Is this a compound tested *in vitro* with high potency and good selectivity, or is it a compound which has been tested in validated animal models for efficacy and safety, and where estimates of potential human doses for both efficacy and safety can be estimated from animal model data? Is the target acted on by your compound novel and therefore exciting, but unvalidated in man, or is there clear evidence from previous compounds of an involvement in disease initiation and progression? Does the compound belong to a chemical class which is unknown, or is there data to suggest that safety issues will not be a problem? Understanding the details behind biological test systems and definitions of activity is a giant step towards being able to identify the value of targets, compounds and potential drugs, enabling the creation of a high quality market place where both vendors and buyers have confidence about the value of what they read in the shared data dossier.

One approach to standardizing data definitions is being pursued by the Pistoia Alliance (http://www.pistoiaalliance.org), a not-for-profit, international alliance of Pharma, vendors, publishers, and academics. Members of the alliance collaborate to lower barriers to innovation by improving the interoperability of R&D business processes. The Pistoia Alliance was initially formed at a meeting held in the Italian city of Pistoia in 2007 with representatives from AstraZeneca, GSK, Novartis and Pfizer. The participants outlined common frustrations and challenges in managing and sharing data relating to Pharma R&D from public databases, incorporating the information into proprietary databases and sharing pre-competitive information with potential collaborators and partners. Over 40 member organizations now support the Alliance's aim to develop frameworks and systems to allow for precompetitive data sharing, and the organization is set to deliver prototype information sharing systems early in 2011.

There are two areas of the Pistoia Alliance work plan which may be of interest to Pharmacologists. The first one relates to linking gene and disease relationships in numerous published biological data sources. The organization refers to this as biomedical knowledge brokering. A prototype of a system for the delivery of this service for a single disease area (Type 2 diabetes) has been completed by the Pistoia Alliance. This project involves an alliance of AstraZeneca, GSK, Pfizer, Roche, Unilever, European Bioinformatics Institute, Nature Publishing Group, Oxford University Press,

Elsevier & the Royal Society of Chemistry. The prototype takes content from several structured data sources and journals. It is intriguing to consider how this service might be applied to give researchers the ability to quickly link findings in patients and animals with potential alterations in gene function.

Another working group in the Pistoia Alliance aims to derive a vocabulary for complex biological targets (multi-protein targets and complexes) which are currently poorly described, often simply as raw text.This project will define a specific set of "rules" regarding the representation of complex molecular targets. Such an effort could feed into the European Union Innovative Medicines Initiative Open Pharmacology activity as an industry-publisher requirement and could gain a quick-start by defining the minimum set of information that should always be present in published scientific articles. The data may then be effectively mined both in situ and when transferred to large data repositories. This could then allow users to search out chemically related molecules, or identify those targeting the same protein target, pathway or process, and provide a starting point in the search for proof-of-concept tools, for novel chemical design, and for understanding the published state of the art in any therapeutic area.

Unlike the activities of many other consortia or standards groups, Pistoia Alliance activities are characterized by working groups that actively engage all the players necessary to identify barriers to collaboration and innovation in life science R&D. These include pharmaceutical informatics specialists, scientific publishers, and suppliers of data analysis systems, software and computing power. Collectively, these individuals aim to deliver services which can be accessed and used across the life sciences. The development of key partnerships to understand the needs of scientists in the life sciences, the potential technological solutions that will address these needs and appropriate business models for delivering the services is part of the activity facilitated by the Pistoia members. High quality data and information analysis is fundamental to the success of this work

The British Pharmacology Society (BPS) has a strong commitment to delivering quality information on biological targets through the publication of its Guide to Receptors and Channels (GRAC) as a biennial supplement to the British Journal of Pharmacology. In a new partnership, BPS are joining forces with The International Union of Basic and Clinical Pharmacology (IUPHAR) to coordinate nomenclature and provide standards for drug targets and plans to create a single online portal documenting the properties of current and future potential drug targets (IUPHAR-DB). The planned open access website, carrying the authoritative backing of both IUPHAR and BPS, will provide dynamically updated, searchable versions of GRAC and IUPHAR-DB; it is intended to assist research in pharmacology and drug discovery, to educate the next generation of biomedical and clinical scientists and to provide the general public with accurate information on how drugs work. This endeavour offers the opportunity to facilitate new relationships between scientific researchers, and to derive new knowledge and new medicines by bringing together information from bench science, clinical trials, patients, hospitals and healthcare providers. Only by integrating this data, looking for patterns, and using validated analytical tools will the benefits for patients be realized. The partnership between the bench scientist, the clinical scientist and information scientist is crucial to the development of systems that can translate data into knowledge and novel ideas.

Strong collaboration through these kinds of academic, industry and publisher consortia will help facilitate productive discussions on pre-completive approaches in R&D. These approaches include: evaluation of data on targets, the development of *in vitro* and *in vivo* models (animal and clinical), the selection of appropriate patient populations, facilitating the search for valuable new medicines (blockbusters or personalized healthcare products) to treat disease in patients. The shape of the life sciences industry landscape is changing in a way that will create new opportunities for collaborative working.

There is a valuable place for learned Societies like the BPS to play an influential role in supporting new activities which will enable biological data to be better understood and better utilized by all those involved in the Life Sciences, through collaborative ventures and training programmes.

My thanks to Martyn Wilkins (Pistoia) and Professor Tony Harmar (University of Edinburgh) for valuable advice and help with this article.

Pharmacology of the future:
a clinical perspective

Donald Singer

Donald RJ Singer
University of Warwick

The ancient Greek origin of 'pharmaco-' may mean treatment, poison or magic charm. Future pharmacologists will need to continue to consider all these aspects: therapeutic treatments, vigilance against the hazards of performance enhancing and recreational drugs, minimising and developing treatment for toxicity, and taking into account 'magical' placebo properties. Without charm in the consultation, long-term adherence to treatment in many is likely to be poor [1].

The political theorist Hannah Arendt viewed predictions as 'never anything but projections of … occurrences … likely to come to pass if men do not act and if nothing unexpected happens'; for her there were too many unknowns for future watching. The further we forecast, the greater the chance that unexpected scientific, clinical, economic or other developments may change the therapeutic agenda. Reflection on the future of pharmacology in 1981 would have been just too early for emergence of HIV-AIDS as an epidemic in need of new pharmacology, and for the 1982 rediscovery in Australia by Marshall and Warren of Jaworski's 1899 observation of spiral micro-organisms in the human stomach [2], leading to the recognition of Helicobacter pylori as a major new treatable cause of upper gastro-intestinal ulcers.

The healthy might also argue that we now have sufficient treatments from previous pharmacology for all the major common and serious diseases.

So why consider the future of pharmacology at all?

From the perspective of health professionals and the public, there is an expectation that there will be major long term clinical need for pharmacology in its three current major roles:

- Educating health professionals, the public and policy-makers in principles and practice of safe and effective use of medicines
- Maintaining scientific training, infrastructure and expertise to lead drug discovery to fill current therapeutic gaps and be ready to respond rapidly to future serious diseases
- Developing biomarkers of disease, to improve diagnosis, and monitoring of disease activity and response to treatment

Secondly, new multi-factor economic challenges for Universities, health services, and the pharmaceutical industry underline the need for active champions so that pharmacology is protected into the future as a vital resource for the continued health of nations.

Obvious areas that merit continued or new focus from pharmacology in the coming years include:

- the obesity epidemic, with its associated burden of cardiovascular, liver, renal, joint and other serious disease
- dementia, which in its vascular and non-vascular forms awaits a rigorous approach to unravelling aetiology and identifying preventive and not just palliative therapeutic targets
- organic strategy against drug resistance for

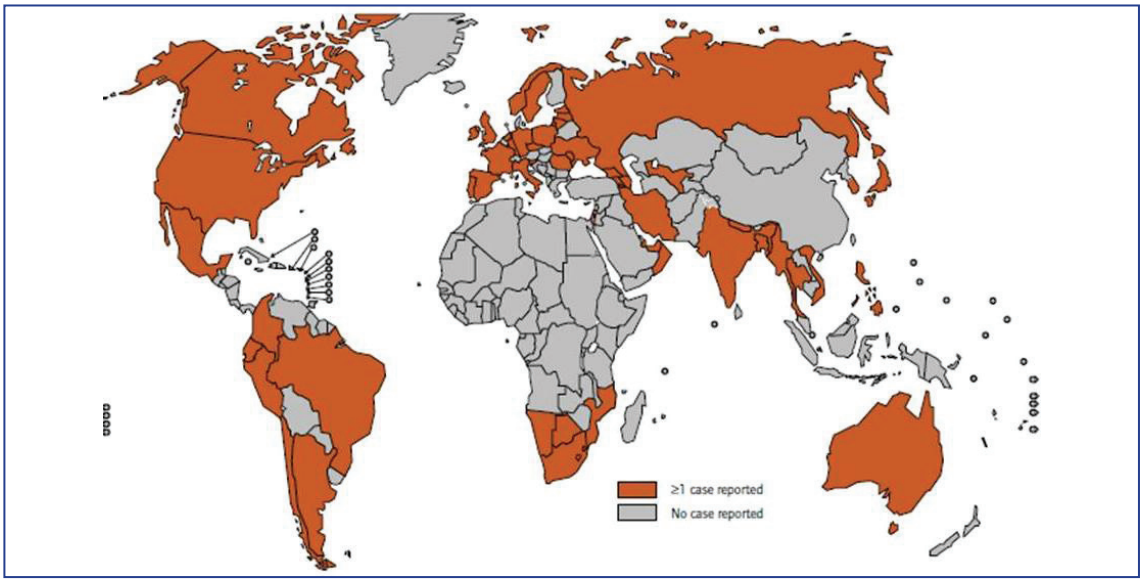

Figure 1. Countries reporting at least one case of extended drug resistant tuberculosis in 2008 [10]

infection [Figure 1] and cancer

- improved pharmacology of psychiatric disease guided by better genome and phenotype profiling
- new viral epidemics, with early warning from the 2009 H1NI pandemic [Figure 2]

Those involved in pharmacology should also take an active role in educating the public about the risks of taking pills to deal with consequences of uncontrolled 'lifestyle' behaviour such as obesity and alcoholic liver disease. Early adoption of long term behaviour changes would, for many, avoid the need for medical treatments.

Personalizing medicines

Implicit in these key themes is the need to integrate new genetic [3] and high definition phenotypic biomarkers into strategies for personalizing development of effective and safe medicines for those identified as failing to respond to treatment, or at high risk of adverse drug reactions. This challenge for pharmacology is amplified by the need to ensure equity of application of pharmacology to research, and development of medicines for diseases in less developed countries, where treatment is poorly effective or unacceptably toxic. Factors to be considered include the high prevalence of low activity genetic cytochrome variants of CYP2D6 in parts of North Africa, and the high prevalence of G6PD deficiency amongst Black Africans, with risk of severe anaemia if the wrong medicine is developed. Pharmacogenetics offers an opportunity to protect patients by assessing important genetic differences in activity of key enzymes and pathways important for drug action and metabolism, due to single nucleotide polymorphisms or to differences in copy number of relevant genes [3]. This allows the prospect of early life genetic screening to inform future prescribing in clinical practice, enabled by the dramatic recent reduction in costs of genetic testing. Less than half the variability in warfarin response appears predictable by new pharmacogenetic methods, illustrating the complexity of the impact of lifestyle factors such as alcohol, and effects of co-morbidity, other drug treatments and variable compliance in assessing treatment response. However in view of the impact of poor warfarin response on risk of death, and the high risk of bleeding complications when effects of warfarin are unexpectedly large, new gene tests remain of major practical interest. The final clinical and health economic translational gaps for pharmacogenetic testing to guide treatment with warfarin are currently being addressed by a European Union-funded consortium of researchers [4].

Who should be involved in the pharmacology of the future?

Obvious key players include:

- researchers, from drug hunters to clinicians
- pharmacologists in clinical practice
- patient champions
- regulators
- toxicologists (wishing for safer medicines, better antidotes, rapid diagnostics, and treatment development, including for toxin-based bioterrorism)
- sports medicine specialists (needing rapid development of diagnostics to detect new performance-enhancing drugs, and drug passports for future detection of currently undetectable and illegal drug use)
- pharmacovigilance teams
- policy professionals

This pharmacology activity will increasingly take place within partnerships among academic centres, small biotechnology companies, the pharmaceutical industry and health service research networks, in collaboration with a wide range of other experts, including chemical and systems biologists, geneticists, immunologists and pathologists, and new emerging variants on relevant scientific disciplines. A new approach for joint working for pharmacology is illustrated by the Health Impact Fund [5]. This aims to incentivize development and delivery of new medicines based on health impact achieved. For maximum success, there needs to be a personalized approach to medicine development and prescribing, to ensure that patients benefit as much as possible, based on objective clinical criteria. Medicines will of course have to reach patients, who will need to adhere to their treatment for greatest possible health gain. This will be a major challenge in developed countries, never mind the least developed countries with most to gain, and provide much fruitful work for all key players interested in the future of pharmacology.

New bioassays and other approaches for identifying new candidate medicines

There will always be a need for improved high throughput bioassay screening methods. There is also great potential for pharmacology of the future to exploit new *in silico* methods, for example LINGO tools for structure-based identification of ligands [6] and new chemical genomic methods such as viral library-based bioassays for identification of ligands for new therapeutic targets [7]. With much safety data already in place for current drugs, there is major scope for reprofiling existing medicines as potential treatments for 'off-target' mediated clinical conditions. That might mean finding an unexpected target organ expressing a similar pathway (e.g. sildenafil for angina and for erectile dysfunction) or recognition that an unrecognized or overlooked mode of action may be relevant to treating a different disorder. Adverse drug reactions [ADRs] also provide a stimulus to defining mechanisms, which may allow chemical modification

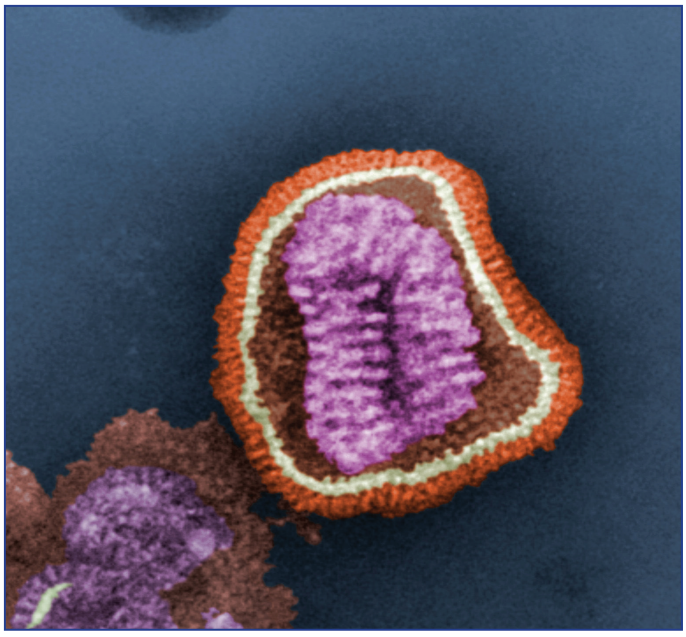

Figure 2. Electron micrograph of a flu virus - CDC/ Erskine. L. Palmer, Ph.D.; M. L. Martin

to create safer treatments, and may also provide insight into mechanisms for the arising ADR, thereby suggesting new treatment options. Large scale initiatives such as UK Bio-bank will help to identify whether high definition phenotyping will be of value in treatment selection and monitoring of treatments for common and serious disorders in routine clinic practice. The Northwick Park experience highlighted the need for great caution in evaluating the expanding menu of potential biological treatments. RNAi [8] has progressed from a lab tool helping to understand protein function, to use as a biomarker of disease risk and to trials of RNAi as a therapeutic option e.g. for treating infection or cancer. In the longer term, RNAi has the potential to offer treatment for diseases where none is currently available, and offers the most realistic current option for 'real time' personalizing of treatment for an individual patient e.g. for a resistant cancer. Major challenges for RNAi pharmacology include the safe, sustained and effective delivery of RNAi treatment to target sites of interest. Herbal remedies and other natural world sources of bioactives contain many unknown active constituents, some of which may be effective in filling gaps in the current therapeutic landscape: the new digoxin, aspirin, penicillin, vinca alkaloid, taxol …. Meantime the European Medicines Agency is leading the way in stressing the need to be rigorous in evaluating potentially toxic, contaminated or adulterated, yet widely used herbal products.

Threats and optimism

As a result of the banking crisis which unfolded in 2008, budgets for medicines and supporting diagnostics are under major threat. Reductions in central funding for universities mean that many sciences, including pharmacology, may be at risk of merger or closure, with echoes of concerns expressed in 1941 by Gunn about the future of pharmacology teaching and research [9]; restrictions on migration still act as a threat to international scientific recruitment, despite recent good news on this front. Major pharmaceutical companies are retrenching in the face of resulting economic pressures on their income, and because many major income-generating medicines are coming off patent. Neuroscience is one example of a major area of industry expertise that is being lost to the UK, and Pfizer's major research centre in Kent is being closed. This removes important national collaborators on pharmacology R & D, centres for training pharmacologists as undergraduate project placement students and as post-graduates working within R & D teams, and as major sources of pharmacology funding.

Despite these threats, there are several major sources of optimism. International genetic consortia are yielding new unexpected targets for study, and affordable pharmacogenetic biomarkers are emerging to allow new translational pharmacology research from lab to clinic. The Wellcome Trust and the Medical Research Council have recently invested in improving training for clinical pharmacology with support for a joint Liverpool-Manchester consortium and for an integrated virtual centre across Scotland. Finally national and international professional societies for pharmacology are well placed to play key roles in supporting pharmacology as a current and future strong discipline.

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Have we lost the plot in the UK Pharmaceutical Industry?

Tom Blackburn

Tom Blackburn,
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Some time ago, a senior UK pharmaceutical executive stated that "the pharmaceutical industry's future was to wait and cherry pick the best bits of biotech." Today, some would argue that Big Pharma is the new biotech and the two are indistinguishable. Whereas, some Big Biotech's are looking to pick off Big Pharma to sustain their rapid growth over the last decade.

Over the last twenty years, biotech companies set themselves apart with innovative drugs based on manipulations of DNA/RNA; many of these early innovators have since fallen by the wayside or became cannon fodder for Big Pharma. The more enlightened ones have moved on from platform technology and have become fully integrated pharmaceutical companies or virtual/ FIPNet (fully integrated pharmaceutical network) biotech/pharmaceutical companies driving drug development in all shapes and sizes.

Conversely Big Pharma companies are trading at the lowest price/earnings ratio of any major industry group: about 10 times projected 2011 earnings. Thus, it seems obvious to all that Big Pharma's drug development record in the past decade has been dreadful. In a report given at the BIO/CEO meeting in New York in February, data was presented that builds on the findings from existing studies and uses a broader, deeper, and larger sample than previous reviews of US clinical trials and approvals data. Using the BioMedTracker (BMT) proprietary database of 4,500 drugs and over 8,000 unique development paths from 2003-year end 2010, the study found that:

- Overall success rates from Phase I to FDA approval is nearly 9%. This number is comprised of lead and secondary indications. When separated, lead indications have close to a one in seven rate of approval and secondary indications have a rate of one in 30
- Clinical Trials that address secondary indications for drugs tend to be far less successful on average. This was seen in all phases of clinical development as well as in all disease areas
- Large molecule drugs are twice as successful in gaining approval than small molecule drugs

The fact that hundreds of billions of dollars have been spent on R&D over the last decade doesn't bode well for Big Pharma and one company in particular. Pfizer reportedly spent $78B with little to show for it. In that context it is sad, though not surprising, that Pfizer recently announced the closure of the Sandwich R&D site with the loss of 2,400 UK jobs. Pfizer are not alone in this restructuring maelstrom, it's estimated that around 500,000 jobs have been lost in the US over the last decade. The message is loud and clear: the industry is reeling on all sides from a litany of financial disasters; major drug failures in late stage (often in what were once thought to be less risky therapeutic areas such as biologics and oncology); unbelievable mismanagement; golden parachute payments; generic competition; process/bonus-driven madness; disruptive technology; patent cliffs, a shifting regulatory environment; trough feeding lawyers; and endemic fraud in all facets of the industry have led to the lack of trust and loyalty, and to the demise of the industry in general.

For further reading around this fascinating subject, several excellent reviews are listed below with web-links.

So what has happened to our industry and how can it be fixed, particularly the UK science/technology based industry where we have lost so much ground in recent years? Numerous government committees were formed to address these issues over the last two decades, sadly with little impact, as witnessed by the continued decline of the UK industry. The easy answer would be to form another government committee, consisting of notable knights of the industry and academia to report back on a cancer that is already malignant.

The most likely answer is, we need to go back to first principles and look at grass root science to reinvigorate our industry. We must take advantage of this moment by encouraging science and technology organizations like the British Pharmacological Society (BPS) to work in greater harmony with national and local government, industry, Universities, schools, patient groups, private investors, investment funds, life science real estate /REIT developers and CROs.

We must seize the opportunity for grass root growth of a viable UK pharma/biotech industry from the freshly painted and expansive remains of UK Big Pharma's facilities to grow and promote UK's leadership in pharmaceutical sciences.

So how do we go about this? Pharmacologists have always been adaptable, picking up other peoples ideas and applying them to their own discipline: "a jack of all trades", borrowing from physiology, biochemistry, pathology, microbiology and statistics, as first described by one of the eminent pharmacologist of our time, Sir John Gaddum.

Engineering has always been part of the pharmacologist's armory in the design, construction, and implementation of bioassays systems, and with my long-standing interest in this line of thought that I was intrigued by

the similarities of the two professions, and the challenges faced by each in the demise of UK science and technology. I was therefore inspired to read and adapt Sir James Dyson's recent report entitled, 'Ingenious Britain', as a template and discussion point for this article in Pharmacology Matters. In his excellent report, he identified five key areas to be addressed for UK Science and Technology to succeed.

Adapting, the Dyson template, I would argue that those working within the UK pharmaceutical / biotech / university / medical charity sectors, working alongside science / technology learned societies, would benefit from his words of wisdom and entrepreneurial insight as one of the UK leading exporters.

The five key areas are (adapted from "Ingenious Britain' and with my own personal thoughts on each area, many of which the BPS are actively pursuing - are as follows:

1. Cultural change to develop high esteem pharmacology/ pharmaceutical national projects and prizes and commitment to "grand projects" like Centers for Research into Personalized Medicine and Biomarkers, to demonstrate the Government's unequivocal ambitions for the nation. See Figure 1.

The Sandwich Pfizer site could/should become a world-renowned facility for such an undertaking together with government, private and specialized health care real estate/REIT consortiums. The UK equivalent of Singapore's R&D Biopolis. A government lead agency dedicated high-tech biomedical park, fostering world-class pharmaceutical sciences, along the same lines as the Alexandria Center for Life Science Park in New York, where Big Pharma, Mid-Cap, Biotech start-ups mingle with CRO's and VC/Investment funds all on one campus (http://www.alexandrianyc.com/).

The GSK Science Campus in Stevenage is certainly a step in the right direction (http://www.stevenage.gov.uk/business). Other, regional sites should also be considered like the Organon site in Newhouse, Scotland would have a site for national government consideration. However, the moment may have been lost with British obsession with auctions that have recently started at the Sandwich site where/ State of the art equipment being sold off at knock down prices, which the British tax payer has mostly likely already bought in beneficial tax credits over the many years the Sandwich site has been in existence. It's a national disgrace that this site may well be under the hammer…

2. Changes at University level to encourage more young people to choose science and engineering degrees related to their chosen discipline, like pharmaceutical sciences, where the cost of bursaries to students are shared by industry and government.

3. Greater freedom for universities in exploiting industry projects/ intellectual property/university collaboration, at all levels (schools, graduates, sandwich students, post docs, scholarships, MSc/PhD sponsorship, clinical trials and drug development).

In the 2010-2011 session report from the National Audit Office, "Educating the Next Generation of Scientists," (13). One of the most telling aspects of the report was the section on 'Image and interest,' where it reports; "that in recent years the UK has lost ground in areas such as enjoyment, interest, and motivation to pursue science and maths further." Thus, the UK's school report card should read - Holds promise but could do much better, if it's to maintain its position as a world innovator. Too much talking in class and fails to achieve its objectives.

4. Changes to improve financing for pharma/biotech start-ups, by increasing the generosity of the Enterprise Investment Scheme (EIS), relief for angel investors, private sector funding and life science real estate/REIT developers that support all aspects drug development and government guaranteed business loan scheme to encourage more leading from banks to innovate pharmaceutical/biotech businesses.

5. Changes to support hi-tech biotech and pharma companies by refocusing R&D tax credits on high tech companies, small entrepreneurial businesses and new start-ups, and delivering on ambitions to deliver 25% of procurement and research contracts through small and medium size UK based enterprises (SME's).

Although scientific opportunities for progress have never been better, a critically important question is who will develop the next generation of therapeutics? The burden on public funds is great, at a time of severe economic belt tightening. Should government agencies take up the gauntlet and become a drug discovery and development agency? The scale of the undertaking should not be underestimated, like most government contracts. Recent figures from the US are a useful benchmark to the extent of the challenge, for example, NIMH estimate that it costs $1.8B across 25 projects to launch a single new drug. The NIMH budget is less than $1.5B; NIMH will clearly not be able to replace industry in the development of new innovative drugs for mental illness. However, it's using its funds to set up workgroups and sponsorship of proof of concept clinical trials to advance desperately needed, truly transformative treatments. The UK government agencies and charitable trust are even more cash strapped, but are advancing along similar creative paths. Thus, the question

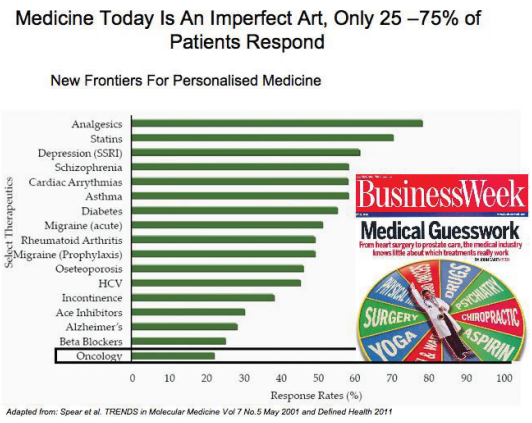

Figure 1 clearly shows the desperate need for better drugs base on personalized medicine and biomakers, as the present list of therapeutic areas is woefully in need of more efficacious drugs.

remains, how should (or if) government agencies fund drug discovery and development, and is the government motivated to take on this challenge? I have presented some personal thoughts and ideas from someone who has returned to these shores after nearly 13 years across the pond looking back at the decline of UK pharmaceutical R&D. I'm sure I may have missed out some of the UK innovative science and education projects and long term R&D strategies in this article and would welcome any additional thoughts and ideas to further promote this discussion. I would refer you to the BPS website to post your comments for the Industrial Pharmacology Community group to review and report back on behalf of the BPS.

As a final comment on the Dyson report (whether you like his vacuum cleaners or not!), it is noteworthy that overseas engineering students in the UK represent the vast percentage of UK graduates who will go back to their own country to apply their skills. Whilst, UK engineering/ Science students are disillusioned and disenfranchised by the burden of higher tuition fees and lost of motivation. Surely, the UK is undermining our national heritage in drug discovery and development - a treasure that is 'Ingenious Britain.'

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Science and Policy:

is the future online?

Imran Khan

Imran Khan, Director, Campaign for Science and Engineering (CaSE)

Imran Khan is Director of the Campaign for Science and Engineering (CaSE). After initial training as a biologist, Imran has worked in science communication and policy with a range of organizations, ranging from the World Health Organization to the BBC and the House of Commons.

CaSE is the UK's leading independent advocate for the science and engineering sectors, and focuses on arguing for more research funding, better science and maths education, a more innovative economy, and greater use of science and evidence by government.

The BPS is an organizational member of CaSE, and regularly collaborates on key science policy issues affecting the science community.

Science and engineering are crucial to the UK's future, so safeguarding that future means continuing to campaign for the health of our sector. But has the way in which we campaign for science in policy seen a fundamental change? The last year may be viewed as a landmark for political activism in the science community, when power and activism was effectively channelled through online avenues.

2010 had the potential to be a watershed for UK science and engineering. In the run up to the UK government's Comprehensive Spending Review in October, we heard that the science budget could see cuts of anything up to a third. Spending reductions on that scale could have been catastrophic for research and development in the pharma industry, and for the wider science community. Tomorrow's science historians might have judged 2010 to be the year when this nation took an irreversible fall from the top table of global research.

Instead, we won a reprieve. The national science budget was frozen in cash terms, which equates to roughly a 10% cut over four years, once inflation is taken into account. It's not ideal, but much better than had been feared.

Going online

Part of the reason that science fared relatively well, compared to other types of public spending, was the campaign mounted by the sector. As well as the highly visible actions of CaSE, there were others. In addition to directly lobbying politicians with our members and supporters, and seeding stories about science funding in the mainstream media, we also helped get the Science is Vital (SiV) movement, kick-started by UCL researcher Dr Jenny Rohn, off the ground.

Science is Vital brought over 100 scientists into Parliament to lobby their MPs, 2,000 protestors onto the streets outside HM Treasury, and 36,000 signatories, including the BPS and its members, to an online petition calling on the government to safeguard science spending. Much of the campaign was 'viral' – it relied on email cascades trying to reach scientists up and down the country, and blogs offering individual perspectives on the cuts and the importance of the campaign. Of course, having Professor Brian Cox spreading the word to his nearly 200,000 Twitter followers didn't hurt either.

The campaign would have been far harder to run twenty five years ago, when CaSE was initially founded. In 1986 it took months of phone-calls to organize a letter signed by 1,500 people to the Times, calling on the Government to 'Save British Science'.

Does this mean we should spend more time and energy focusing on the online element of campaigns, in future?

Such online activity will play an increasingly important part in election campaigns, and we saw that during CaSE's work on the 2010 General Election. Alongside our established political work – including briefings and letters to the leaders of the parties – we used online media to engage as many people as possible. We blogged on our own site and others - often the New Scientist, used Twitter to keep up interest and commentary, and even organized a webcast science policy debate.

There were 55,000 hits to our blog in April 2010, when the letters to CaSE from each of the main party leaders outlining their science and engineering policies were posted. The blog was well advertised and accessible which meant that prospective parliamentary candidates were happy to write for it. As a first foray into utilizing online tools to boost our reach it was pretty successful.

Traditional campaigns

Other recent campaigns have followed a more conventional curve. For instance, CaSE was one of the first organizations to raise concerns over the Government's proposals to cap non-EU economic migrants. The move could have inflicted enormous damage on our research base and international standing, but thanks to loud and vocal protests from the science community, we look set to escape its worst effects.

Key to this campaign was a succession of stories in the press highlighting just how absurd the restrictions were in practice, and the high-level lobbying of ministers – including David Cameron himself – by figures including University vice-chancellors and industry chiefs. The day after Cameron's first speech at Conservative Party conference as Prime Minister, his party woke up to

the front page of *The Times* carrying news of eight Nobel prize-winning scientists criticising his plans in a letter organized by CaSE.

While Twitter and blogs were utilized by the anti-migrant cap campaign, they played nowhere near the same role as they did in the fight against cuts. Yet, arguably, they were even more successful. We are still set for a research funding cut, whereas scientists and engineers look set to get unprecedented recognition in new immigration rules. So perhaps the success of Science is Vital was a one-off?

What have we learned?

As with all things, the answer lies somewhere between the two extremes. Even with the Science is Vital movement, the online aspect of the campaign formed a small part of the overall picture. As well as the tweets, blogs, and the petition, an enormous amount of work was done on the ground – from organizing the logistics of the Whitehall rally and lobby of Parliament, to fundraising and getting high-profile backers for the campaign.

In addition to Science is Vital, the summer and autumn of 2010 saw ordinary members of the public, researchers, businesspeople, journalists, learned societies such as the BPS, civil servants, and politicians all, in their own way, making the case for continued spending on research. CaSE and others continued with traditional lobbying and evidence-based advocacy to highlight the danger to politicians. We can't run the 'controlled experiment' to see what made the difference, but we do know that we barely left a stone unturned – and that was key.

The threatened demise of Britain as a scientific nation is something that caught people's imaginations. Issues like the migrant cap and specific instances of evidence-based policy-making might not inspire the public into action in quite the same way, but we need to make sure that the community understands that there are mechanisms for successfully influencing politicians, even when it seems like nobody else cares.

However, there will be issues where lots of people do care. The influence of Twitter and blogs for Science is Vital was crucial. It allowed us to rapidly mobilize an unprecedented number of people under one banner, and allowed those people to get their voice heard by government. We were told that getting scientists out of their labs and into the streets was impossible, and yet people came from all over the country, taking time off from work, to show their support. In the aftermath of the rally we heard that Danny Alexander, Chief Secretary to the Treasury, had asked the Science Minister whether it was he who had sent the protestors to George Osborne's department instead of Vince Cable's.

We can be sure of two things. First, with every passing month and year, the influence of online media will grow. Second, there will be lots of challenges for science over the next four years. It's crucial that we're alert to the power of online tools and mass movements, and are able to identify those issues and campaigns where they can add the most value. Ultimately, British science and engineering may depend on it.

www.sciencecampaign.org.uk

If you'd like to join CaSE as an individual member, please go to tinyurl.com/casejoin

The Future of Pharmacology and Therapeutics

Young Pharmacologists' Committee

The future of Pharmacology surely lies in the hands of our younger members. In recognition of this, more than five years ago, the BPS had the foresight to establish a younger members committee for our society. The BPS appears to have been ahead of the game as many scientific societies are also recognizing the need to encourage and empower their younger members. We asked our younger members committee to comment on the 'Future of Pharmacology and Therapeutics'. Their vision is enlightening and - fortunately for the future of pharmacology, hugely encouraging!

Since its advent in the early 20th Century, pharmacology, through its application in scientific research, the pharmaceutical industry, and clinical practice, has revolutionized therapeutic intervention in human disease. The science of pharmacology has a fascinating history, an abundance of great contributing minds, and is ever-evolving. In this article we will seek to consider the future of pharmacology in relation to advances in knowledge and education, and consider how the next generation of pharmacologists might face the inevitable challenges of modern medicine in modern times.

Traditionally, pharmacology has been driven by receptor theory, in more general terms a drug will not act unless it is bound. This concept will continue to be applied in future pharmacological practices, but as our understanding of the pathophysiology of human disease continually increases so does the complexity of the pharmacology. The more we discover the more questions that arise. New concepts in pharmacology are continually emerging, manifested by the development of new drugs, biomarkers and bioassay systems. Discoveries made by pharmacologists are being followed by the public and press more avidly than ever before. This shift in interest will require more media-savvy scientists to head public discussion and debates on the advances of modern medicine.

Modern day pharmacology encompasses and advances traditional small molecule drugs as well as the newer resource of biological therapies. In the case of small molecule agonists/antagonists, we used to think in simple terms: a molecule binds to a particular region within the binding pocket of a receptor to cause a response. However, we now know that molecules are able to interact with receptors in more complex ways, which will undoubtedly inform us in the future and allow for development of more specific drugs with fewer side effects. In the case of biological therapies, the scope for treatment of human disease is truly vast. We are now able to engineer antibodies, interfering RNA molecules, and host/donor stem cells to target specific pathways that were previously difficult to manipulate.

However, in some respects our ability to produce biologic drugs has run ahead of our ability to screen their efficacy and safety. This is illustrated by rare, but disastrous, examples of biological drugs inducing severe side effects in first in man studies, where no inflammatory signal was seen previously in traditional animal toxicology studies or in simple cell-based screens. The progress of biologics will increasingly rely on the development of pharmacological bioassay screens. The role that pharmacologists will need to play in assessing these new types of 'drugs', has never been more apparent. This exciting but challenging aspect of therapeutic advancement will be a key area for young pharmacologists to embrace.

Pharmacology is now, and always has been, a field that embraces new technology, relationships and collaborations. A good example of how this can be facilitated, at the level of education of young pharmacologists, is by the continuation of diverse and cross-cutting training programs where pharmacology can interface with other areas of science such as engineering, clinical medicine, chemistry, and drug development. It is also critical that academia and industry form close collaborations in pharmacology training with programmes such as CASE awards and other related collaborations.

The field of pharmacology continues to provide an enriching environment for scientists. Our focus in the future, as in the past, will be on the development of life-saving and life-improving agents and to utilize new technologies as they emerge. It is an exciting time to be a pharmacologist with advancements in cancer treatments, including drug breakthroughs for chronic myeloid leukaemia and breast cancer. Not to mention HAART (highly active anti retroviral treatment) which has turned HIV/AIDs from a death sentence into a chronic condition, clearly highlighting the benefits of successful research. Developments in the understanding and treatment of cardiovascular disease have also been driven by pharmacology, ranging from success in disease modelling to drug therapy and even tissue engineering. These successful advances would have been hard to imagine even as recently as the 1960s, our colleagues would be astounded at the jumps which have been made even in this time.

In developing new drugs and treatments, pharmacologists can impact local and global healthcare. Our end-point of research should not be forgotten amongst the politics, policies and need for profits that are an inevitable part of our social and work environment. Providing effective and affordable drug treatments for the world will be the legacy of today's pharmacologists and those who choose this career in the future.

Five Great Drugs of the Last Century: The contraceptive Pill

Robin Plevin

Robin Plevin
The University of Strathclyde

In this series Robin Plevin looks back on the development and significance of five of the 20th century's most important drugs.

Throughout early history women relied on rather rudimentary approaches to prevent conception- withdrawal, abstinence, prolonged breast feeding and abortion. None of these were very desirable or effective. By the late 19th century due to advances in rubber production, the use of rudimentary condoms and diaphragms had became more widespread, but availability was not universal, they were relatively costly and a preserve of the wealthy. Families were large, and populations were rapidly expanding. But in the 1950's a drug was developed that revolutionized contraception and the lives of women forever. That drug was the contraceptive pill.

Hormonal Problems

The idea of using a drug to prevent conception was not the preserve of the 20th century. Historical records suggest experimentation with various preparations took place in ancient times. But by the late 19th century, considerable scientific advances had been made in the understanding of that most mythical part of a woman's physiology - her reproductive cycle. Classical experiments identified the ovaries as the key organ for regulating the cycle and oestrogen and progesterone as the crucial hormones in controlling ovulation, oestrogen in the first part of the cycle, progesterone, derived from the *corpus luteum* in the second. This crucial knowledge allowed the Austrian physiologist, Ludwig Haberlandt to announce in 1921, what other physiologists already knew, that it would be possible to create a female contraceptive pill.

Generation of a pill - the forty year wait

Incredibly, The Pill was not marketed until 1960. Why such a long wait? Firstly, the chemistry to make The Pill, at least on an industrial scale, was not sufficiently developed and secondly, society in the early 20th century didn't want a contraceptive pill. In America, the Comstock laws banned contraceptive research in a large number of States. The Catholic Church, a profound influence on contraceptive habits in many countries, campaigned to prevent scientific progress in this area. Pharmaceutical companies showed little interest: social disapproval could destroy their reputations and sales. Scientists in the field had to be seen to be working on fertility problems or menstruation, not reproduction. Without government support, research was left in the hands of independent charitable research institutes, and finances were often scarce.

So how was this impasse broken? How did a contraceptive pill get developed and tested despite no funding from the pharmaceutical industry and harassment from government authorities? Well, it took a woman. Not a scientist, nor a doctor, but an American women's rights campaigner, Margaret Sanger. Sanger had fought tirelessly for the legalization of contraceptive access for over 30 years and believed a pill would cure the problems of overcrowding, overpopulation and poverty. In 1951, a chance meeting with Gregory Pincus, a leading but controversial reproductive physiologist, changed the course of contraceptive history. Despite his misgivings, Sanger persuaded Pincus to work towards the generation of a contraceptive pill and helped him secure a small grant from the Planned Parenthood Federation of America. When that ran out she engaged the help of millionaire Katherine Dexter McCormick. After a 15 minute meeting with Pincus, McCormick wrote a cheque for £40,000, the first of many. Pincus had hit the jackpot, McCormick eventually bank-rolled the project to the tune of £2 million (£15M in today's money) and it was she, the Bill Gates of her time, who financed the development of The Pill.

Margaret Sanger

Testing and trials

But what drugs could Pincus and his colleague, Dr Min Chueh Chang, test as oral contraceptives? Luckily by this time compounds were becoming available. Russell Marker had developed a new method to make industrial quantities of progesterone from Cabeza de negro, the wild Mexican Yam. It was the humble yam that enabled Marker, through his new pharmaceutical company Syntex, to advance the synthetic chemistry of progresterone.

On the 15 of October 1951, Carl Djerassi, together with an undergraduate student Luis Miramontes, finished the synthesis of a progesterone analogue, they called norethisterone. History does not suggest it to be the 'eureka' moment it should have been. It was, after all, the first ever compound synthesized suitable for use as an oral contraceptive. Six weeks later, Syntex submitted the first patent application for a contraceptive pill Ortho-Novum.

Pincus however, didn't use norethisterone for testing. By this time the pharmaceutical companies weren't running quite so scared and in 1952 at GD Searle a young chemist, Frank Colton, synthesised an analogue of norethisterone, norethynodrel. Pincus and Chang

used norethynodrel, due to its lack of androgen-like actions, not norethisterone, in subsequent testing and found it to be excellent at suppressing ovulation. They also discovered that it was more effective if it was contaminated with oestrogens. The cleaner the preparation the less reliable it was.

This ground breaking work using norethynodrel, patented as Enovid, required the ultimate confirmation in humans, a proper clinical trial. This was problematic, criminal prosecution awaited anyone promoting contraception. So Pincus and his collaborator Dr John Rock, a fertility specialist and ironically a devout catholic, went south. To Puerto Rico; poverty stricken, over populated and institutionally naive, with no laws prohibiting testing. Even better, it was the domain of an American, Dr Edris Rice-Wray, the director of the Puerto Rican Family Planning Association and a pioneer in birth control. It was she who organized the first human clinical trial for the contraceptive pill.

The trial was done against incredible odds, sampling and testing was conducted in the absence of proper laboratory facilities. There were problems with compliance, many women were innumerate and illiterate and found the instructions difficult to follow. There were objections from husbands, catholic priests, local press, and government officials. The initial concentration of Enovid (10 milligrams) was undoubtedly too high and led to nausea, dizziness, headaches, vomiting, and a dropout rate of nearly a fifth. But the results of this and other trials was universally impressive, Enovid was almost 100% effective.

In 1959, Enovid, in the form of 10mg Ethynodrel and 1.5% mestranol was submitted by GD Searle to the US Food and Drugs Administration for clinical approval as a contraceptive pill. It was based on a clinical trial designed by Gregory Pincus and funded by Catherine McCormick, testing 897 women, 132 of which had taken Enovid for over the year. But despite FDA approval the following year, it never made it to market as a contraceptive in this form. High dose Enovid had already been prescribed for menstrual problems since 1957. By 1960 however, everyone knew its real purpose and almost million women in the US were already using Enovid. In 1961, a low dose form of Enovid was marketed by GD Seale to physicians as a contraceptive for the first time and by 1965 there were almost a dozen variations of The Pill on the market in the USA and Britain, including Syntex's Ortho-Novum. By 1970 it was over thirty. Significantly, one of these pills was based on the compound norgestrel, chemically synthesised without the need of Russell Marker's Mexican Yams. Third generation synthetic progestogens are used primarily in oral contraceptives today.

Success and backlash

The uptake of the contraceptive pill was remarkable. Within five years of its launch over ten million women were users, principally in the US, Britain, Australia, and New Zealand. In some instances a third of married women of child bearing age were taking The Pill. Eventually after several years and several high profile court cases single women were also allowed The Pill and by the early 80's became its main users. For many women a new sense of autonomy was born. The dissociation between sex and pregnancy liberated the sex lives of many women. The Pill also opened up new possibilities for women in terms of family size, careers, and relationships. It was also good for the country's economics, as a new and enthusiastic work force was now available.

However it wasn't all sweetness and light, problems came from many directions. Increasingly it was being reported that women were developing blot clots. Other side effects - sickness, depression and sore breasts - could be dismissed as psycho-somatic. Thrombotic problems were harder to ignore. The women's liberation movement started to see The Pill as an issue about sexual control by men and the medicalisation of women. Even the Pope got involved, banning the use of The Pill in his decree encyclical Human Vitae. Mostly women just ignored him: "As my husband says. Pray to god and go to mass but keep taking the pills because if we have any more children the Pope isn't going to give us a hand to educate them"

The Pill Today

The Pill today comes in pop-out multi pack indicating daily usage, the first drug to be packaged and marketed in this way. There are also other types of Pill, an injectible form you can take for a three months period and 'the morning after pill', which primarily prevents egg implantation in the womb. The potential risks from long term use, particularly of thrombotic disorders, remain and to obtain The Pill in the UK a health check prior to prescription is required. There is a significant increased risk of deep vein thrombosis with 3rd generation progestogen pills. Cancer is also an issue, studies show that the contraceptive pill may increase the risk of both breast and cervical cancer but protect against ovarian and uterine cancer. Also the use of The Pill has changed. Whilst, initially for married women already with a child, to plan and limit family size, today The Pill is predominantly used by single women to prevent pregnancy or married women to delay the first pregnancy.

If Margaret Sanger was alive today she would have been disappointed, The Pill did not solve the problem of excessive population growth and poverty in the places that most needed it. In Third World countries problems of costs, religion and local customs have prevented its widespread use. The Republic of Ireland, a strongly catholic country, legalised The Pill only in 1979 whilst Japan outlawed it until as late as 1999. In other developed countries take-up of The Pill has declined as media fuelled health scares persist. The spread of sexually transmitted diseases, principally HIV/AIDS but also others such as chlamydia, have made the condom almost as popular as a contraceptive choice. Universal adoption of The Pill remains an unattainable goal.

Nevertheless, The Pill played a crucial role in gaining sexual freedom for women, and achieving financial and social independence from men. Many believe it was an important contributor to the struggle for equal rights for women. Unforeseen in its initial conception, design and purpose, The Pill has had significant social impact, and was one of the first, and possibly greatest, lifestyle drugs of the modern era. It may not have become the great panacea hoped for, but in the 50 years since its inception it still remains an important drug for women in the decision to control their own fertility. In the UK it remains the most frequently used form of contraception for women. Around 25% of women between the ages of 16-49 rely on The Pill as their primary method of contraception, some 3.5 million users. Today over 100 million women use the drug worldwide.

The contraceptive pill is without doubt one of the great drugs of the last century.

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PHARMACOLOGY MATTERS

Honey and Beeswax in Medicine and Pharmacology in Roman Egypt

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Introduction

The last two decades have witnessed something of a rediscovery of the pharmacological and medicinal properties of honey. [1] Different types of honey have been sourced from a variety of locations around the world and scientifically analysed in order to investigate their pharmacological potential, while a series of medical trials have utilized the antimicrobial, antibacterial, and antifungal properties of honey to treat medical conditions ranging from simple skin wounds to more complicated and even chronic infections.[2]

Prior to these developments, the cultivation of honey for the purpose of harnessing its pharmacological and medicinal properties already had an incredibly long history; honey actually appears as an ingredient in a prescription in the world's oldest medical text, a Sumerian tablet dating from the Third Dynasty of Ur, circa 2158-2008 BC.[3] In fact, honey was not alone in occupying a prominent place in prehistoric materia medica; beeswax and even bee-glue (propolis) were also exploited. Both honey and beeswax were commonly utilized in ancient Egyptian pharmacology, appearing frequently in the medical papyri dating from the Pharaonic period. The Ebers papyrus includes honey as an ingredient in 147 prescriptions intended for external application and 102 to be taken internally, while beeswax is included in 32 prescriptions, all for external use.[4]

The medical papyri dating from the Roman period provide the most extensive insight into the consistent use of honey and beeswax in medicine and pharmacology in the ancient world. An examination of the prescriptions recorded on papyrus containing honey and beeswax identifies strong parallels between how the inhabitants of Egypt during the Roman period used those items in medicine and pharmacology, and how modern medical trials are suggesting the same products can be effectively utilized in modern medical practice.

Honey and Beeswax as Materia Medica

During the imperial period, using honey and beeswax in *materia medica* was not only publicized but positively encouraged by a range of medical and pharmacological treatises; Dioscorides' *Materials of Medicine* (*circa* AD 65) and Pliny the Elder's *Natural History* (*circa* AD 77) frequently mentions honey and beeswax, while Galen's *On the Properties of Foodstuffs* includes a lengthy section on the healthy properties of honey when eaten as a foodstuff rather than taken as a medicine, information that was subsequently repeated by Oribasius in his *Medical Compilations* (circa AD 355). However, these works were not necessarily intended to be read and utilized by everyone; Dioscorides, for instance, was not very encouraging of those he considered φιλιατροῦσι, or 'amateur physicians', although Galen was slightly more open-minded with regard to his belief in the importance of διωρισμένη πεῖρα, 'qualified experience'.[5]

In comparison, the medical papyri recovered from Egypt provide more representative evidence for the practice of ancient pharmacology and medicine. The three hundred or so medical papyrus fragments, translated so far, not only provide us with extracts from medical writers such as Dioscorides and Galen, but also offer an insight into what both professional and amateur medical practitioners were actually doing on a daily basis. For example, in one letter sent during the summer of AD 58, Chairas wrote to his doctor friend Dionysius about his ulcerated feet:

You sent me two prescription copies, one of the Archagathian, the other one of the caustic plaster. The Archagathian is rightly compounded, but the caustic does not include the relative weight of resin. Please tell me of a strong caustic which can be safely used to cauterise the soles; for I am in urgent need. As to the dry plaster, you wrote there are two kinds. Send me the prescription for the resolvent kind; for the four drug plaster is also dry.[6]

The recipe for the Archagathian plaster, supposedly invented by Archagathus, the first professional physician to practise medicine in the city of Rome, survives in Celsus' *On Medicine*.[7] He writes that it contains 'boiled antimony sulphide and calcined copper, each 16 grams, boiled white-lead 32 grams, turpentine-resin 40 grams, litharge 24 grams'.[8] Although this particular plaster does not contain either honey or beeswax, it is the exception with regards to the *liparae*, or 'soothing', plaster recipes given by Celsus' *On Medicine*.[9] However, this papyrus provides evidence of two medicinal plasters being prescribed and utilized in Egypt during the first century AD, just as Roman medical treatises recommended. Therefore we can infer that the medical papyri that record recipes containing honey and beeswax, were being used in a similar manner.

Μελί: Honey

Honey was frequently used as a crucial ingredient in ancient prescriptions, both as a remedy in its own right, and as a means by which other remedies could be taken or applied with ease. One such recipe dating from the second century AD calls for μέλιτο[ς] καλλισ[του], 'the finest honey', to be

pounded and mixed with rose petals, burnt copper, red sumac and Cilician saffron in order to make a dry plaster for [π]άντα τὰ ἐν τῷ στομα[τι πάθη], 'all problems in the mouth'.[10] Since it specified the use of high quality honey and imported saffron, this was likely a very expensive remedy.

By comparison the remains of a pharmacological manual also dating from the second century AD, contain fragments of a whole series of recipes for plasters of varying levels of complexity and cost. The first recipe is very simple, indicating that a sweet raisin should be pounded and applied with honey.[11] The sweet raisin was often praised for its medicinal applications in antiquity, particularly its cleansing properties, which were specifically noted by Galen in *On the Properties of Foodstuffs:*

In sweet raisins there is always astringency, as also a moderate cleansing capacity; so that as a consequence of both properties they dull minor irritations at the mouth of the stomach…since it is obvious that more severe irritation demands more intense remedies.[12]

The third surviving recipe is for ὄρχεων πόνον κα[ὶ] φλεγμονάς, 'pain and inflammation of the testicles'; it contains rue leaves and bay leaves that are ground up with honey.[13] Both rue and bay leaves were considered beneficial for inflammations in antiquity, as well as being readily available through either private cultivation or purchase.[14] The seventh surviving recipe is intended as a decongestant, ὀρθόπν[ο]ιαν αὐθημερεὶ στῦσαι, 'to stop difficult breathing immediately'; it contains nose-smart, seed of henbane and white pepper pounded up and shaped into an Egyptian bean with honey or castor oil, to be taken with honey and wine.[15] Henbane was used as an analgesic and pepper for chest complaints, while castor oil was believed to increase the efficacy of plasters.[16]

Ὀξυμελίκρατον: Honey mixed with Vinegar

Dioscorides included a recipe for ὀξυμελίκρατον, 'oxymel', in his On *Medical Materials*.[17] Pliny the Elder also included one in his *Natural History*:

Vinegar has even been mixed with honey; nothing, in fact, has been left untried by man. To this mixture the name of oxymel has been given; it is compounded of ten pounds of honey, five semi-sextarii of old vinegar, one pound of sea-salt, and five sextarii of rain-water. This is boiled gently till the mixture has bubbled in the pot some ten times, after which it is drawn off, and kept till it is old.[18]

A recipe for a purgative dating from either the second or third century AD contains a blended mixture of salt, honey, vinegar and water, to be drunk on an empty stomach.[19] Both salt and vinegar were commonly used in purgatives, while honey was believed to act as a diuretic.[20]

Μελίκρατον: Honey mixed with Water

A list of medical prescriptions from Oxyrhynchus and dating to the first century AD contains three recipes for draughts to be prepared for and taken by patients with ἡπατικός, 'liver complaints'.[21] The first recipe contains a mixture of sweet flag, opopanax, spikenard and parsnip and the instruction 'drink slowly with sweet wine or honey'.[22] The second recipe is very similar; it also contains a mixture of sweet flag, opopanax, spikenard and parsnip, albeit with different quantities specified, and the instruction 'drink with sweet wine and honey mixed with pine cones'.[23] In both of these recipes, honey is evidently being used as a means of ingesting the medicine prescribed, the sweetness and sticky consistency of honey utilized to make the medicine more palatable, either alone or in conjunction with sweetened wine.

The third recipe is more complicated and is classed as ἐνεργὲς ἱκανῶς, 'sufficiently strong'; it recommends mixing large quantities of cinnamon, myrrh, spikenard and Ethiopian seseli with egg and centaury juice, then taking a dose ἡλίκον Αἰ[γύπ(τιον)] κυάμου, 'the size of an Egyptian bean', with μελικρ[ά]τωι θερμῶι, a 'warmed mixture of honey and water'.[24] Μελίκρατον, a mixture of honey and water, was a common means of taking honey medicinally; in an extract from a codex containing a treatise on surgery which dates to the third century AD, μελικρατον is included in a list of remedies a physician should have on hand when treating a patient about to undergo surgery.[25]

Κῆρος: Beeswax

The first century AD writer Columella devoted the whole of the ninth book of his treatise On Agriculture to apiculture, and included an entire section on beeswax advising that 'wax, though of little monetary value, must not be overlooked, since its use is necessary for many purposes'.[26] Like honey, beeswax was a crucial ingredient in ancient plasters and poultices. The *Michigan Medical Codex*, thought to date to the fourth century AD, is devoted to such recipes and beeswax appears as an ingredient in a number of them. The first surviving recipe is for the Πάρυγρον, 'Parygron', plaster, which contains pig fat, white beeswax, white lead and litharge.[27] The Parygron plaster was evidently a well-known and extremely popular plaster; it is promoted in treatises by medical writers such as Hippocrates, Galen, Aetius and Paul of Aegina.

Another recipe included is for the Ἀζανίτης, 'Azanites', plaster.[28] It comes highly recommended for 'malignant sores', particularly those that result from infected surgical incisions and contains pitch, wax, oesypum, pig fat and bull pat, and pine resin. It also instructs that more should be used to treat ulcers, less to encourage cicatrisation. Like the Parygron plaster, the Azanites plaster is promoted by medical writers; Galen himself stated that it 'has many uses and is highly esteemed'.[29]

Conclusion

The medical papyri that survive from Roman Egypt contain a range of recipes that include honey and beeswax. There is certainly a degree of correlation between the medical conditions that these remedies are intended to treat and more recent uses. Honey in particular, has been used by pharmacologists and physicians undertaking medical trials.

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Education Update

Figure 1: The away team triumph at skittles.

We have been very busy with education activities since the last edition of Pharmacology Matters.

Diploma in Advanced Pharmacology

Congratulations to our Diploma students who graduated at the Winter Meeting: David Winpenny and Felicity Gavins. We are currently implementing the outcomes of the recent Diploma Review and we will keep you informed of changes as they progress.

Workshops

Two workshops were run in conjunction with the Winter Meeting:

- General and Advanced Receptor Theory
- Pharmacology of Stem Cell Research and Regenerative Medicine

Our Hypertension workshop, held at the Royal Infirmary of Edinburgh convinced a range of delegates to join their colleagues north of the border. The southerners showed they were made of tough stuff by beating the home team at skittles in Scotland's oldest pub, The Sheep's Heid, the evening before the workshop. (See figure 1.)

We have a full programme of workshops planned for 2011:

- Personalized Medicines (Warwick, 24-25 March 2011, New workshop format)
- Integrative Pharmacology (Bristol, 4 April 2011)
- General and Advanced Receptor Theory (21-22 July 2011)
- Enzymes as Drug Targets (London, date TBC)
- Safety Pharmacology in Drug Development (University of Surrey, date TBC)

Please check out the Education section of the website (www.bps.ac.uk/education) for further details and to register your interest.

Careers

We have travelled across the country to careers fairs, talking to students about pursuing a career in pharmacology and what the BPS can offer them. Along with our sister societies* we organized two *Life Sciences Careers Conferences* for bioscience undergraduates and postgraduates. Held at King's College London (24 November 2010) and Aston University (2 March 2011), these conferences showcased the wide range of careers open to bioscience graduates - from academic research to science communication, working in industry to science policy. Look out for next year's events on our website!

Promoting Women's Careers

The Women in Pharmacology committee has been busy over the last few months. Professor Sue Brain received the AstraZeneca Women in Pharmacology Prize at the Winter Meeting. She gave an inspiring talk on her career in academia which was encouraging to the many young scientists in the audience. The BPS mentoring scheme attracted more applicants than ever from academia, industry, healthcare and beyond. On 8 March, the Women in Pharmacology committee, working with the UKRC, ran a *Leadership Skills for Women* at Angel Gate, which was oversubscribed. This provided women in leadership positions, and those aspiring to them, with a forum for the discussion of leadership issues, networking with peers and practical experience of developing leadership skills and leadership language. Later on this year there will be a seminar on *Work-Life Balance*. Keep an eye on our website and eBulletin for further details.

Higher Education

We are working with the Society of Biology on their plans to accredit bioscience degrees, particularly with respect to their *'in vivo'* science degree pilot programmes. Please see the Society of Biology's website or contact Annie Geraghty (arg@bps.ac.uk) if you are interested in finding out more about this.

* The Biochemical Society, the Physiological Society, the Society for Endocrinology, the Society for Experimental Biology and the Society of Biology.

Book review:

Aspirin – a drug that still changes the world

Book Review: Acetylsalicylic acid by Karsten Schrör, Wiley VCH (2009), 390 pages, ISBN-10: 3527321098, ISBN-13: 978-3527321094

Aspirin – a drug that still changes the world
By Christoph Thiemermann

Over the years, a number of books have been written about *'remedies that changed the world'* in order to honour the progress made by pharmacologists and physicians in the treatment of a number of diseases. One of the oldest and still most important of such remedies is aspirin (or acetylsalicylic acid) and, hence, the excellent monograph recently published by Professor Karsten Schroer is long overdue.

Hippocrates (*ca.* 460 BC – *ca.* 370 BC) first recommended the use of willow bark and the leaves of the willow tree and while the Reverend Edward Stone recommended the use of extracts of willow bark for the treatment of *'aigues and intermittent disorders'* in the late 18th century, it was not until the late 1820 that salicilin was identified as the active, anti-pyretic ingredient of willow bark. Acetyl salicylic acid was first synthesised by Felix Hoffmann in 1897 while working at Bayer laboratories in Elberfeld in Germany under the direction of Dr Arthur Eichengrün.

I must confess that I have written this review less as an expert on aspirin, but as a grateful student of both the author and the late Sir John Vane, both of whom were mentors and had tremendous influence on my scientific endeavours. When I began reading this book, I was under the impression that I knew about the history and pharmacology of aspirin and its clinical use. I must admit that even after the first 50 pages I had to realize that the author, like Sir John, has probably forgotten more about the pharmacology of aspirin than I ever knew.

The content of this very comprehensive monograph ranges from the history of the discovery of the antipyretic effects of extracts of willow bark, to the early synthesis of acetyl salicylic acid, the discovery of the mechanism of action (by Sir John and his colleagues), then elaborates on both pharmacology and toxicology of this blockbuster drug, and finally provides an extensive review of all possible clinical applications of this amazing therapeutic and its ever changing use. Professor Schrör provides us with a delightful insight into the early history of the discovery of aspirin which includes a review of plants as natural sources of salicylates, copies of laboratory records of Dr Felix Hoffmann from 1897, copies of early patents protecting the chemistry of aspirin, and insights into decisions reached by Bayer AG when deciding to develop acetylsalicylic acid as a drug.

As the first review of the pharmacology of aspirin was published in 1899 by Dr Dreser, it is surprising to realize that an entire monograph on this amazing drug is not only warranted, but also needed today. This work-of-love recently published by Professor Schrör is a must-read for every pharmacologist or physician who wishes to further their understanding of the pharmacology of aspirin and the treatment of inflammation, thrombosis, and secondary prevention of cardiovascular disease.

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