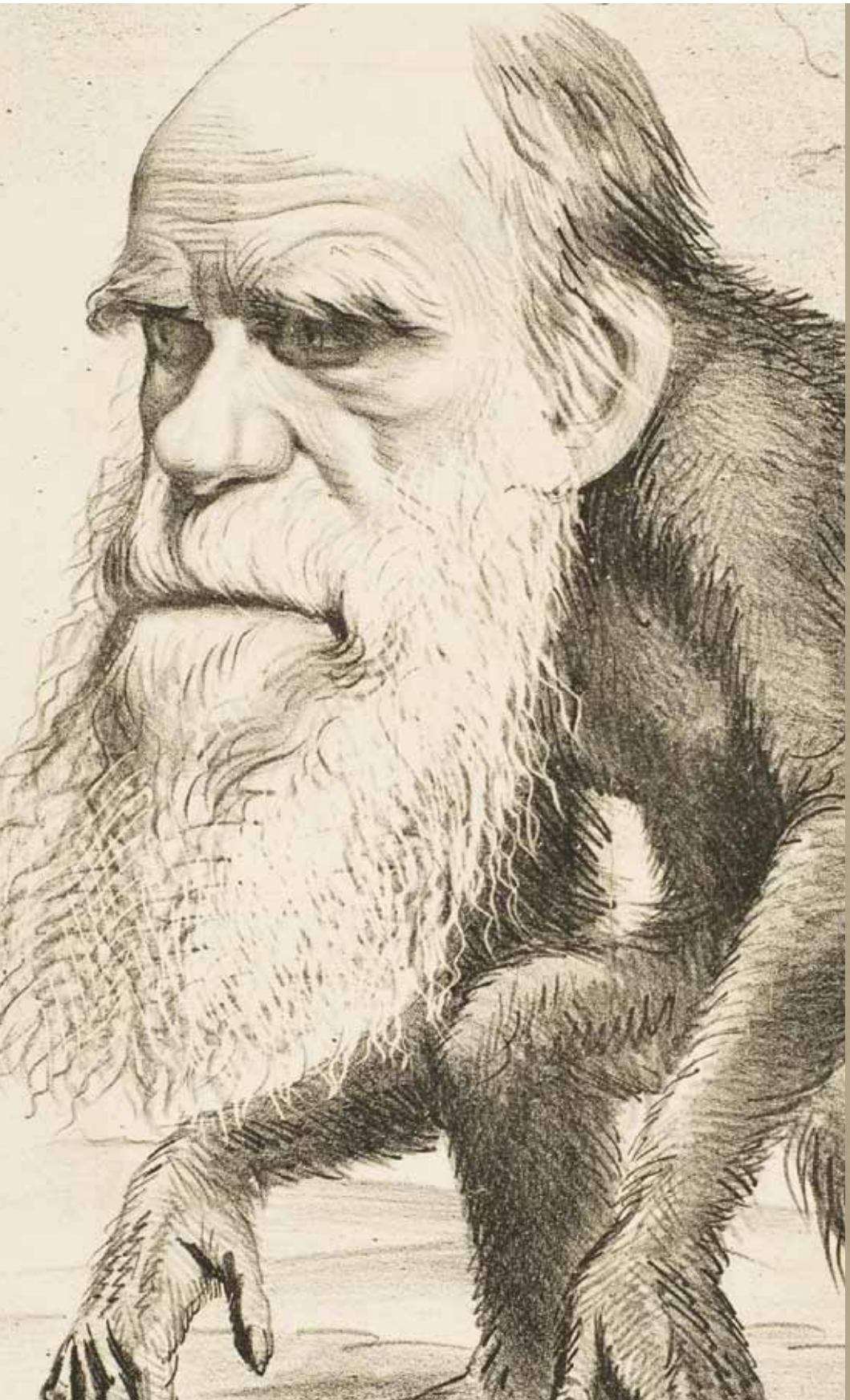
Pharmacology Matters

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

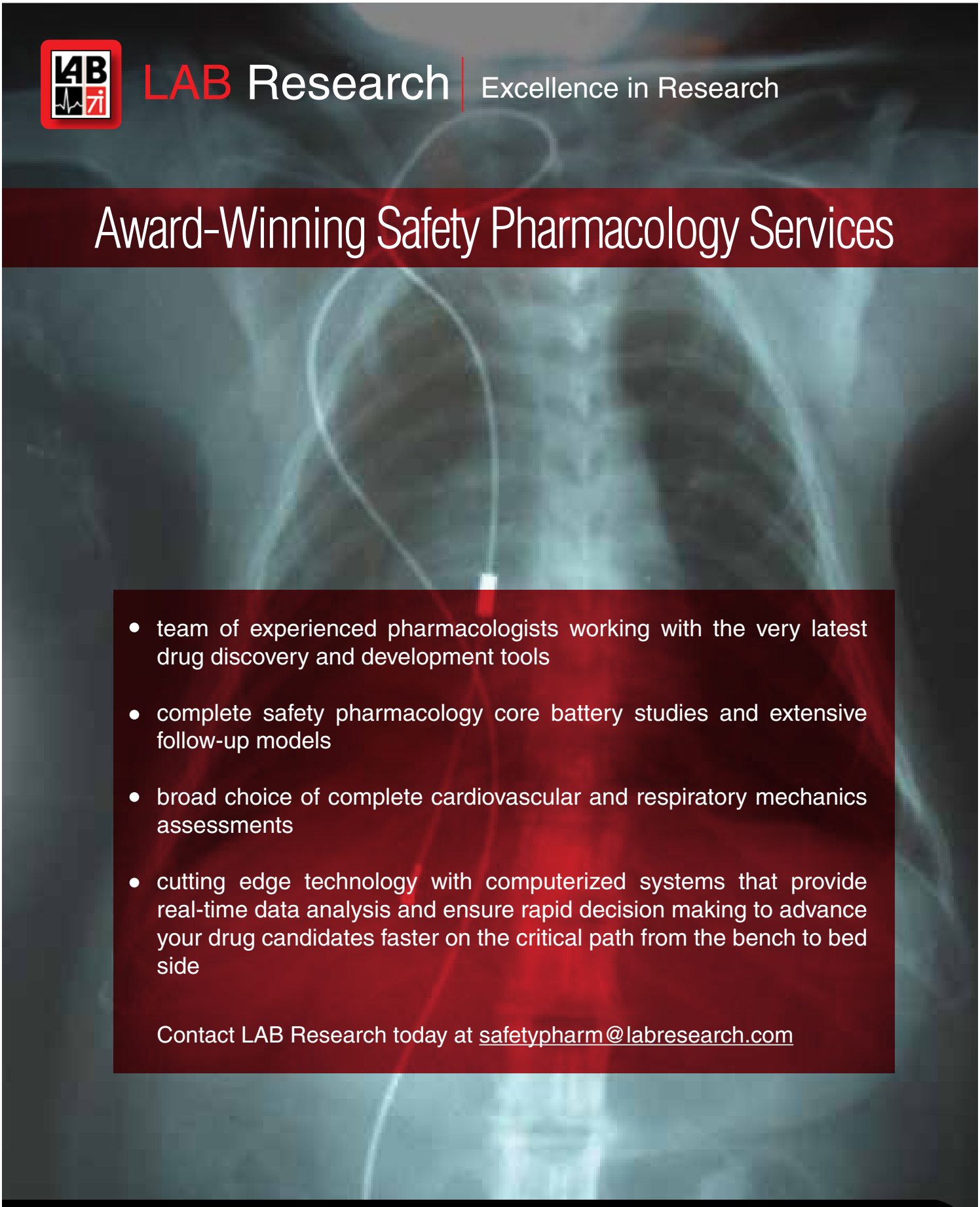
ISSN No: 1757-8175

The Newsletter of the British Pharmacological Society
Volume 2 Issue 3, December 2009



Celebrating Charles Darwin

In this Issue:



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busdevna@labresearch.com

LAB Research Denmark

Hestehavevej 36A, Ejby,
DK-4623 Lille Skensved
Denmark
T: +45 56 86 15 00
F: +45 56 82 12 02
Info@labresearch.dk

LAB Research Hungary

Szabadságpuszta
Veszprém, H-8200
Hungary
T: +36 88 545 200
F: +36 88 545 301
busdev@labresearch.hu

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

Front cover Image:
A venerable orang-outang.
Originally published in the Hornet, a satirical magazine, 22 March 1871.

Charles Robert Darwin FRS was born on 12 February 1809 and died on 19 April 1882. This issue celebrates the 200 years that have passed since Darwin's birth and acknowledges his legacy to pharmacological research.

Charles Darwin was an English naturalist who realized and presented compelling evidence that all species of life have evolved over time from common ancestors through a process he called natural selection. The relevance of his work to genetics was only fully realized after the rediscovery, in 1900, of Gregor Mendel's paper *Versuche Über Pflanzen-Hybriden*.

The understanding of genetics has influenced pharmacology profoundly. This issue contains an array of articles covering the discovery of DNA's structure, see the Rosalind Franklin article on page 9; the Human genome project and the emerging field of genomics on page 10 and 11; the promise of personalised medicines, on page 13; and the embracing of genetic techniques by pharmacologists in their everyday research and thinking, covered in the workshop report, and Sara Rankin's profile, both on page 17.

The BPS president, Jeff Aronson, has, rather prolifically, authored three articles for this issue. The triptych includes his presidential valedictory 'A Great Instauration' which can be found on page 4. 'CPT or Huliatrics?' and 'A Model for Academic Clinicians' complete the set and can be found on pages 22 and 24 respectively

Finally, I would like to take this opportunity to thank Cherry Wainwright, whose term as Pharmacology Matters Executive Commitee representative will come to an end at the end of this year. Cherry presided magnificently over this publication's transition from pA_2 to Pharmacology Matters, and her experience and advice during that process proved invaluable. Thank you Cherry.

Hazel O'Mullan
Managing Editor

Contents:

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A Great Instauration

Jeff Aronson, President, BPS

Is clinical pharmacology fit enough to survive? In his Presidential valedictory article Jeff Aronson explains why he thinks it is.

In a letter to his unhelpful uncle, Lord Burghley, in 1592 Francis Bacon outlined a plan. He wanted to bring about a reorganization of learning, which had languished during the Middle Ages and beyond, despite Roger Bacon's recognition of the importance of experimental science, mathematics, and language in his *Opus Maius* of 1267. The latter-day Bacon constructed his plan as a programme that he called *Instauratio Magna*, a Great Instauration, which was the title he gave to a preliminary description of it, published in 1620 and dedicated to King James. Bacon's 'grand edifice' was in seven parts:

1. Introductory principles
2. Classification of sciences
3. Scientific methods
4. Experimentation
5. Historical survey of scientific developments
6. Foresight of scientific developments
7. Practical applications to ensure the betterment of mankind

The time was ripe for change. The words 'pathology' and 'physiology' had just entered the English language, and 'therapeutics' and 'pharmacology' were soon to do so [1]. The book with which Bacon began his never-to-be-completed campaign was called *The Advancement of Learning* (1605), a preliminary version of a longer Latin text *De Augmentis Scientiarum* (1623), in which he described the decline of scientific method, reviewing the weaknesses of academics and universities, a current lack of scientific collaboration, and the neglect of science by governments. This book was an introduction to Bacon's major work, the *Novum Organum* (1620), in which he reaffirmed the importance of experimentation and outlined the inductive method of reasoning. *The New Atlantis* (1627) was a utopian fable, in which Bacon imagined a paternalistic government, supporting science through the establishment of a Royal College of Research, and predicted numerous inventions and techniques, such as aircraft and submarines, telephony and refrigeration. It was while undertaking experiments in the last of these that he died from an affection acquired while stuffing a fowl with snow.

Through this fragmentary body of work, Bacon earned the title 'high priest of modern science'. His plan was a grandiose one, intended to culminate in a kind of earthly paradise through the instauration, or restoration, of scientific learning and method. Although some of the above account has strong contemporary resonances, it would be excessive to claim that the Society's aim of restoring clinical pharmacology as a scientific and practical discipline is as exalted as Bacon's was, but it is true nevertheless that we are currently experiencing an exciting period of instauration or, as others have called it, renaissance.

Manpower problems

There is a long prehistory to clinical pharmacology, from the *Materia Medica* of Dioscorides through to the invention of the terms 'human pharmacology' and 'clinical pharmacology' in the first half of the 20th century, but it can reasonably be said that the subject came of age in 1960, when Dilling's *Clinical Pharmacology* and Laurence's textbook of the same name were both published. After a period of quiet growth in the 1960s, two reports, one from the Royal College of Physicians of London (1969) and one from the World Health Organization (1970), highlighted the need for more practitioners [2], and between 1970 and 1990 the number of consultant clinical pharmacologists in the UK increased to about 70. However, following the first research assessment exercise to cover the entire higher education sector (1992), and in my view related at least in part to that event, the number started to fall. I shall not detail here all the reasons for this decline, but we know, based on a thorough search of the manpower figures by Simon Maxwell and David Webb [3] that by the year 2003 the number had fallen to just over 50, or less than one per million of the UK population. My own count of the current manpower, based on those whom I know personally or have knowledge of through other sources, is similar. For comparison, Croatia, which some of us visited two years ago by courtesy of the British Council, has about 30 clinical pharmacologists for a population of only 4.5 million, one per 150,000.

Promoting clinical pharmacology

Our Great Instauration began when four of us—Graeme Henderson, my predecessor as President of the Society, Mike Rawlins, David Webb, and I—persuaded Fiona Fox at the Science Media Centre in the Royal Institution to hold a press briefing that she called a 'drugs bust'. We told the assembled science correspondents that the lack of teaching of medical students in the science and practices of therapeutics was endangering patient care, some of the resulting headlines were lurid. The Editor of the *Student BMJ* asked us to write an editorial on the subject, and the text that we submitted, based on an earlier editorial [4], was picked up by the *BMJ* and published there instead [5]. Later, in my FitzPatrick Lecture to the Fellows of the Royal College of Physicians in 2007, I reiterated our concerns [6].

The correspondence columns in response to the BMJ editorial resounded with support, but the then Chairman of the Teaching Committee of the General Medical Council, Peter Rubin, himself a Professor of Therapeutics and today Chairman of the GMC, wrote to chide us for making rash statements in the absence of evidence [7]. We protested that we had evidence and had referred to it in our editorial, but suggested that it would be more productive to conduct the debate outside the correspondence columns of the Journal [8]. We proposed a meeting of various interested parties, and that was arranged in January 2007. Even though we were convinced of the justice of our case, we were surprised at the amount of support that we received at that meeting from

medical students, junior doctors, nurses, pharmacists, and others.

At this point the GMC and the Medical Schools Council set up a working party, at which the problems of teaching practical therapeutics to medical students were discussed, Simon Maxwell being our main spokesman. This led to a report [9], in which it was recommended, among other things, that there should be a statement of the required competencies of all Foundation doctors in relation to prescribing in the draft version of *Tomorrow's Doctors*, the GMC's blueprint for training medical students [10]. That draft version went out for consultation. David Webb then gave evidence to the House of Commons Health Committee in January 2009, after which he and I gave a further press briefing at the Science Media Centre. Our views were later supported by the Health Committee, in their report 'Patient Safety' (3 July 2009), in which they noted that 'there are serious deficiencies in the undergraduate medical curriculum, *Tomorrow's Doctors*, which are detrimental to patient safety, in respect of training in clinical pharmacology and therapeutics' and recommended that '[this] must be addressed in the next edition of *Tomorrow's Doctors*' [11]. At about the same time, support also came from NHS managers, through a questionnaire study carried out by the organization 'Skills for Health', in which they highlighted their concerns about prescribing and the need for more undergraduate teaching in both the basic sciences of pharmacology and clinical pharmacology and the practicalities of prescribing [12]. The final version of *Tomorrow's Doctors* contained the original text about prescribing, exactly as it had been drafted by the working party [13]. This document will come into force at the start of the academic year 2011-12, and it will be up to medical schools to see to it that the appropriate teaching is available to ensure that its requirements are fulfilled. We shall continue to suggest that that will best be done by appointing clinical pharmacologists [14].

There is clear evidence of dissatisfaction among current medical students about their preparedness to prescribe and of the need for more teaching of practical therapeutics based on scientific principles; it is the quantity of teaching about which the students are concerned, not the quality, which they report to be high [15]. Evidence of students' worries originally came from studies carried out by members of the British Pharmacological Society in 2006–7 [16,17,18,19], and was therefore open to the criticism of vested interests. However, a subsequent independent study, funded by the GMC, confirmed that medical students feel prepared for all the duties that they will be expected to carry out as newly qualified doctors—except prescribing [20].

As part of our efforts to improve undergraduate education, the Society, led by Simon Maxwell, has gone into partnership with the Department of Health to create an e-prescribing website [21]. This will be launched in 2010 and made freely available to all UK medical schools.

The charge of special pleading has long bothered us. If experts cannot point to a problem that needs rectifying without being accused of trying to feather their own nests in the process, change cannot come about in important areas that need expert attention. However, when those outside the field become concerned as well, there is an opportunity for change. And that is what has been happening in the past year.

In 2008 the Royal College of Physicians (RCP) established a working party, under the chairmanship of the Editor of *The Lancet*, Richard Horton, 'to review the current and future conditions for, and barriers to, a dynamic, productive and sustainable relationship between the NHS, academic medicine and the pharmaceutical industry' [22]. Clinical pharmacology was not represented on the working party, but the Society submitted evidence, and the final recommendation of the report (published in February 2009) was that 'The RCP should create a Pharmaceutical Forum —Ways to trigger a renaissance of clinical pharmacology should be a priority issue for this Forum' [23]. A forum (now called the Medicines Forum) has since been established and has reaffirmed that priority; I am currently chairing a working party of the Forum, looking into ways of furthering this aim.

Other positive developments have occurred at an even higher level. Following a meeting between the government and representatives of pharmaceutical companies, a new Government Office for Life Sciences (OLS) was established in 2009 under the leadership of Lord Drayson, Minister for Science and Innovation at the Department for Innovation, Skill & Universities [24]. The scope of the OLS was widened from pharma to include biotech companies and those producing medical devices and diagnostics, with the aim of implementing a strategic plan of action to ensure that the UK fully realizes its position of leadership in this area during the current economic downturn. The Society was invited by the ABPI to discuss how the development of clinical pharmacology could be enhanced under this initiative, and Martin Wilkins and I contributed. The Life Sciences Blueprint that was subsequently published in July 2009 [25] stated that 'The Government will, in partnership with the HE sector and industry, establish an industry and HE forum… [whose] first two tasks…will be to assess the curriculum for clinical pharmacology in medical and pharmacy degrees and higher medical training, and evaluate the impact of the significant public and industry funding in addressing the *in vivo* sciences (pharmacology, pathology, toxicology and physiology) skills gaps'. The Blueprint also recognized that 'The provision of high quality-care requires clinicians to be familiar with the relevant practices in clinical pharmacology and pathology. This is important to enable them to evaluate and prescribe innovative medicines.'

The Forum mentioned in the Blueprint has been established and has set up a working party, the 'Task and Finish Group', under the chairmanship of John Posner. Membership includes several members of the BPS—Jeff Aronson (Oxford), Simon Constable (Icon Development Solutions), David Cox (Department of Health), Steve Jackson (KCL), Simon Maxwell (Edinburgh), Fraz Mir (Cambridge), John Posner (John Posner Consulting), Duncan Richards (GSK), Phil Routledge (Cardiff), and Martin Wilkins (Imperial)—as well as representatives from drug companies, the Wellcome Trust, the Medical Research Council (MRC), and the Medical Schools Council.

Following the publication of the Life Sciences Blueprint, highlighting the critical skills gap, the MRC announced £3.7M funding for two new Clinical Pharmacology and Pathology Fellowship Programmes [26]. It is likely that these programmes will fund the training of 10-12 new clinical pharmacologists over the next six years.

Another welcome (pun intended) research initiative arose from a meeting that members of the Society (Jeff Aronson, Alasdair Breckenridge, Colin Dollery, David Webb, and Martin Wilkins) had in September 2007 at the Wellcome Trust with Sir Mark Walport, Director of the Trust, Dame Sally Davies from the Department of Health, and the Chief Medical Officer, following which the Trust established four major programmes in translational medicine and therapeutics [27], all led by clinical pharmacologists, all with industrial collaborators. Stimulated by this, I have chosen as the title of my opening lecture to be given at WorldPharma2010 in Copenhagen 'Found in Translation' [28].

The time lines of all these positive developments are shown in Figures 1 and 2. Figure 1 shows the events during 2006–8 and Figure 2 the events during 2009. I had originally intended to include this information in a single figure, but the pace of activity during 2009 made it necessary to construct a separate figure. The colour key in these figures gives extra

insight into the nature of these events, black indicates publications by members of the Society and light blue our press briefings at the Science Media Centre; green shows meetings with other bodies, orange, reports by other bodies, and red, funding streams. The period 2006–8 is dominated by black, green and orange are less prominent. However, during 2009 the green and orange events started to become more frequent, showing the concern that those outside the Society have started to show. I am confident that more red will start to appear as we go into 2010 and beyond.

Other Society activities

Throughout the last four years, the BPS has been highly active in bringing to public attention its concerns about deficiencies in undergraduate training and the relative lack of expertise in pharmacology and clinical pharmacology. One initiative that we undertook in 2007 was the appointment of a Prescribing Initiative Fellow, Sarah Ross from Aberdeen. She has already produced two major systematic reviews on the teaching of practical prescribing [29] and medication errors made by junior doctors [30]; both were published in the special June 2009 issue of the *British Journal of Clinical Pharmacology* on medication errors [31]. Sarah is currently working, among other things, on revising the undergraduate curriculum. Our postgraduate training programme is also currently under review through discussions with the Postgraduate Medical Education and Training Board (PMETB), whose merger with the GMC is planned for next year. Peter Jackson and latterly James McLay have been leading for us, and a new training programme has been developed. Dual accreditation in CPT and General (Internal) Medicine will continue to be available, but dual accreditation in CPT with other specialties will be more difficult to achieve, because of PMETB's new rules, although still possible.

The Society also collaborated in 2007–8 with Tilli Tansey and her colleagues in the Wellcome Trust in holding two Wellcome Witness Seminars, at which the future of clinical pharmacology was discussed by a large number of clinical pharmacologists and others, in the light of the history of the subject, as viewed by its exponents [32].

Other activities that we have undertaken include the further development of the BPS Prescribing Group for allied health professionals, under the chairmanship of Simon Maxwell, SpR training days at the Winter meeting, organized by Albert Ferro and then David Williams, support for regional clinical pharmacology group meetings (e.g. the Clinical Pharmacology Colloquium), the development of an efficient response mechanism to national consultations, interactions with the Science Media Centre, and podcasts related to Society lectures (see the BPS website) under the direction of Donald Singer.

We have also held successful meetings, including a joint RCP/BPS meeting on 'Rational Prescribing', held in the RCP on 7 May 2008, organized by Robin Ferner and Albert Ferro; BPS sponsored sessions at the Cheltenham Science Festival: 'NHS Funding—NICE or Nasty?' (Mike Rawlins, 4 June 2008) and 'The Science of Curry' (Clive Page and colleagues, 3 June 2009); a BPS sponsored symposium 'Clinical Pharmacology: Working With Patients', which Simon Maxwell and David Williams organized at the meeting of the European Association for Clinical Pharmacology and Therapeutics, which was in turn orchestrated by Simon Maxwell, David Webb, and their colleagues in Edinburgh in July 2009, affording a superb showcase for UK clinical pharmacology; a hypertension symposium at the same meeting; and a joint BPS/RPSGB symposium on diabetes mellitus during the British Pharmaceutical Conference on 9 September 2009. The last was part of our continuing programme in developing relationships with other learned societies, such as the British Toxicology Society and the Faculty of Pharmaceutical Medicine of the Royal College of Physicians, of which I am delighted to be an Honorary Fellow. We have plans for further joint meetings of this sort.

Future challenges

Several challenges remain, among which the most important will be to persuade Universities and NHS Trusts, perhaps including Primary Care Trusts (PCTs see pages 20-22), to establish new posts in clinical pharmacology. Although the number of consultant clinical pharmacologists in the UK has gone down since 1993, the appetite for training in clinical pharmacology has not diminished, according to my analysis of the 191 medical practitioners who are currently registered with the GMC as specialists in Clinical Pharmacology and Therapeutics. Furthermore, the BPS Diploma in Advanced Pharmacology [33] has attracted considerable interest from clinicians, particularly for workshops such as Pharmacokinetics and Early Phase Trials of New Drugs. Our problem is not lack of interest in the subject among trainees; it is a lack of jobs for them when they have qualified. We shall continue to put the case for creating new posts and shall seek to forge links with other clinical medical specialities and primary health care, to ensure that when earmarked clinical pharmacology posts do not exist, those with training in CP&T can find jobs in other specialties, of which cardiology and geriatrics are currently the most popular among our trainees, so that clinical pharmacology expertise can be further spread through the medical community. Creating portfolio jobs may be a way of doing this. Discussions with other learned societies will be important: 'Every physician should also be a clinical pharmacologist' [34].

Envoi

It has been an enormous honour for me to have been President-elect and then President of the British Pharmacological Society, one that I appreciate greatly. As the first clinically active President it was my stated aim from the first to try to kick-start a great instauration of clinical pharmacology. I did not think that so much would actually transpire in four years (Figures 1 and 2). That it has is a tribute to all those in the Society who have worked hard to make things happen,

including several others besides those mentioned above and in the reference list. Kate Baillie, Kevin Kearns, and their staff at Angel Gate have all unstintingly supported these endeavours, and I am sure that without an efficient, full-time, professional secretariat fewer of these developments would have taken place.

The British Pharmacological Society aims, among other things, to be the leading society for the presentation, promotion, and discussion of all matters relating to both pharmacology and clinical pharmacology & therapeutics, and to provide advice on standards of teaching and practice to policy makers. We have striven to fulfil these aims during the last 4 years, and I am confident that under the leadership of Ray Hill the pace of change will be maintained. I look forward to witnessing it from the sidelines.

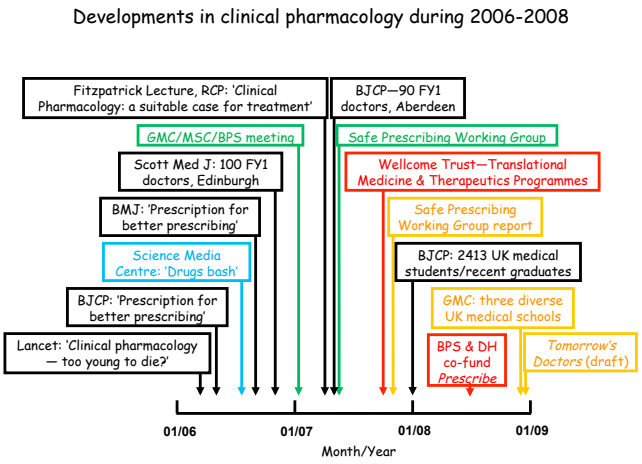

Figure 1. Developments during 2006–8; the colour code is explained in the text.

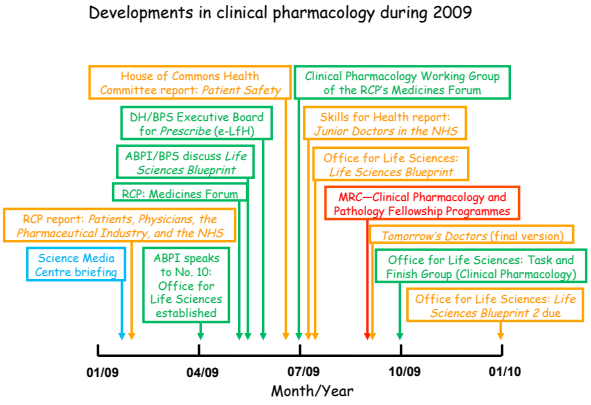

Figure 2. Developments during 2009; the colour code is explained in the text.

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View From Angel Gate

Kate Baillie
Chief Executive,
BPS

The view from Angel Gate has changed considerably in the last few months. First, we have almost completed the restructuring of the BPS secretariat and are delighted to welcome two new senior managers, Jonathan Bruun, Head of Communications and Development, and Vicky Adrienne, Head of Education and Meetings, who started work with the Society in late August/early September.

In addition, we have recruited Amalie Brown as Education and Meetings Co-ordinator. Amalie will take over from Claire Emson, our interim manager, in mid-October, and on behalf of the Society I would like to thank Claire for her assistance in ensuring that the Summer Meeting, James Black conference, Education workshops, and advance preparation for the Winter Meeting have all gone smoothly.

Claire's efforts in delivering the meetings programme have been supplemented by support from other members of the BPS team, who have, while waiting for the appointment of new permanent staff, put in considerable extra effort in this interim period. I would also like to extend my thanks to them for pulling together so well in what has been a period of considerable change and uncertainty.

New staff have also now been appointed at Wiley-Blackwell, to run the Editorial Offices for both BJP and BJCP – Katie Gibb, Managing Editor, is based at the Oxford office and Suzanne McNeill, Editorial Assistant, in Edinburgh.

Over the past few months they have worked closely with former BJP office staff, Hazel O'Mullan, now BPS Publications Manager, and Paul Tizard, Membership and Office Administrator, to ensure as smooth a transition to the new working arrangements as possible.

In addition, the Society's offices have undergone a major refurbishment over the Summer. To engender a team spirit, we have moved to an open plan office layout, arranged over two rather than four floors, and have mixed the teams to encourage greater interactions between different functions; thus far, this new arrangement has worked very well.

We are also now fortunate to have a ground floor meeting room, which can accommodate up to 22 people boardroom style and 35 theatre style. For smaller meetings, the room can be divided into a room for 7 and another for 16 — this will enable the majority of Society committee meetings to be held at Angel Gate and should also encourage greater interaction between staff and BPS members.

We shall be happy to offer these facilities to members who may wish to hold meetings at the BPS headquarters. Further details of the booking process and hire charges (when applicable) will shortly be available via the BPS website.

We have also introduced a "hot-desking" facility, to enable members and officers to work at the Society's offices when they are in London; we hope that members will find access to these facilities a useful additional benefit.

Other recent developments in the future of clinical pharmacology are highlighted in the President's article in Pharmacology Matters, 'A Great Instauration'.

With these changes to the office staffing and facilities, we are now better positioned to face the considerable and exciting challenges facing pharmacology and clinical pharmacology, and look forward to reporting back on progress in the months to come.

Kate Baillie MA MBA, Chief Executive BPS

Prizes and Awards 2010

BPS A J Clark Studentship
Deadline for applications 11 December 2009

Schachter Awards
Deadlines for applications 30 January and 30 June

J R Vane Medal
Deadline for nominations 31 March 2010
Designated area for the 2010 award will be
Molecular, cellular and signalling pharmacology

Gaddum Memorial Award
Deadline 31st March 2010

The Novartis Prize
Deadline 31st March 2010

Aptuit Prize
Deadline 31st March 2010

Bill Bowman Travelling Lecturership
Deadline 31st March 2010

BPS Teaching Prize: "The Rang Prize"
Deadline 31st March 2010

(Part of the ASIF Initiative) Anniversary Strategic Initiatives Fund (ASIF) Awards:
1. Vacation Studentships
2. Post-doctoral Support
3. Research Collaboration Initiating Grants
Deadline 31st March 2010

GlaxoSmithKline Prize for Research in Clinical Pharmacology (Clinical Section)
Deadline for nominations 30 June 2010

Clinical Pharmacology Section Prizes for Medical Students
Deadline for nominations 23 July 2010

Rosalind Franklin: Historical Perspectives

The 'Women in Pharmacology' committee was established in 2005 by the British Pharmacological Society to promote the development of women's careers in pharmacology. In the mid 1820's while Charles Darwin was briefly a medical student in Edinburgh, he would have received teaching in 'Materia Medica' and may have been introduced to the Edinburgh Pharmacopoeia, which subsequently became the British National Formulary. However, he is unlikely to have had any female colleagues. At that time the establishment of pharmacology as a discipline was still some time away, and any concern with the careers of women in science non-existent. It was a further 70 years or so before women were even formally allowed entry to the Edinburgh Medical School.

Today many young women study science and medicine. To encourage them to pursue careers in science we aim to motivate them with successful role models, contemporary and historical. There are few from the 19th century, but by the early-mid 20th century women were beginning to have an impact in science. Among these, Rosalind Franklin, whose pioneering use of x-ray crystallography captured the first images of DNA, must surely be one of the most inspiring [1].

Her discoveries laid the foundations for description of the DNA double helix by Watson and Crick [2] (Watson and Crick, 1953). They are key to modern molecular genetics that has brought Darwin's observations in the 'Origin of Species' up-to-date by identifying the mutations in DNA that allow one species to change into another, and indeed to pharmacogenetics that offers the tantalising possibility of personalised medicine. In his writings Charles Darwin gave fair credit to his competitors and it is unfortunate that Franklin has become as well known for her lack of recognition in the award of the Nobel prize to her male competitors, Watson, Crick and Wilkins, (The Nobel Prize in Physiology or Medicine, for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material, 1962), as for her scientific contribution. In today's more enlightened age we strive to ensure that women do receive the credit they deserve and use it to build successful careers.

Rosalind Franklin's own scientific career began in 1938 when she went to Newnham College, Cambridge. On completing her studies in 1941 she was awarded only a titular degree, as women were not entitled to degrees (BA Cantab.) from Cambridge at that time. She went on to receive her PhD from Cambridge in 1945.

Gillian Gray, Edinburgh University, Women in Pharmacology sub-committee

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[1] Maddox B (2002). 'The Dark lady of DNA'. Harper Collins

[2] Watson JD, Crick FH (April 1953). "Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid". Nature 171 (4356): 737-738

A short biography of Rosalind's life and work follows, reproduced with permission from Wellcome Trust.

Rosalind Franklin at work in a laboratory © Henry Grant Archive/Museum of London.

Rosalind Elsie Franklin (1920-1958) was born on 25 July 1920 in London and was educated at St Paul's Girls' School before attending the University of Cambridge in 1938. At the age of 22, she gave up her fellowship to take her first position as a physical chemist at the British Coal Utilization Research Association in London.

In 1947, Franklin went to Paris to work under Jacques Méring, learning X-ray crystallographic methods, and to continue research into carbon. In 1951, she moved to King's College, London, to work on DNA by making very thin threads of it, bundling them and hitting them with a super-fine X-ray beam. She soon discovered the two forms of DNA. The easily photographed A form was dried, while the B form was wet. While much harder to photograph, her pictures of the B form showed a helix. Since the water would be attracted to the phosphates in the backbone, and the DNA was easily hydrated and dehydrated, she guessed that the backbone of the DNA was on the outside and the bases were therefore on the inside. This was a major step forward in the search for the structure of DNA.

In November 1951, Franklin presented her A and B form data to an audience that included James Watson, who was working in Cambridge with Francis Crick on the X-ray crystallography of protein. On hearing her lecture, the two men built their first model of DNA: a triple helix with the bases on the outside. However, in May 1952, Franklin got her first good photograph of the B form of DNA, showing a double helix. This was another major breakthrough. Franklin then continued working on the A form as it provided more data.

In early 1953, Watson and Crick saw some draft work by the American Linus Pauling and were given access to Franklin's data and B form photographs that showed DNA to be a multiple helix. From his work on proteins, Crick realized that her data implied an antiparallel double helix. Franklin had reached this conclusion with regards to the A form, but had yet to apply this theory to the other form.

Franklin moved to Birkbeck College, London, where she continued some work on DNA and was given charge of a virus research group. Between 1953 and 1958 she published 17 papers on viruses, laying the foundations of structural virology and establishing the relationship between ribonucleic acid (RNA) and protein (the virus coat protein) for the first time.

Diagnosed with ovarian cancer in 1956, in her last years she continued research on a polio virus, but died on 16 April 1958, aged 37, within minutes of her last paper being read at the Faraday Society.

The following three articles by BPS members: Stephen Haydock, Munir Pirmohamed & Richard FitzGerald, and Donald Singer, set the background to and provide views on the implementation and impact of advances in genetics to pharmacology. Stephen Haydock introduces genomics, Munir Pirmohamed and Richard FitzGerald discuss pharmacology in the post genomic era and Donald Singer discusses Personalised Medicines.

Introducing Genomics and its Offspring

Dr. SF Haydock
MA MB B Chir PhD
FRCPS

Dr Haydock is a consultant physician at Addenbrooke's Hospital, Cambridge. He obtained his PhD from the Department of Biochemistry at Cambridge in 1991 for characterisation of the biosynthesis of the lactone core of the antibiotic erythromycin. He was formerly Fellow and Director of Studies in Biochemistry at St. Catharine's College, Cambridge His research interests are in the use of DNA sequencing technology to characterise the metabolic pathways to natural products of biological interest, with a view to genetically manipulating the clusters to obtain novel analogues.

The term 'genome' is believed to have been first used by Winkler circa 1920 as a conjunction between *gene* and *chromosome*. The term 'genomics' was itself first coined by the mouse geneticist Tom Roderick to describe the study of DNA at the level of the chromosome, entire genomes or large clusters of genes. The term sought to distinguish newer forms of genetic study that were distinct from the traditional approaches that focused on the study of a single gene, families of structurally related genes, or DNA sequences. The definition of genomics remains imprecise but is generally considered to be concerned with the analysis of the complete genome sequences of organisms. It uses rapid advances in DNA sequencing technology to determine the entire DNA sequence of the specified organism. This information is used to identify the coding regions and associated regulatory elements. The protein sequences are predicted from the identified genes from the DNA sequence. The likely function of gene products is assigned and protein structures predicted by comparison with sequenced genes encoding for proteins of known function, and or structure. It is characterised by the creation and use of large databases, intensive computer analysis and extensive laboratory automation. Such an approach requires a 'capital intensive' process compared to that of the traditional pre-genomics approach. This field of study has attracted funding from government through conventional means together with the major pharmaceutical companies and growing biotechnology sector.

A key endeavour has been the sequencing and analysis of the entire human genome. The Human Genome Project (HGP) is the largest international collaboration ever undertaken in the field of biological science. It was anticipated that the completed genome would go a long way to explaining the human phenotype in health and disease. In effect, it would be a blue-print for making a human being. Many scientists in many countries have collaborated, culminating in the publication of the working draft genome sequence in 2001 (**1,2**) and the 'gold standard' human genome in 2004 (**3**). The human genome is encoded by 2.85 billion bases and encodes 20-25,000 genes. This came as something of a surprise to the scientific community as this was many fewer than originally predicted (Human Genome Sciences alone took out patents on 100,000 gene fragments during the race to 'patent the genome'). It was clear then that things were going to be a lot more complicated than we had expected. The HGP is regarded by many as a huge technical and scientific achievement and constitutes a scientific milestone on man's quest to understand the world around him. In that context it is biology's 'man on the moon'. However, given the general lack of understanding of, and consequent apathy towards science, the man in the street wants to see tangible outcomes from the huge number of tax payers pounds, euros and dollars that have been spent. He or she has been rewarded by numerous newspaper headlines announcing 'breakthrough' upon 'breakthrough' that will revolutionise the medicine of the future ('future' being the key word).

We can attempt to summarise the medical and pharmaceutical expectations of the genomics era into several key areas. Analysis of the human genome will provide important insights into genes that contribute significantly to common human diseases. It will thus identify novel drug targets that can form the basis of drug development programmes. Individual human genomes can be analysed to optimise drug therapy for that individual, including identifying the most efficacious agent for a disease area, taking into account genetically determined variability in drug metabolism. Important insights will be gained into the genetic mutations that confer malignancy on cell lines resulting in the development of haematological malignancies and solid tumours; this will again open the way to new drug targets and "treatments for cancer". Furthermore, comparison of the human genome with that of other closely and distantly related species will explain man's uniqueness and shed light on his evolution.

Whilst there have clearly been many exciting discoveries, much of the promised benefit still lies in the years to come. What of the 'breakthroughs' in understanding the genetic basis of common human diseases? The well accepted approach to such analysis has been genome wide association

studies (GWAS). These analyses attempt to identify common mutations that contribute small but significantly increased risk in the development of a common disease. Many loci have been identified for numerous common diseases and have provided very important insights into the pathogenesis of some conditions, key successes being in the fields of age related macular degeneration (**4**) and Crohn's disease (**5**). However, the magnitude of risk for individual loci remains in most cases very small and the combined risk for all identified loci constitutes only a small percentage of the overall risk. Such loci have not in general provided a fruitful area for drug development. In order to increase sensitivity, workers have proposed larger and larger studies with ever increasing cost to identify further loci with smaller risk contributions. What some see as the lack of success of GWAS has led to the increasing view that a lot of the missing genetic risk is to be found in rare mutations that confer a very high risk. GWAS identifies risk genes at around 10% frequency in the disease population. Rare alleles that carry a very high risk may occur at less than 1% in the disease population. These genes are found in the population at very low levels as the higher disease burden they confer means that Darwinian natural selection operates strongly against them. It is hoped that such genes can be identified by the "1000 Genomes Project". This programme intends to identify rare high risk genes for common diseases by sequencing the genomes of 1000 anonymous participants.

The cost of sequencing has fallen such that the sequencing of an individual patient genome is feasible, but we do not understand enough to make such an approach useful. This has not stopped companies from coming forward to offer such a service at a price.

We have learned much about the mutational development of malignancy but again one must sound a cautious note. A comparison of malignant cells with non-malignant cells from the same host suggests that malignant cells acquire mutations that make further mutations more likely. For instance, comparison of the genome of a chronic myeloid leukaemia cell with that of a skin cell from the same individual shows 63,277 mutations. The question as to which are important, however, remains unanswered.

So if the promise still lies in the future, how do we get there? If the complexity of species is not written in the DNA then we need to look further. DNA makes RNA makes protein. The complexity of the human species in health and disease comes from the complex regulation of expression of individual genes that may themselves be variably spliced. Thus people have studied the *transcriptome*: microarray techniques have been developed to analyse the entire mRNA profile of a cell. But since the products (i.e the proteins) themselves are of primary interest, research has moved in to the realm of *proteomics*. So although the human genome project may well identify a gene, how much protein is produced, how it is post-translationally modified, how the gene is spliced, and what the quaternary structure of the multiprotein assembly is, are complexities which the discipline of proteomics helps us to understand. This still leaves the need to comprehend how these components interact with each other. *Metabolomics* has evolved to study how proteins interact to constitute metabolic pathways of primary and secondary metabolism. But we need to understand how such pathways themselves interact. Hence, *systems biology* seeks to study this interaction of components of a complex biological system to explain how it gives rise to identified functions and behaviours of the system in question.

So, in a way we have come full circle: the reductionist approach of breaking the human organism down into a series of genes encoding for a specific healthy or diseased gene has progressed through studies of the transcriptome to the proteome and the metabolome until we have arrived at 'systems biology'. Eventually the aim would be to attempt to explain the organism in terms of subtle and complex interactions between all its component parts. If nothing else, then one of the important lessons we have learned is that it is a lot more complicated than scientists expected and drug companies hoped. The original promises of genomics still lie tantalisingly in the future. In between now and then lies time, further scientific discoveries and developments, and a large amount of grant money!

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Pharmacology in the Post Genomic Era

Munir Pirmohamed is NHS Chair of Pharmacogenetics at the University of Liverpool and Consultant Physician at the Royal Liverpool University Hospital. He is NIHR Senior Investigator, Director of the Wolfson Centre for Personalised Medicine and Deputy Director of the MRC Centre for Drug Safety Science. Richard FitzGerald is a Specialist Registrar at the University of Liverpool.

Introduction

The completion of the human genome project was without doubt one of the greatest achievements of science. However, it was accompanied by a lot of hype about how we would be able to cure diseases and treat patients in a more personalised way within 5 years. Not surprisingly, progress has been slower than expected, and this has led to a degree of pessimism. So as we progress through the post-genomic era, what can we expect?

Genetics in pharmacology

2009 is the bicentenary of Darwin's birth. His theories still retain credence in modern genetics, and can for example, explain why the smallest units of genetic variation, single nucleotide polymorphisms (SNP), vary with geographic location and time. For example, recent positive selection, a marker of positive selection occurring in distinct geographical locations after migration from Africa, has been demonstrated in a number of genes that are important in pharmacology, such as the ATP binding cassette (ABC) drug transporter genes [1]. Darwin's work laid the framework for future work that was carried out by Mendel and Garrod, and together this led to the development of the field known as pharmacogenetics (named by the German pharmacologist Vogel in 1957), and the introduction of the term pharmacogenomics in 1997. These terms refer to the study of how genetic variation, in single or in a small number of genes, or at whole genome level, and either at the level of DNA or RNA (or both), impact upon drug response.

The question that needs to be asked now is whether our increasing knowledge of the human genome, of the function of its genes their interactions and how the function of the genes is regulated at RNA, DNA and protein levels, will impact on pharmacology, with respect to drug development and the use of existing drugs.

Pharmacogenetics/omics

Following the completion of the human genome project, this area has received a large amount of attention, and has been deemed to be amongst the first that will affect patient care. Indeed, this is gradually being seen in many areas. Without doubt, the discovery that *HLA-B*5701* predisposes to hypersensitivity reactions with the antiretroviral abacavir, and its subsequent implementation into clinical practice, which has had the positive outcome of reducing the incidence of hypersensitivity in a cost-effective manner, represents the prime example of translational research [2,3]. Pharmacogenomic approaches have been particularly successful with respect to serious adverse reactions, further aided by the use of genome-wide association scans (GWAS), which allow an unbiased assessment of predisposing loci throughout the human genome. Unlike complex diseases, where thousands of patients have been required to identify and validate genetic factors (with low effect sizes), much smaller numbers have been successful with serious adverse drug reactions, as seen with the association between flucloxacillin cholestasis and *HLA-B*5701*, demonstrated with only 51 cases [4]. Stratification of new therapies in cancer is also becoming commonplace – for example, the response to EGFR inhibitors such as panitumumab seems to be better in patients with the wild-type form of KRAS [5]. The recent examples of how genetic polymorphisms in the P450 isoforms can determine response to clopidogrel (CYP2C19) and tamoxifen (CYP2D6) again remind us how drug disposition, as determined by metabolism, is an important determinant of response to therapeutic agents [6,7].

The drive towards stratified medicines

Although the above examples represent success stories, the majority of drugs that we use in clinical practice today show variability in response, although despite this we still continue to prescribe them on the basis of "one dose fits all". This is because we have not yet identified genetic determinants that can be implemented in clinical practice, or because variability depends on other factors. To this end, much more work needs to be done on the epigenome, on microRNAs, and on the proteome and metabolome, as well as on identifying rare genetic variants (less than 1% minor allele frequency); the latter is likely to be more accessible as we approach the era of the $1000 human genome. With increasing knowledge of the genome, proteome and metabolome, we need to start developing better methodologies that capture all the sources of variation. Ultimately, 'systems biology' approaches that integrate information from the various technological platforms will be needed to identify pathways that are perturbed in disease, that are activated when a drug is given or when a drug causes an adverse effect. This will not only help in identifying determinants of drug response, and the development of (in many cases multi-marker) diagnostic technologies, but it will also help identify novel therapeutic targets and develop new applications for existing drug targets. Indeed, such approaches are becoming commonplace in Industry for identifying new targets and developing new therapeutic agents. We can only hope that this will reverse the decline in the registration of new compounds, which has caused a great deal of concern to all those involved in modern pharmacology.

The future

It is now 150 years since Darwin published the "Origin of Species". This laid the framework for modern biology, and in the postgenomic era it will have an increasing influence on modern pharmacology [8]. As with any new "technology", unrealistic expectations are often placed on the rapidity with which it will lead to benefits. This was certainly true of the human genome project. We are now beginning to understand better the complexity of the human genome, and with the development of new technologies and methodologies are likely to reap benefits from this. Pharmacologists will be key players in identifying new drug targets, developing new chemical and biological entities, and defining the mechanisms by which these work in the human body. The clinical pharmacologist will be essential in driving the development of these medicines for patient benefit, and for implementation into modern health care. There are obviously many challenges that need to be overcome, but the opportunities far outweigh the challenges. The discipline of pharmacology needs to seize these opportunities.

Richard J FitzGerald, Munir Pirmohamed, Wolfson Centre for Personalised Medicine, Department of Pharmacology, The University of Liverpool, Liverpool, L69 3GE

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Professor Donald Singer, University of Warwick

The idea of personalised medicines is not new. Over 3 millennia ago, if you were to interview a passing physician in Babylon, he would have been able to discuss rational approaches to a selection of treatments applied using bandages, creams and pills. His diagnostic handbook offered a range of potentially effective treatments, including plant sources rich in salicylates, oestrogens and anti-bacterials [Biggs, 2005]. His focus on personalised medicines would have been kept sharp by the Hammurabi legal code [Figure], with penalties ranging from a fine to loss of limb or worse, for inappropriate choice and cost of treatment for his patients. Indeed traditional medical values have always concerned dealing with patients as people rather than generic sufferers from a particular disorder.

There are several facets to personalising medicines. Many of these general principles would have been familiar to the ancient Greek, Egyptian and Babylonian healers. On the specific issue of therapeutics, taking a personal approach to the patient includes having regard to concerns in relation to becoming a patient through starting treatment. Active discussion of treatment options, relative benefits and possible risks is vital to encourage treatment adherence. It is recognised currently that adherence to treatment for chronic disorders such as high blood pressure and rheumatic diseases is likely to fall to around 50% within 12 months of prescription of a treatment that a physician may expect the patient to take for up to several decades. This element of personalising medicines is at risk at present from pressures to take an "ology" rather than holistic approach to a disorder, shorter consultation times, the move to one-stop clinics and the decreasing likelihood that a given patient will be seen consistently by the same physician.

Prologue to the Hammurabi Code created in Babylonia ~1790 BC. It included description of the serious penalties faced by physicians who overlooked the importance of personalising medicines [Louvre, Paris].

A further element of importance for personalising medicines arises from increasing recognition that inter-individual differences in genetic and lifestyle factors play a major role in influencing the likelihood of response to a given treatment as well as the risk of developing serious adverse reactions to that treatment. Prescribing becomes increasingly complicated in patients who may need multiple treatments for different disorders, some of which may include failure of effective function of vital drug-metabolising organs, such as the liver and kidneys.

Charles Darwin, as a pioneer of evolutionary biology, would have recognised the vital significance of his concept of natural selection [Darwin, 1859] for the development of diversity as a variable biological template among individuals. Darwin would also have understood the importance of effects of natural selection on challenges to effective management of infectious diseases and cancer, because of acquired resistance in response to selection pressure rising from anti-microbial or anti-cancer chemotherapy. Careful selection of antibiotic treatment, if necessary in combination, is vital to minimise the chance of drug resistance developing as a consequence of natural selection, as survivor rapidly dividing organisms are selected for their resistance to treatment. This also underpins the current approach to use of medicines for treating cancers. Cocktails of anti-cancer treatments in combination maximise the chance of tumour regression and minimise the risk of tumour relapse through resistance.

Haldane speculated that genetic diversity may have contributed to protection from 'pestilences' [Haldane, 1949]. Proof of this concept has emerged from insight into reduced susceptibility to HIV infection from chemokine receptor variants – also a stimulus to development of new therapeutics [Corbeau et al, 2009]. Pharmacogenetics offers the opportunity to protect patients by assessing important differences amongst patients in activity of key enzymes and pathways important for drug action and metabolism [Ingelman-Sundberg, 2001]. Around 2/3 of adverse drug reactions have been reported to be associated with genetic variation in liver enzyme activity either due to single nucleotide polymorphisms or due to major differences in copy number of the relevant genes. Pharmaceutical drug development now includes major efforts to avoid molecules likely to be susceptible to genetic variability in their handling.

It remains to be seen how helpful genetic profiling will be in clinical practice for personalising selection of medicines outside key very high-risk areas. This issue describes some encouraging recent examples [Pirmohamed and FitzGerald, 2009]. Already, however, surrogates for genetic and phenotypic profiling are well established for some common diseases, most obviously in the BHS NICE algorithm for selection of blood pressure-lowering treatment. The low-renin genotype of black African origin patients and the low-renin phenotype of older patients are recognized to be indications to favour diuretics or calcium channel blockers as first-line treatment in these patients [NICE/BHS, 2006].

Donald RJ Singer, Professor of Clinical Pharmacology and Therapeutics. Clinical Sciences Research Institute, University Hospital Campus, Warwick Medical School, University of Warwick, Coventry CV2 2DX

donald.singer@warwick.ac.uk

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The call for papers is now open and abstracts should be submitted via the BSG website by 1st December 2009.

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Scotland

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Fax +44 (0) 141 249 6700
BSG2010@mci-group.com

www.bsg.org.uk

Morris Brown
University of
Cambridge

Morris Brown is Professor of Clinical Pharmacology at the University of Cambridge and Honorary Consultant Physician at Addenbrooke's Hospital, Cambridge. He was President of the British Hypertension Society 2005-2007, co-author of NICE/ BHS guidelines in 2006, and now chairs the BHS Research Working Party. He is leading a British Heart Foundation funded programme of three trials investigating the role of renin measurement in the routine management of hypertension. In 2008 he became Director of one of the Wellcome Trust-funded centres for Translational Medicine and Therapeutics in Cambridge, UK.

Without drugs there would be no pharmacology, and no Clinical Pharmacology. The existence of drugs creates a requirement for pharmacologists and Clinical Pharmacologists to teach and advise on their use. However most disciplines draw their vigour from innovation and we can expect that the attractiveness of Clinical Pharmacology will vary with the degree of new drug registrations, and the specialty's involvement in these.

I was fortunate that my early years in the specialty coincided with the advent of the three classes of antihypertensive drugs which now account for almost 75% of scripts in the Western world for hypertension. In the days when trainees regarded working an 80-hour week as part-time, only a brain-dead trainee could fail to be excited by the opportunities for participation in innovative, translational research. Cardiovascular medicine in general was entering a golden era of new treatments—some were genuinely new molecules; others were old molecules with new uses—aspirin being the most spectacular example—where clinical pharmacologists like Garret Fitzgerald could make their reputation in designing mechanistic studies that eventually predicted the debacle with Vioxx and other COX-2 inhibitors. Today, the cutting edges have moved, and it should be seen as a great plus of Clinical Pharmacology that it can follow these into where the action is in medicine. Most of today's smart trainees will be working in areas such as oncology and therapeutic immunology where Pharma and Biotech companies look most likely to deliver interesting small molecules, antibodies and cell based therapy. There are few areas in medicine where, at both the training stage and the many years thereafter, the practitioner can find something that (s)he enjoys doing, spend most time doing it, and aspire to influencing daily practice as much as is attested by the concentration of Clinical Pharmacologists among the higher echelons of our profession.

One of the fascinations for me has been the recognition that the rules and concepts governing the body's handling of drugs are exactly the same as those that govern endogenous molecules. Currently, for instance, we are investigating whether a previously described PET scanning technique for adrenal adenomas can be established as a sensitive and specific test for Conn's tumours that will avoid the need for selective adrenal vein sampling. The ligand, metomidate, is a 11C-methyl derivative of the anaesthetic agent etomidate, following its recognition as an inhibitor of cortisol synthesis. To be diagnostically useful, the metomidate must bind selectively to the aldosterone synthase of the Conn's adenoma, but not the cortisol synthase (11β-hydroxylase) of normal adrenal tissue.

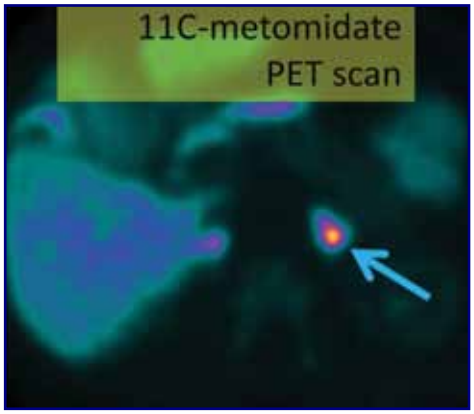

Figure 1

This requires a knowledge and exploitation of properties such as the relative selectivity of the R- and S-isomers of metomidate for these two highly homologous enzymes and half-life of the enzymes after inhibition of their stimulation by ACTH. Preliminary results (Figure 1) suggest that we will be successful in finding a duration of dexamethasone pre-treatment that is several times the 16-hour half-life of 11β-hydroxylase.

As a small specialty that can fly under the radar, and avoid many of today's bureaucratic missiles, Clinical Pharmacology can benefit from times of change. At the beginning of Calman, we persuaded the powers that be to double the number of trainees—without noticeable impact on local or national budgets. We utilised dual, even triple certification in Cambridge to establish attractive posts which in turn trained attractive specialists who now occupy teaching hospital posts in Endocrinology, Respiratory Medicine, Nephrology and Cardiovascular Medicine. Furthermore, the versatility of Clinical Pharmacology led to a number taking the first consultant posts in the new specialty of Acute Medicine. While lack of flexibility seems to be the watchword of MMC, Clinical Pharmacology's traditional in-built flexibility makes us the natural home for those medics who are ambitious enough to hope for a successful academic career, but want the fallback of our excellent record in placing trainees in a wide variety of teaching hospital posts.

Last year, our confidence as an evolving and modernising specialty received a shot in the arm from what we could regard as randomised controlled evidence that Clinical Pharmacology is among leading academic disciplines. This evidence was the Wellcome Trust's competition in Translational Medicine and Therapeutics (TMAT). For the first time, the Wellcome Trust entrusted a large sum of money—£5.5M jointly with the local pharmaceutical partner—to each of four institutions - proposing imaginative programmes that aim to deliver doctors skilled in bringing new medicines to their patients. Eighteen institutions applied, and of the four that were successful, three were led by departments of Clinical Pharmacology. At a time when medical training outside these programmes is increasingly constrained by the fallout from the MTAS debacle, Clinical Pharmacology has the opportunity of guaranteeing both clinical and research training in a single, specialist academic centre, protecting the trainee from the distributivist tendencies and dislike of teaching hospitals shown by many Deaneries. It is no accident that our bid to the Wellcome Trust had the support of one

of the most sympathetic deans in the country who agreed without demur to establishing six local academic clinical fellowships (ACFs) to underpin the programme. Our programme in Cambridge offers all possible permutations between a cradle-to-grave academic track training, and jump-on, jump-off entry and exit between exposure to TMAT (Figure 2). Another distinguishing features of the TMAT programme is the formal instruction in an array of bench-to-bedside topics in our new TMAT Masters; and the mantra that all trainees will learn how to design, execute and analyse a clinical trial.

This issue of Pharmacology Matters is celebrating the Darwinian revolution. In the evolution of specialties and of individual careers, Darwinian selection plays a large part. As the pattern of disease changes, and genetic advances dismantle barriers between existing disease definitions, specialties and doctors need to adapt—only the strongest will survive and flourish. As discussed above, it is of the nature of Clinical Pharmacology to be adaptive and embracing of change. Even if personalised medicine is hyped by the believers, pharmacogenetics is already a reality in upmarket clinical practice. There is little doubt that the greater simplicity of drug response than of disease pathogenesis will render our specialty an earlier beneficiary than most of the genetic revolution.

But the greatest impact of Darwin and genetics on Clinical Pharmacology will be the large number

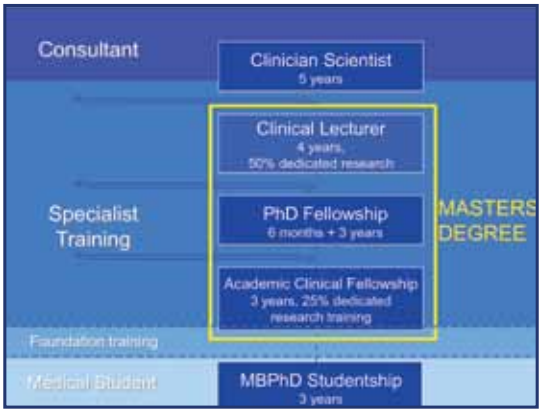

Figure 2

of drugs beginning to come out of a knowledge of genome sequences both wild-type and those which are mutated in disease. Once again, we will have the new drugs that do most to excite us and justify our existence. This time, there will be the extra challenges that drugs are increasingly developed against a molecular target without prior knowledge of the patients most likely to benefit. This makes it essential to have a cadre of trained academic physicians who can not only be entrusted with performing early study of a company's new drug (without causing years of regulatory headache), but design imaginative, pivotal proof-of-concept studies in various patient groups. Yes we have suffered since 2004 from inane regulations and regulators, but Dame Sally Davies at NIHR has now publicly committed herself to their removal.

At the end of our presentation to the Wellcome Trust last year, we showed Figure 3. We rebutted the notion that Clinical Pharmacology was withering on the vine and welcomed the opportunity of grafting new onto old to produce a stronger fruit. But in deference to my own hybrid education in Classics and Medicine, we pointed out that nothing is as new as it seems, since Dionysus had translated the fruit of the vine into medicinal use – with studies of half- life and therapeutic ratio along the way. 3000 years later, Darwin's writing about vines provides a suitable aspiration for Clinical Pharmacology. "Plants became climbers," he wrote, " . . . to reach the light and to expose a large surface of their leaves to its action and to that of the free air." There is no excuse for gloom about our specialty, and every reason for optimism. Thanks to the number of genes in the genome, and endless modifications of these, there is no limit on the free air to which we can grow to expose our leaves.

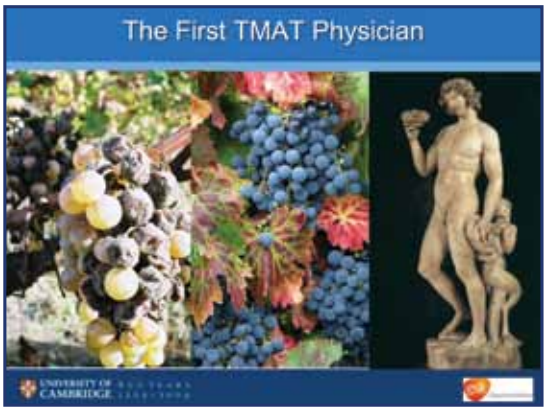

Figure 3

Morris Brown, MA, MSc, MD, FRCP, FAHA, FMedSci, University of Cambridge, UK

morris.brown@cai.cam.ac.uk

BPS Diploma Workshop Report: Harnessing the Power of Molecular Biology in Pharmacology

The workshop on Molecular Biology Techniques in Pharmacology is a one-day workshop designed to serve as an introduction to the terminology and techniques of molecular biology and to illustrate the usefulness of molecular biology in the study of drug targets and mechanisms. Although intended initially for students enrolled on the BPS Diploma in Advanced Pharmacology, the Molecular Biology Techniques in Pharmacology workshop is one of a series of workshops in pharmacology run by BPS and now open to all www.bps.ac.uk/site/cms/contentCategoryView.asp?category=396.

Designed around a series on short seminars delivered by experts in their respective fields, the morning and afternoon sessions have subtly distinct flavours. In the morning session, the presentations cover the theoretical aspects of molecular biology including polymerase chain reaction, gene cloning and expression and the production of transgenic animals; whilst the afternoon is taken up by short "case studies" during which the speakers illustrate how the techniques discussed in the morning have been applied in their laboratories to address pharmacological research questions.

Lunch falls between these two seminar-based sessions followed immediately by a computer aided learning session during which participants are given hands-on experience of how to access and use a number of the bioinformatics databases available on the internet.

Feedback on the first running of the workshop has been very positive although a number of participants asked whether it might be possible to incorporate some laboratory work into the programme, even if this meant extending the workshop over 2 days, and this is something we are currently looking into for the re-run in the Autumn of 2010.

Ian McFadzean, King's College London, and BPS Diploma Steering Committee member

Profile: Sara Rankin

The evolution of Pharmacology—from basic principles to more specialised applications

Sara Rankin, Imperial College London

Profile: Sara Rankin, a pharmacologist with a multidisciplinary approach to problem solving.

Sara Rankin is one of many of our members keen to embrace a multidisciplinary approach to her research. We profile her in this Darwin themed issue, where she explains how her understanding and application of Pharmacology has evolved during the course of her career from basic principles to applications in the fields of immunology, stem cell biology and regenerative medicine.

Sara obtained her PhD in 1989 in Pharmacology from King's College London, where her research focus was on investigating monocyte-driven oxidation of lipoproteins and the inhibitory effects of plant-derived flavonoids on this process. She held post-doctoral positions in the Department of Medicine, UCSD, and for the Imperial Cancer Research Fund (now Cancer Research UK) before joining the Leukocyte Biology Section of the NHLI in 1995, where her research was funded by a Wellcome Trust Career Development Award and a Wellcome Trust University award.

Now a Reader in Leukocyte and Stem Cell Biology at the NHLI, Imperial College London, Sara's current research focuses on understanding the role/impact of the bone marrow in inflammatory diseases and elucidating the molecular mechanisms regulating the exit of leukocytes and stem cells from the bone marrow.

Sara is a member of the BPS Education and Training Committee with special interest in outreach activities in schools. She is an editor of the British Journal of Pharmacology.

Can you outline your current research interests?
For the last 15 years I have been investigating the role of the bone marrow in inflammation. We have shown that fundamentally different factors and molecular mechanisms regulate the mobilization of distinct populations of mature leukocytes from the bone marrow during specific inflammatory reactions. Elucidation of these pathways increases our understanding of the pathogenesis of the disease and identifies novel therapeutic targets. I am now applying my expertise in this area to examine the mobilization of adult bone marrow stem cells. My group has recently identified a novel drug combination that mobilizes subsets of stem cells involved in tissue regeneration (endothelial progenitor cells and mesenchymal stem cells) from the bone marrow into the blood. We are currently investigating the impact of boosting stem cell numbers in the blood on tissue regeneration.

You studied for your degree and PhD in the Pharmacology Department at King's College London which was part of the Biomedical Sciences Division and now work at Imperial College, a multi-disciplinary institution. How important do you think it was for you to study and work in such environments?
My Pharmacology degree/PhD at King's gave me an excellent grounding in the basic principles of Pharmacology that still informs by experimental approach today. While my research as a PhD student and postdoc was focused on cells and molecules, since joining Leukocyte Biology I have come to

appreciate the necessity for Integrative Physiology and Pharmacology to interrogate disease processes. As such my research is now a fusion of these different experimental approaches. Working in the NHLI I have benefited from interactions and collaborations with Immunologists further, the large number of research-active Clinicians present within the Division has served to keep me focused on the end goal. My current research in stem cell biology is opening up new and exciting opportunities for cross-disciplinary collaborations, for example with the tissue- and bio-engineers across campus.

Your current research focuses on stem cells. What are the main areas of research that involve stem cells that pharmacologists can get involved with?
Regenerative Pharmacology is a new area of Pharmacology, it encompasses a number of different areas including:

- The use of pharmacology (drugs) to differentiate stem cells (embryonic or iPS)
- The use of differentiated stem cells for drug screening—for example embryonic stem cells differentiated into cardiac myocytes could be used by the Pharmaceutical Industry to study the effects of new drugs on cardiac function and/or for toxicological screening of new drugs – very much in line with the 3Rs
- The use of drugs as a necessary adjunct to stem cell therapies, for example to guide stem cells to sites of tissue injury

Have you any advice for young pharmacologists who would like to get involved?
You can find out what's going on in the UK with respect to stem cell research, plus all the national and local meetings, from the website of the UK National Stem Cell Network *www.uknscn.org*. Attend the BPS workshop on *Pharmacology of Stem Cells and Regenerative Medicine* to be held in association with the Dec 2010 Winter BPS meeting in London www.bps.ac.uk/site/cms/contentCategoryView.asp?category=396

Where does in vivo work fit in?
Stem cell therapies will require the administration of stem cells to patients. Animal models are therefore necessary to investigate and optimise the modes of delivery and compare the efficacy of different stem cell populations in disease. Specifically with respect to my current research we are investigating how stem cells are mobilized from the bone marrow and traffic to sites of tissue damage; this process cannot be recapitulated *in vitro*.

You are involved in several outreach activities through your activities with both BPS and Imperial. How important do you think it is to engage with the public/schools in this way?
I am passionate about these activities for two main reasons:

1. To inspire young people to take up a career in science. I am involved in a number of different schemes at Imperial, including INSPIRE (a scheme that provides PhD students with a PGCE course plus master classes and workshops from Scientists at Imperial) and Creative Futures (an experience designed to help young black and minority ethnic pupils achieve their full potential and encourage them to think about science and higher education). I use my interactions with pupils to promote science and demonstrate that careers in science can be diverse, exciting and rewarding.

I also use these workshops as an opportunity to explain to pupils what Pharmacology is, as I have yet to find a single student who knows what Pharmacology is. I hope my work with the Education and Training Committee of the BPS will change this in the future.

I am interested in engaging with a wider audience and as such I am currently involved in a collaborative project with artist Gina Czarnecki, so watch this space.

2. To increase awareness and understanding of stem cell biology and technology by the general public, such that policy makers and patients can make informed decisions. (eg whether or not to bank stem cells or be part of a clinical trial involving stem cells).

And the future?
In terms of research I will continue in the field of regenerative pharmacology to investigate stem cell trafficking. I am also interested in defining the role of specific stem cell populations in diseases such as asthma and atherosclerosis. Through collaborations with the Pharmaceutical Industry I look forward to the opportunity to translate my research into novel therapies.

Sara will be speaking on behalf of BPS and the Biochemical Society in the *Biology in the Real World* symposium at the annual conference of Association for Science Education on January 8th 2010 (www.ase.org.uk/. Along with Sian Harding (Imperial), Sara is running a workshop on *Pharmacology in Stem Cell Research and Regenerative Medicine* in association with the BPS Winter meeting in London. The workshop is open to all and can also be used by those enrolled on the programme towards the award of the BPS Diploma in Advanced Pharmacology; please contact jmh@bps.ac.uk for details.

Interview by Jude Hall, Education and Training Delivery Consultant for BPS

Sue Brain

Sue Brain,
Vice-President

Professor Susan Brain retires at the end of 2009 as Vice-President (Academic Development) of the BPS and from many years of committed and effective work for the educational activities of the Society. Like the teaching of Pharmacology in general, the efforts made by the BPS to preserve, foster and improve Pharmacology Education in academic institutions receive much less attention and publicity than the research components of the Society. Nevertheless, as in Universities, the educational aspects of Pharmacology are as critical to the success of the discipline, as are the advances in research. This is not a Valediction to Sue Brain, but an Appreciation of all that she has done for the Society, for its members and for the discipline in general, in terms of Education in Pharmacology.

In the mid-nineties, Departments of Pharmacology were disappearing at an alarming rate into "rationalised" Divisions of Bioscience / Neuroscience / Molecular Toxicology etc. Adding to this loss of academic identity, the pharmaceutical industry, the major employer of Pharmacology graduates, was almost totally converted to the "Give me the gene and I'll give you the cure " approach to drug discovery. Thus, both in academia and in the industry, the focus was on molecular biology, and the skills, recognised since Gaddum's time as characteristic of Pharmacology, were being lost and not being replaced.

Jude Hall, Ian Morton and Sue Brain

Thankfully, Sue Brain and her colleagues in the various Education Committees of the BPS were determined to take action, and a Pharmacology Training Group was set up with Sue in the Chair. The first major project Sue became involved in was to re-instate the teaching of whole animal pharmacology in undergraduate courses — the "*in vivo* classes" project. Supported by money from the pharmaceutical industry and from the BPS, this project encouraged and supported academics to keep their *in vivo* practical classes, both for the benefit of the students and to ensure that *in vivo* skills were passed on to a new generation of teachers.

Critical to the (now undoubted) success of this project was the vigorous and continuing support of some senior members of pharmaceutical R&D departments, who still saw a need for "non-molecular" pharmacologists—sometimes against the tide in their own departments—and had the ability to commit money to ensuring that need was met by the Universities. Val Alabaster, who during her time at Pfizer (Sandwich) was an influential, enthusiastic and effective proponent of this *in vivo* project, told me "Sue Brain was not only involved in organizing these projects, but also actively participated in some of the practical sessions. *In vivo* skills and knowledge and understanding of integrated pharmacology are essential to successful drug discovery, and these initiatives of the BPS ensured that graduates would be available to the pharmaceutical industry who would be able to capitalise on the new molecular biology."

Academic support for the project was equally vital, and Sue had the academic standing, the energy and the commitment to convince and encourage her fellow teachers that *in vivo* classes were academically valid and crucial to the survival of this uniquely pharmacological skill. Sue's crucial role in this project's success was summarised on the academic side by Ivor Williams, who for many years had been concerned about the long-term sustainability of the *in vivo* practical classes for the Pharmacology courses at Bath. In his words, "Without the support of Sue and the funding from the BPS Integrative Pharmacology Fund, these classes would have disappeared, along with their undoubted value for the students. On a different note, he added, " I should also like to thank Sue for acting as the BPS liaison to the Animal Sciences Committee of the Biosciences Federation chaired by Clive Page. The survey, "*In vivo* sciences in the UK: sustaining the supply of skills in the 21st century", commissioned by the ABPI and the Biosciences Federation, highlighted the vital need to increase these skills and provided clear and solid evidence to Government. Sue played an important role in this project, always finding time to help in the preparation of the academic data for this survey. Her contribution and efforts were, typically, understated but vital". Sue was also instrumental in securing funding for the joint BPS/Physiological Society short courses in integrated *in vivo* pharmacology/physiology which have now been running for over 8 years. These courses (funded by the pharmaceutical industry, BBSRC, Wellcome Trust, BPS and the Physiological Society) enable undergraduates and postgraduates to attend a Home Office training course (modules 1-4) and a subsequent *in vivo* training course.

Another of Sue Brain's educational successes to celebrate is the BPS Diploma in Advanced Pharmacology. This idea to provide a clearly post-graduate, in-work, education in Pharmacology needed support from both academic and industry pharmacologists and this took time. Throughout this prolonged gestation, Sue was an active advocate for the Diploma, talking, persuading and convincing until the Diploma was eventually launched in Summer 2006. Even after its first event in July 2007 with 35 students enrolled and with Judith Hall as a dedicated Diploma Organiser, Sue maintained her support and the interest of the BPS Education Committees in the Diploma, determined to see this project and the students through to a satisfactory finish. Judith Hall said of Sue's work for the Diploma, "having known Sue since we worked together at King's in the early 1990s, it was no surprise to me that firstly Sue had the foresight to identify that an advanced training course in Pharmacology was needed and secondly that through quiet persistence, she managed to persuade BPS of her conviction that a Diploma in Advanced Pharmacology was the best mechanism by which this could be achieved. Sue's commitment to education, generosity with her time and forward vision should be much better known."

Apart from these major projects, Sue has been quietly but enthusiastically involved in the long running e-learning programme of the BPS. She played a major role in producing two learning packages on Inflammation and in the Teaching and Learning Resource Pharmacology Workbooks. These Workbooks provide both a resource, helping teachers

to incorporate, successfully, computer based learning into their courses and the appropriate exercises to assess the students' understanding.

A crucial aspect of Pharmacology in the UK is its interaction with the Home Office over the regulation of animal experimentation and the BPS provides an important voice in these discussions, together with other scientific societies. Sue was first involved in this function of the BPS in 1995, over the accreditation of courses for Home Office Licences and ever since has been one of our major "negotiators", particularly for the *in vivo* classes project and the BPS Diploma. Val Alabaster said Sue's negotiations with the Home Office to obtain the necessary licences (for the *in vivo* classes) would have defeated many, but her quiet determination and perseverance won through. Over these last 15 years, Sue has continued to express that quiet, persistent and patient commitment and determination that is essential to success in dealing with Government departments. If for nothing else, Sue's efforts at *this* interface alone deserve the thanks of every practising pharmacologist, student or professor, research scientist or director of drug development.

Of course, Sue has not been the only one concerned with these projects, but her enthusiasm and consistent support for these and several other educational projects of the BPS has undoubtedly been a major factor in their success. I suspect there are many members of the BPS and many other pharmacologists who do not know either of the efforts to keep Pharmacology alive in the Universities or of Sue Brain's crucial contributions. It is typical of Sue's character that all her efforts have been low-profile and widely unrecognised, as is much of the educational work of the Society. Now, as Sue steps down from a formal role in Educational affairs, it is entirely appropriate that her efforts are appreciated more widely.

So I would say to Sue Brain – Many, many thanks for your stalwart service to Pharmacology Education at a critical time, a service whose outcome has been the strengthening and survival of our discipline. And, as you leave behind the formal responsibilities, I say welcome to the back-benches of the BPS, where we Senior Members can still shout encouragement, instructions and, when needed, insults from the side-lines. But above all, our thanks again.

Y S Bakhle (the help of many of Sue's colleagues was essential, generously provided and very gratefully acknowledged)

Clinical Pharmacology and Primary Care

David Mant, Oxford University Department of Primary Health Care

Professor David Mant was an undergraduate student at Churchill College Cambridge (1969-72) and Birmingham Medical School (1972-77). He subsequently undertook post-graduate training in general practice and public health. He began his clinical academic career in 1983 as a clinical lecturer in general practice at University of Oxford and part-time general practitioner at South Oxford Health Centre.

In 1993 he was appointed Professor of Primary Care Epidemiology at the University of Southampton. During his time in Southampton he was seconded for 2 years to the post of regional director of NHS R&D and he chaired the national working party on R&D in Primary Care. He returned to Oxford as Professor of General Practice in October 1998 to lead the newly established Department of Primary Health Care. In addition to this academic role, he continues to work as a general practitioner in the NHS. Professor Mant's research focuses on the prevention and early diagnosis of common diseases in primary care.

About 16 years ago, in the British Journal of Clinical Pharmacology, Tom Walley challenged clinical pharmacologists in the UK to promote more rational prescribing in primary care [1]. He pointed out that while primary care accounted for 80% of NHS prescribing and 70% of GP consultations resulted in a prescription, clinical pharmacologists were invariably hospital-based and too often had 'a narrow perspective of drug use, only understanding the medical model of prescribing (i.e. prescribing for pharmacological effect)'. Has any progress been made in meeting this challenge?

Most NHS prescribing still takes place outside hospitals, and primary care is responsible for about three-quarters of the NHS drugs budget [2]. Clinical pharmacology is still a hospital-based discipline. But this does not mean that clinical pharmacologists have made no impact on primary care prescribing. Clinical pharmacologists have a major influence on the British National Formulary (and the recently added Children's BNF), which is still the information source that GPs consult most often during clinical consultations. Many have contributed to the national guidelines on which the financially incentivised quality outcome framework (QOF) for general practice has been based and, for two chronic diseases, there is evidence that this has led to better prescribing [3]. And clinical pharmacologists also contribute nationally to clinical practice and research in many other ways, for example through their activities in the MHRA, CHM, HTA, and NICE. Nevertheless, it is hard to argue that clinical pharmacologists

have successfully provided the "bottom-up" promotion of rational prescribing in primary care that Walley proposed.

Those who have engaged most with general practice prescribing have been the pharmacy advisers in Primary Care Trusts (PACT). They collate PACT prescribing information for each practice, promote generic prescribing, provide general advice on the relative cost-effectiveness of "me too" drugs, and often target individual education at practices with atypical prescribing patterns. However, the valuable work of pharmacy advisers needs to be evidence-based. The development of this evidence base for primary care practice still needs the strong support of clinical pharmacologists.

A good research example is our programme on the clinical monitoring of common drug therapies [4]. Two practical questions we have recently addressed are how often to measure serum cholesterol during statin treatment and when to up-titrate treatments for heart failure [5,6]. Formulating these clinical questions, and indeed developing the study methods, needed only our primary care expertise. However, to interpret the timing of the therapeutic response, and particularly to make recommendations on appropriate monitoring intervals, would have been impossible without clinical pharmacology expertise on the pharmacokinetics and pharmacodynamics of the drugs involved.

The need for clinical pharmacology input in developing other aspects of the evidence-base for primary care practice is perhaps less obvious. Many commentators have pointed out that prescribing in primary care is complex, driven more than in hospital by factors other than anticipated pharmacological effect [7]. For example, a GP is more likely to prescribe an antibiotic if a patient about to go on holiday consults with respiratory symptoms. This doesn't imply a belief that an impending holiday makes a viral infection less likely or an antibiotic more likely to be effective, but it does reflect the fact that accessing health care if symptoms worsen is often more difficult on holiday. The small average reduction in duration of illness achieved by prescribing is probably also more valuable to the patient when they are on holiday than at work. It is probably fair to say that clinical pharmacologists have shown little enthusiasm for exploring this type of complexity in an effort to improve prescribing. For example, the research on "delayed prescribing" (giving a prescription to be used after a specified period if the symptoms have not started to improve), adoption of which has resulted in a 25-50% reduction in antibiotic use in NHS general practice, was done without clinical pharmacology input [8]. More clinical pharmacology engagement with this type of pragmatic research would be helpful.

Polypharmacy pharmacy

Another common complexity that needs to be better addressed through research and education is the increase in polypharmacy. General practitioners are encouraged by guidelines and financial targets to prescribe for an ever-increasing range of conditions. Patients leave hospital with an ever increasing list of discharge medications, usually including a number of drugs prescribed for secondary prevention as well as treatment of the immediate symptoms. Although this prescribing is usually based on good scientific evidence of efficacy, it ignores the fact that people receive medicines for more than one condition and many of them are elderly – the average number of items prescribed for those over 60 has doubled (from 21 to 41) over the past decade and 20% of people over 70 now take five or more drugs [9]. Poor compliance is endemic in this section of the population and presumably correlated with the number of drugs prescribed. Moreover, when taking drugs for more than one chronic condition there are necessary trade-offs, often mediated less by recognised drug interactions than the need to prioritise which drugs really must be taken. Disease-specific guidelines continue to proliferate from national bodies such as NICE, and are then integrated into incentivised targets for primary care, without sufficient attention to these trade-offs. This is an issue which general practitioners and clinical pharmacologists need to address in partnership.

The fourth key area of research for which we need strong clinical pharmacology support is what has been termed "personalised medicine" [10]. Although the term was coined by those hopeful to exploit the potential of genomics to achieve tailoring of drug therapy for the individual patient, its relevance to general practice lies in the financial incentives now given for prescribing to all patients in defined risk groups. This may well not provide optimal care for an individual. The incentives are invariably evidence-based, but they underplay the significant heterogeneity around the average effect in a clinical trial [11]. The personalisation of drug therapy through genomics is not straightforward [12] and a more promising approach from a primary care perspective is to estimate benefit directly by promoting "n of 1" trials - particularly when there is known to be substantial variability between individuals in both efficacy and adverse effects [13]. This sounds far-fetched but could certainly be done in an NHS service context, with the support of the pharmaceutical industry, at lower cost than much genome-based research. "Start-up" packs, containing active and placebo drugs in a predetermined randomized order to facilitate a crossover design trial, could be a standard prescribable option for suitable conditions. Any patient with a newly-diagnosed chronic condition could then opt to conduct a formal trial of self-efficacy before committing to long-term, sometimes life-long, treatment. They could also offer their individual data for aggregation, so that their trial would contribute to a more finely-grained picture of overall cost-effectiveness. For such an approach to become a reality, primary care and clinical pharmacology collaboration would again be essential.

As research expertise in primary care has increased over the past decade, so has our role in teaching. To some extent, this has reflected increasing specialisation in hospitals; the task of teaching general medicine to medical students, including clinical method and therapeutics, is falling increasingly on general practitioners. In one new medical school with a strong emphasis on primary care-based teaching, clinical pharmacologists are not thought necessary to teach clinical therapeutics [14]. Although I welcome an emphasis on the practical aspects of therapeutics, teaching prescribing as series of black-box decisions without clinical pharmacology input is not the answer. Future general practitioners need to be taught to prescribe rationally and safely now, but they also need to continue to prescribe rationally and safely in the future. Surely they will be much better able to adapt their clinical practice to changing knowledge and circumstance if they have a conceptual understanding of how drugs work? Again, active collaboration between general practitioners, pharmacy advisers, and clinical pharmacologists in both devising and teaching the therapeutic curriculum must be the way forward and should be applied to continuing professional development as well as undergraduate teaching.

In Oxford the senior clinical pharmacologist in the University (Jeffrey Aronson) is now based in the Department of Primary Health Care. Medical schools vary in their organizational structures and this would not be the ideal solution in all

Universities. However, it does reflect an emerging symbiosis in research on therapeutic issues and a stimulus for joint teaching. General practitioners and clinical pharmacologists share a generalist role, and usually an interest in applied clinical research and teaching, which may be at odds with specialist or methodological silos that facilitate more basic clinical research. Achieving greater collaboration is therefore not only likely to promote Walley's aim of rational prescribing in primary care but may also strengthen and protect both academic disciplines.

David Mant, Professor of General Practice
Oxford University Department of Primary Health Care

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Acknowledgements
Dr Peter Rose and Dr Keith McDermott provided very helpful comments on the initial draft of this paper.

Jeff Aronson, President, BPS

CPT or Huliatrics?

Which is the oldest medical specialty? Figure 1 shows various ologies against the dates of their first recorded uses, as listed in the *Oxford English Dictionary*. That is not to say that these specialties did not exist before their names were invented or first recorded—all subjects have a prehistory and there may be earlier citations to be discovered. But pharmacology comes first by a long way, barring the three other cornerstones of medical science, anatomy, pathology, and physiology. The first recorded instance is in *Essays on the Preservation & Recovery of Health* (1704) by the Reverend Thomas Curteis, in which he described pharmacology as a 'boundless field'. Clinical pharmacology, in the guise of materia medica, dates from no later than 1771, when Tobias Smollett mentioned it in his epistolary novel *Humphry Clinker*. And toxicology was not far behind, first appearing in Robert Hooper's *Compendious Medical Dictionary* in 1799.

The term 'materia medica' was originally a direct translation of the Greek title of Dioscorides' five-volume herbal treatise, written in the first century AD, Περι υλης ιατρικης (peri hulēs iatrikēs), which literally means 'about healing stuff'. It first appeared in sixth-century Latin translations of Dioscorides and came into English in the middle of the seventeenth century. It was used to describe the remedies employed in the practice of medicine, or a list of such, and was incorporated into the titles of textbooks, such as William Cullen's *A Treatise of the Materia Medica* (1789). In the late eighteenth century it came to mean the branch of medicine that deals with the origins, preparation, and use of those remedies. *Elements of Materia Medica and Therapeutics* (1845) by Edward Ballard and Alfred Baring Garrod is one of about 800 titles in the catalogue of the Bodleian Library to contain the term.

The term 'clinical pharmacology' does not itself appear in the *OED*. The earliest instance that I have found dates from 1914, in the English translation of the title of a German textbook, *Die experimentelle Pharmakologie als Gründlage*

der Artzneibehandlung, by Hans H Meyer and R Gottlieb, translated by John Taylor Halsey as *Pharmacology Clinical and Experimental*. Not quite 'clinical pharmacology', but precious close.

As a medical student in Glasgow in the 1960s I studied materia medica, and the recommended textbook was *Dilling's Clinical Pharmacology*. It was first published in 1884 by John Mitchell Bruce, under the title *Materia Medica and Therapeutics. An Introduction to the Rational Treatment of Disease*. Later, this was amended to *Bruce and Dilling's Materia Medica and Therapeutics*, and in 1960 the 20th edition was published as *Dilling's Clinical Pharmacology*. The first edition of Desmond Laurence's textbook *Clinical Pharmacology* also appeared in 1960, and these two are the earliest books to have used the term 'clinical pharmacology' in their titles.

It is thought that the precise term 'clinical pharmacology' was first used by Harry Gold, who was appointed the first Professor of Clinical Pharmacology in Cornell in 1947 and pioneered clinical pharmacological studies of cardiac glycosides from the 1920s onward. John Gaddum, who at the time was Professor of Materia Medica in the Department of Materia Medica and Therapeutics in the University of Edinburgh, called his Walter Ernest Dixon Memorial Lecture, given to the Royal Society of Medicine on 8 December 1953, 'Clinical pharmacology'.[1] 'I propose,' he wrote, 'to discuss some of the clinical implications of pharmacology. I had already decided that the title of my lecture would be "Clinical Pharmacology" when I found that Dr Harry Gold (1952) had used the same words to describe the same thing.' Gaddum's seminal paper includes more dose-response curves than you will see in a year in all current general medical journals put together. There is also a paper from March 1952 describing, in Spanish, the clinical pharmacology of Aureomycin (chlortetracycline).[2]

However, the term 'klinische pharmakologische' had already been used by the German pharmacologist Paul Martini, in his 1932 textbook *Methodenlehre der Therapeutischen Untersuchung*.[3] For this reason, it has been suggested that Paul Martini was the first clinical pharmacologist.[4] But even if Martini did use the term 'clinical pharmacological' first, that does not necessarily qualify him to be called the first practitioner of clinical pharmacology. Others in the history of therapeutics could have been so described. For example, the fourth-century Chinese physician Ge Hong[5] and the eighteenth-century English physician William Withering.[6]

Although by the 1960s the term 'clinical pharmacology' had prevailed, 'human pharmacology' was for a short time a competitor. In 1959 Desmond Laurence edited the proceedings of a 1958 symposium titled 'Quantitative methods in human pharmacology and therapeutics'.[7] Gold contributed. His lecture was called 'Experiences in human pharmacology'. 'Many of you,' he said, 'are probably familiar with Dr Gaddum's Dixon Memorial Lecture under the title 'Clinical Pharmacology', but I believe your term 'Human Pharmacology' is a better one, free of the meanings of the term 'clinical', which tend to identify it with the art of therapeutics, the practical care of patients.' A strange comment this, coming from one who had contributed so much to therapeutics. But the newly fledged clinical pharmacologists were wedded to the bedside, as they continue to be, and 'clinical pharmacology' triumphed.

These days, and fully reflecting Gold's observation, 'clinical pharmacology' is usually twinned with the much older term 'therapeutics'. 'Therapeutic' (singular), meaning the art of healing, first appears in the *OED* in a citation from 1541. In its now usual plural form it first occurs in William Salmon's *Synopsis medicinae, or a compendium of physick* (1671). 'The Therapeuticks, or active part of Physick,' he wrote, ' is either Material, or Relative'. The word comes from the hypothetical Indo-European root DHAR, meaning 'hold'. Indian words include many 'holders': aumildar (an office holder or tax collector), chobdar (an attendant or servant, literally a stick bearer), jaghirdar (a holder of land and its rent as an annuity), jemadar (a lieutenant), killadar (a commander of a garrison), ressaldar (a cavalry commander), silladar (an armour bearer), subadar (the governor of a province, a captain), tahsildar (a district tax collector), talukdar (an estate holder), and zemindar (a land holder); all can be found in that wonderful lexicon, Hobson-Jobson.[8] In Greek DHAR yields θεραπεία (therapeia), meaning attendance, service, or treatment.

'Clinical pharmacology and therapeutics' are respectively the science and practical applications of drug therapy. And since the Latin adjective 'medicus' meant not only 'medical' but also 'medicinal', 'materia medica' says it all, and more succinctly. Perhaps we should take a lead from peri hulēs iatrikēs, Dioscorides, and call the subject 'huliatrics'.

This article was first published in the *Quarterly Journal of Medicine* (© J K Aronson)

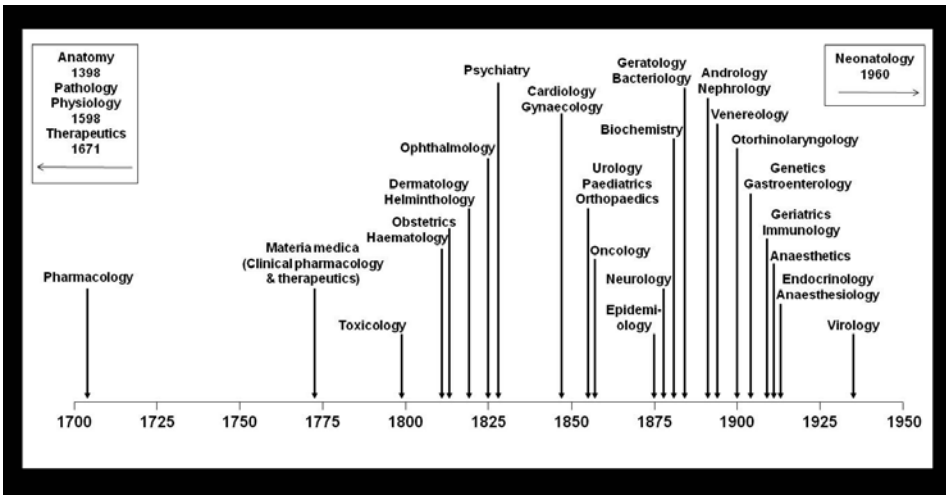

Figure 1. The dates of first citations of subject names in the Oxford English Dictionary

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A Model for Academic Clinicians

Jeff Aronson,
President, BPS

The idea that academic clinicians cannot fulfil all of the roles that are expected of them—as innovative (revolutionary) researchers, authoritative clinicians (whether in hospital or general practice), and inspiring teachers, setting aside administrative tasks—is not a new one, but it is one that has been rejected in the past [1]. However, in recent years the increasing complexity of clinical medicine, and in particular the advent of new types of therapeutic agents and techniques, and the similarly increasing complexity of research techniques, have made it truly much more difficult for them to excel in all aspects of their profession. Even those who have the capacity to do so do not have the time, especially now that there are fewer of them—it is not only in clinical pharmacology that numbers have been falling, although clinical pharmacology has been particularly badly hit and has suffered more because it started from a low baseline.

The model

I suggest that we should therefore encourage the development of those who excel at any two of the three vital academic skills (research, clinical expertise, and teaching) and formally establish the following categories (Figure 1) [2]:

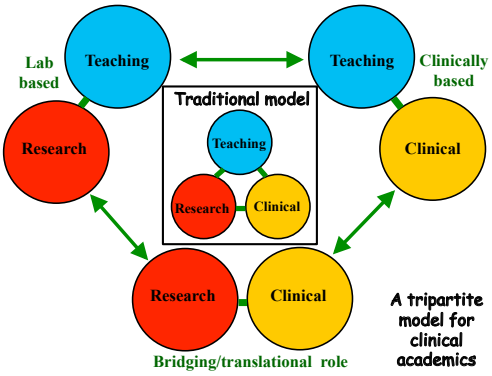
- researcher—teachers: innovative researchers, training young academics; mainly laboratory based;

- clinician—teachers: authoritative clinicians and inspiring teachers; mainly clinically based;

- clinician—researchers: combining clinical and research skills, bridging the other two groups.

There should be freedom to change category during a career, if aptitude allows it. I believe that these categories already exist but are not formally recognized as such. I offer this suggestion to stimulate debate on the nature of academic medicine and how it should best be structured.

Figure 1. A model for clinical academics. The small central diagram is the traditional model; the three outer diagrams show a model for three interacting types of academic clinician; policy making is omitted for the sake of clarity



Researcher—teachers

This category will be relatively small. It is unrealistic to expect all scientists to be revolutionary. Truly revolutionary scientists are scarce. We should develop ways of identifying such individuals, especially before they have established themselves. We should train and enable them to be élite (in the best sense of the word), but discourage them from behaving in an élite fashion (in the worst), since they must be prepared to liaise with normative scientists (as described by Thomas Kuhn [3]) and practising clinicians. We should protect them from external duties that will divert them from their research. We should then nurture them, by, for example, giving them unrestricted grants for extended periods, subject to only occasional review, and give them freedom from administrative duties. Some enlightened grant-giving bodies have done this in the past.

Clinician—teachers and clinician—researchers in clinical pharmacology

Methods of training clinician—teachers and clinician—researchers are already established, and clinical pharmacology, as a strong translational discipline, is well placed to provide academic clinicians of both types. Interactions among these types of clinicians, and with non-clinical scientists, would stimulate the development of translational medicine. Describing academics in these categories as clinician—teachers and clinician—researchers does not rule out the possibility that the former will do some research and the latter some teaching; however, such duties should not be part of the general expectation. Both groups would, however, be expected to take part in administrative duties and policy development, locally, nationally, and internationally when relevant.

Funding

Joint funding streams could be set up to help enable such posts, sharing the costs among universities, grant-giving bodies, the NHS, and industry (e.g. pharmaceutical companies). Figure 2 shows some potential joint sources of funding, such schemes are not new (Table 1). Clinician—teachers have for many years been jointly funded by Universities and the NHS (in what used to be called 'A+B' posts). Similarly, schemes for joint funding of researcher—teachers, by for example, grant-giving bodies and pharmaceutical companies, have a long history, the most recent example of this being the Wellcome Trust's programmes in translational medicine and therapeutics [4]. The ABPI/NHS scheme of a few years ago [5] was an excellent example of joint funding of training posts for clinician-researchers by drug companies and the NHS; it could be revived, but with more strict criteria about how it should be used than last time round. The MRC's forthcoming Clinical Pharmacology and Pathology Fellowship Programmes [6] provide an example of how joint funding by a grant-giving body and the NHS will generate clinician—researchers in clinical pharmacology.

Table 1 Examples of joint funding schemes

University + drug company	Contract work in departments of clinical pharmacology; clinical trials of new agents
University + NHS	Traditional academic clinicians ('A+B' posts)
University + grant-giving body	Traditional research grants (now eroded by full economic costing)
Grant-giving body + drug company	Wellcome Trust Research Programmes in Translational Medicine and Therapeutics
Grant-giving body + NHS	MRC Clinical Pharmacology and Pathology Fellowship Programmes
Drug company + NHS	ABPI/NHS training scheme for clinical pharmacology; clinical trials of new agents

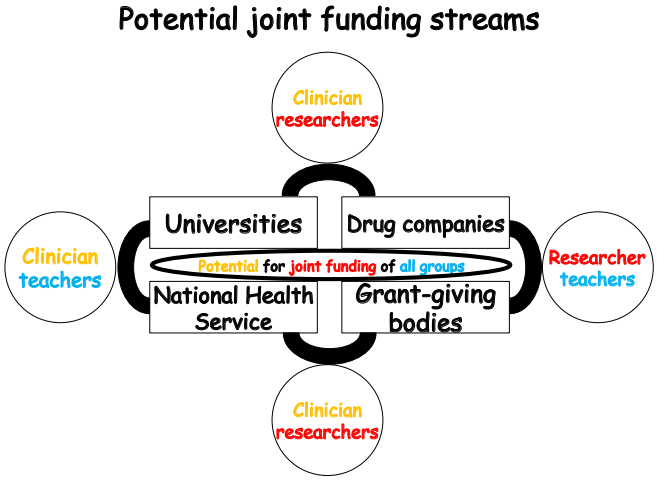


Figure 2. Possible joint funding streams for the different types of clinicians outlined in Figure 1; the illustrated possibilities are not comprehensive

Conclusions

If we are going to stimulate academic medicine in general, and clinical pharmacology in particular, we must make academic careers more attractive and ensure that our trainees, the specialists of the future, are bred in such a way as to be able to practice their discipline most efficiently. Current demands on clinical academics are excessive. We should lighten the burden of expectation, increase their efficiency, and give them more freedom to pursue the art and science of being an academic clinician. The need for role models is evident, and our new trainees will eventually take over that role if we breed them properly.

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Meetings Report

Robin Hiley, Vice-President Meetings

The Society has recently focused on having smaller and more frequent meetings and this year has continued that theme. In early February we held a joint meeting with the Royal Society of Chemistry on "Ion Channels as Therapeutic Targets" at the Novartis Horsham Research Centre. This was received enthusiastically by the 150 who attended, despite the time of year at which it was held. Several participants felt that the venue was important to the success of the meeting and welcomed the opportunity to network with academic and industrial pharmacologists - we are very grateful to our hosts for the warmth with which we were received and the facilities offered.

Spring sunshine welcomed a lively group of 185 participants to Leicester in April for the "Third Focused Meeting on Cell Signalling" and this again brought together a mixture of leading figures in the field and those at earlier stages in their careers. It was centred on GPCRs and the breadth of ligands that interact with this family of receptors. The talks included discussions of allosteric modulation, drug discovery at free fatty acid receptors, the pharmacology of extracellular Ca^{2+}-sensing receptors, and single-event analysis of regulated GPCR membrane trafficking.

These two focused meetings successfully fulfilled a central purpose of the Society - that its meetings should engender excitement about the science being reviewed. This derives in large part from the fact that they blend the depth of vision and understanding of more senior researchers with the enthusiasm and broader recent backgrounds of newer entrants to the field.

In May, a joint meeting on New Drugs in Cardiovascular Research was held in Dresden with the German Societies of clinical and basic pharmacology. From a personal point of view this started ominously as the German stereotype of efficiency bit the dust when the Lufthansa pilot starting the journey from London City Airport announced he had arrived without the maps to let him take off. After an hour a printer was found that could handle the file and we were on our

way. It was, fortunately, the limit of the problems, as our German hosts took good care of us and reinstated the expectation of friendly efficiency. There were just under 200 registrants, about a third from the BPS. BPS contributions included a symposium on "New Antiarrhythmic Drugs" and a BPS-sponsored EPHAR lecture given by Desmond Fitzgerald on "Pharmacogenomic Approaches in Drug Therapy". One British contributor, Gareth Beevers, sportingly took on the "no" side of a debate on "Do we need new antihypertensive drugs?". Despite his denials that this was the full statement of his position, he made a convincing case that better use of what we have could very effectively advance cardiovascular therapy.

The Summer Meeting, with just under 300 registrants, was held in Edinburgh where we were all received with splendid hospitality and, once again, bright sunshine. Keynote lectures included a masterclass in vascular pharmacology from Chris Garland in his Vane Lecture entitled "Endothelial cells, Hyperpolarization and Vascular Control". David Colquhoun aimed his critical and analytical axe at pseudoscience and managerialism in his Paton Lecture on the "Past Present and Future of Pharmacology" while John Peters gave a fascinating account of "Ion Permeation in Pentameric Ligand-Gated Ion Channels" in his Gary Price Memorial Lecture.

Some nine symposia were held on the three days covering a wide range of topics including "Circadian Rhythms", "Vascular Pharmacology and Oxidative Stress", "Cell Death Signalling" to "Metabotropic Glutamate Receptors". Sadly, there was a big mismatch between the numbers indicating that they would attend these sessions and those turning up - both upwards and downwards, though, in the main, the audience was less than indicated from the registrations. Perhaps the other attractions of Edinburgh proved too good, but it was disappointing for the organizers of the sessions to see their efforts, and those of their invited speakers, rewarded by thinly-populated lecture theatres. Clearly we will have to think about the number of parallel sessions, and the sizes of theatres used in our main meetings. Fortunately the low numbers didn't reflect a lack of enthusiasm for discussion from those present and the outcomes were thought-provoking and stimulating. Poster and oral sessions also showed that much interesting work was still being done by members of the Society and most of those attending seemed to enjoy their participation.

But what do low numbers at the Edinburgh meeting mean? Perhaps members wish to concentrate their attendances on tightly focused meetings. If you have not been to a meeting this year, is it because you feel that none of the sessions was for you? So, if you think your field should be represented in the activities of the Society, why not propose a focused meeting or a symposium at the 2010 Winter Meeting? The Meetings Committee will shortly be making up the programme for 2011/12; if you have a proposal, send it to us soon.

Robin Hiley, Vice-President Meetings

Future Meetings

2009

14-15 December—Drug Discovery Workshop. Open to all (including non-diploma attendees) London, UK. E-mail: meetings@bps.ac.uk

15-17 December—BPS Winter Meeting. The Queen Elizabeth II Conference Centre, London, UK. E-mail: meetings@bps.ac.uk

2010

31 March—Advancing Cardiovascular Research Methods - The role of model systems—joint meeting with the Physiological Society and NC3R's (organized by AWIP). Venue TBC

10 May—Statistics Workshop for PhD students. King's College London, UK. Email: meetings@bps.ac.uk

11 May—Statistics Workshop. Open to all (including non-diploma attendees), King's College London, UK. E-mail: meetings@bps.ac.uk

17-23 July—WorldPharma 2010, 16th World Congress on Basic and Clinical Pharmacology. Copenhagen, Denmark. London, UK. E-mail: meetings@bps.ac.uk

Details of all BPS meetings can be found at www.bps.ac.uk

BRITISH PHARMACOLOGICAL SOCIETY

Today's science, tomorrow's medicines

Winter Meeting 2009

QE2 Conference Centre, London, 15-17 December

Translational Pharmacology-Optimizing Academic/Industry Partnerships, 16 December 2009

Organized by the Younger Members Committee

What is this about?

Industrial/Academic partnerships have been promoted by Government, Research Organisations, and Industry as a means to drive the conduct of more translational pharmacology research. This symposium at the BPS winter meeting will cut through the jargon of high level policy documents to give a practical perspective on what these partnerships mean in practice. The speakers have been chosen for their practical experience of such partnerships and there will be a panel discussion at the end to allow for debate on some of the issues raised.

Who will be speaking?

Big Pharma, SMEs, and Academia working together in pre-competitive research- the AddNeuroMed experience
Professor Simon Lovestone (Professor of Old Age Psychiatry at the Institute of Psychiatry, King's College London and Director of the NIHR Biomedical Research Centre)

Academic/Industrial Partnerships: what Industry has to offer
Dr Richard Peck (Global Head of Clinical Pharmacology, Roche Products Limited)

Two views from the front line- Academic/Industrial partnerships in practice
Tom Longden and Owen Scudamore (BBRC 'CASE' (Collaborative Awards in Science and Engineering) students University of Manchester)

The changing landscape of academic/industrial partnerships- new opportunities and new challenges
Dr Duncan Richards (Clinical Director, GSK Academic Discovery Performance Unit)

Panel Discussion chaired by:
Dr Jim Hagan (CEO GMEC (Global Medical Excellence Cluster))

Who should attend?

There are lots of reasons to attend the BPS winter meeting but we hope that this symposium will be a particular reason to attend this year's event.

The symposium is being organized by the Young Persons' Section of the BPS but the agenda has been designed to appeal to all members of the BPS whether you work in non-clinical or clinical research and whatever the stage of your career.

Further information:
Website: www.bps.ac.uk
Tel: +44(0)20 7239 0110

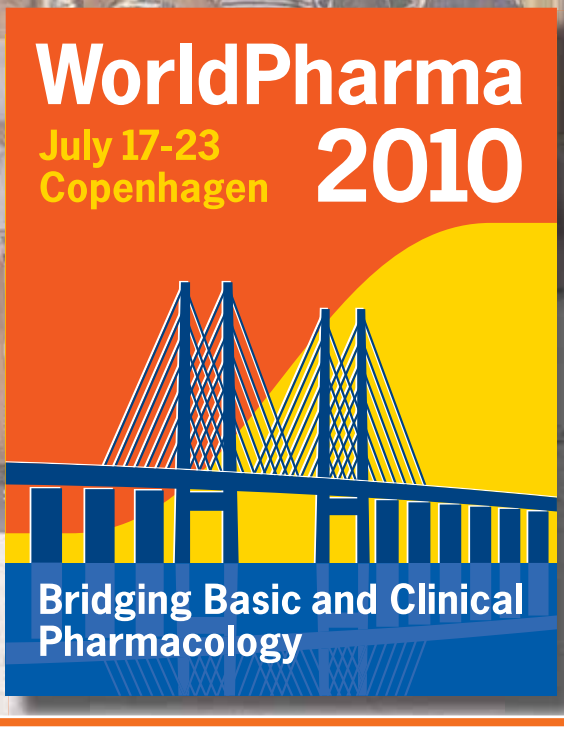
What are your plans for the summer 2010?

How about spending a week in Wonderful Copenhagen in the company of 3000 other top scientists within basic & clinical pharmacology?

In July 2010 basic and clinical pharmacology will come together again to encompass the whole process of drug development from molecular biology to clinical practice.

Here we will discuss how we can work together to meet the needs for safe and effective medicines at affordable prices.

Please find more information on:
www.WorldPharma2010.org



BPS Bain Memorial Bursaries Available!

Up to £1,000 per person for members who are presenting their abstracts at WorldPharma 2010.
Applications welcome until 15 January 2010.
See www.bps.ac.uk for more details and to apply online.