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PHARMACOLOGY MATTERS

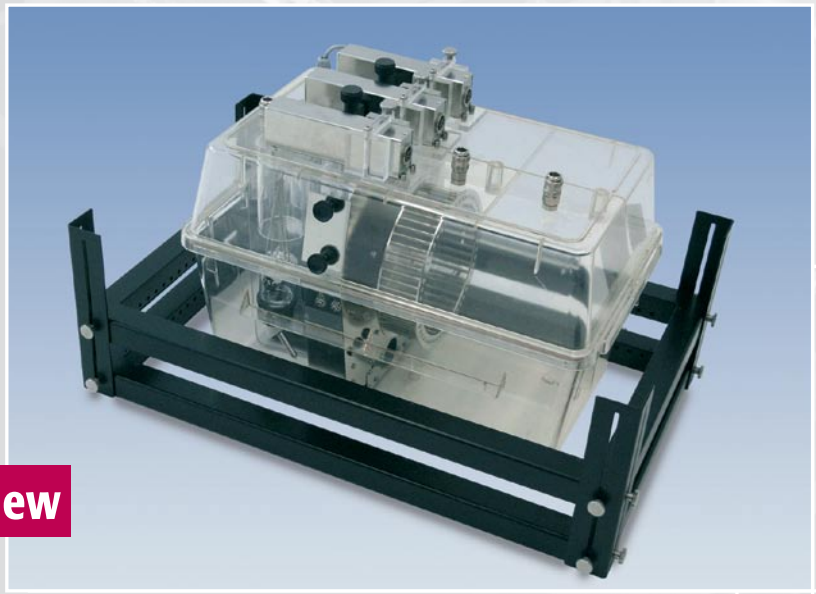
The Newsletter of the British Pharmacological Society
Volume 1 Issue 2

Neuroscience – Phenotyping – Drug Screening

Sophisticated
Life Science Research
Instrumentation

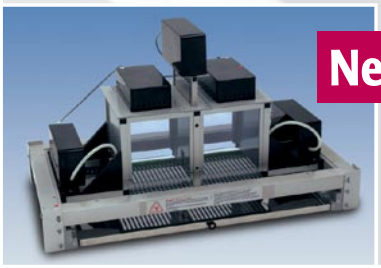
TSE systems

Modular Integrated Phenotyping Systems



New

■ *PhenoMaster System*



New

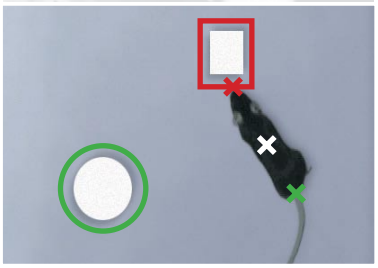
■ *Multi Conditioning System*

■ *LabMaster – Integrated Modular Monitoring System*

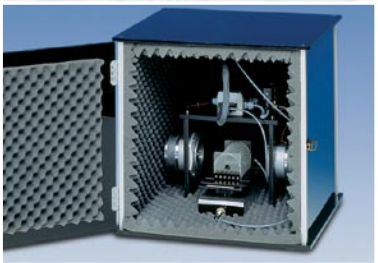
Classical Dedicated Systems

- Conditioning
- Active & Passive Avoidance
- Learning & Memory
- Anxiety & Depression
- Startle Response / PPI
- Activity & Exploration
- Motor Function

■ *Fear Conditioning System Advanced*



■ *VideoMot2 - 3-Point-Tracking*



■ *Startle Response / PPI System*

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Editorial

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

Front cover Image:
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Left-Right
1st row:
E Bülbring
JR Vane
JW Black
2nd row:
JA Gunn
HH Dale
HO Schild
3rd row:
WE Dixon
JH Gaddum
M Vogt

British Pharmacological Society is a company limited by guarantee, registered in England with No. 2877400, Registered Charity no. 1030623.

As readers may be aware, the BPS was founded in 1931 by three pharmacologists: H.H Dale, W.E Dixon and J. A Gunn (see front cover). The very first Society meeting took place in the winter of 1931, with approximately 20 pharmacologists in attendance; 77 years later and the BPS is recognized as one of the premier Pharmacology Societies in the world with an international membership of over 2500 pharmacologists, clinicians, and associated health practitioners.

In this issue of Pharmacology Matters we highlight a selection of the Society's past and present activities, to reflect our continued commitment and contribution to the future of pharmacology.

The first section is composed of two historical articles, including Humphrey Rang's retrospective look at the Gaddum and Picarelli paper, 'The impact of the tryptamine receptor'. This article, first published in 1957, is Gaddum's most highly cited paper.

Following this, we move into a section authored by several young winners of the following BPS awards: AJ Clark, Schachter, and the ASIF Vacation Studentships. Their individual accounts of how the awards and BPS support have helped them and their career development makes great reading, and I hope it will encourage more of our younger members to write articles for PM.

The third section includes several articles detailing our efforts in education and career development. Over the last 12 months, for instance, we have focused on improving the accessibility and appeal of pharmacology to secondary school students (Practicals in Schools pg 19) and continue to assist the career development of post-doctoral researchers (BPS Diploma pg 21 and Women in Pharmacology pg 26). Finally on page 32 you will find the regular report from our Meetings Vice President, Mandy MacLean, who is also the latest winner of the Estelle Grover Award.

Enjoy!

Hazel O'Mullan
Managing Editor

Contents:

Sign up for BPS Media Team!

The BPS is trying to increase their media profile and is currently looking to recruit a panel of experts to provide media support for the media enquiries that the society receives on a regular basis. To be part of this initiative, you will need to be available at short notice for any TV, internet, press, and radio interviews relating to your area of expertise. The BPS office will be the first point of contact for enquiries, volunteers will not be **contacted directly by journalists. Should you wish to partake, please provide a very brief CV containing the following:**

Title, Name, Current Appointment, Current Affiliation, Address, Email, Land line, Mobile Phone, Area of Expertise and Previous Media Training

For further information, please contact Anna Muir at aam@bps.ac.uk or 0207 239 0184

View From Angel Gate

Kate Baillie
Chief Executive, BPS

EPHAR 2008

As BPS members will have seen from recent e-versions of *Pharmacology Matters*, the major activity for BPS since the last issue was the successful delivery of the EPHAR 2008 Congress in Manchester.

Attracting nearly 800 delegates from 49 countries, the meeting provided an ideal opportunity to showcase the BPS. Furthermore, bursaries provided to delegates from 16 countries enabled those who might not otherwise have been able to attend to present their work, gain exposure to cutting edge science, and network with colleagues from all over the world.

The Society's ASIF (Anniversary Strategic Initiatives Fund) also provided financial support and bursaries for the International Workshop on Methods in Cardiovascular Pharmacology, held directly after the meeting. This gave non-UK PhD students and young researchers the chance to learn more about modern methods in cardiovascular pharmacology, from single cell fluorescence and electrophysiology to myography and whole-heart dynamics. In addition to lectures and poster presentations, delegates were able to participate in practical demonstrations of related techniques.

We also received considerable internet media coverage of the event – the intriguingly titled press release *Weeding out the highs of medical marijuana*, based on Roger Pertwee and Chris Fowler's work, resulted in interviews with BBC Radio Manchester and BBC Radio 4, and an article published in the Spanish newspaper *Publico*.

Thanks are particularly due to Alex Waddington and Aeron Howarth (from Stehm Media), Mick Bakhle, and Anna Muir for their hard work in co-ordinating press and public relations during the EPHAR Congress. Given the success of this pilot, the BPS External Affairs Committee has agreed to support further proactive media relations activities at the Winter Meeting in Brighton.

BJP and BJCP

Other news of major importance to the Society is that from 1 January 2009, Wiley-Blackwell will publish both the British Journal of Pharmacology (BJP) (currently published by Nature Publishing Group) and the British Journal of Clinical Pharmacology (BJCP).

The interest shown in our journals by companies keen to publish them on our behalf was considerable, and from eight tenders received, four were short-listed. Major advantages will result from having the same publisher for both journals, especially the potential for coordinating strategy and contents so as to cover the whole span of pharmacology in a more integrated way. This will undoubtedly reinforce the points raised by Jeff Aronson in his article on page 6 about the continuing need for close collaboration across the basic–clinical spectrum.

The BJP editorial office will remain at Angel Gate until mid-2009, to ensure a smooth operational transition to the Wiley-Blackwell office in Oxford.

Education

On the educational front the BPS continues to be proactive, particularly since the appointment of Jude Hall at the start of the year as Education and Training Manager. Readers will find articles of interest in this issue related to the Diploma in Advanced Pharmacology (page 21), the launch of the Biosciences Federation/Nuffield Curriculum Council website aimed at biology students in schools and colleges www.practicalbiology.org (page 19), and the Women In Leadership seminar organized by the Women in Pharmacology subcommittee (page 26).

Prescribing

The BPS Prescribing group has recently transferred from the auspices of the Education and Training committee to the Clinical Section, and we are delighted to announce that Simon Maxwell has agreed to Chair this group, Helen Leathard having stepped down. Many thanks to Helen for all her hard work.
Simon has highlighted some of his plans for this group on page 24, and we can also confirm that the BPS has agreed to sponsor a major symposium at the EACPT meeting in Edinburgh next July, with the title *Clinical Pharmacology—Working with Patients*, following on from the success of this year's joint BPS/RCP meeting on *Rational Prescribing* in May.

Kate Baillie, Chief Executive, BPS

Renaming Ionotropic Glu Receptor Subunits

Resolution of a Sticky Problem?

'Scientists would rather share a toothbrush than nomenclature' goes the adage. However, to facilitate communication and to avoid unnecessary confusion, widely agreed nomenclatures for all pharmacological targets are highly desirable.

The International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) is a body that issues recommendations for receptor and ion channel classification. It addresses contemporary issues in pharmacology, classifying the major receptor and ion channel systems in the human genome and depositing the data on a freely available web site (www.iuphar-db.org). The development of the database is currently financially supported by several sources, including a prominent contribution from the BPS. NC-IUPHAR has recently directed its efforts in receptor nomenclature to include the ligand-gated ion channels (LGICs) (Collingridge *et al.*,2008). The frequently heteromultimeric nature of the LGICs makes this a daunting task, but their component subunits present a tractable starting point. The LGICs are usually defined as the nicotinic acetylcholine, 5-HT_3, $GABA_A$, glycine, ionotropic glutamate, and P2X receptor families. In surveying the literature, the nomenclature across all but the ionotropic glutamate receptor subunits is quite consistent, with the exception of the variable use of subscripts to denote the identity of a subunit within a structural family. For the reasons detailed in Collingridge *et al*. (2008), it is recommended that subscripts should not be used to denote a subunit but instead reserved to indicate stoichiometry when this is known. Thus, the major $GABA_A$ receptor isoform in the brain would be designated $(\alpha1)_2(\beta2)_2\gamma2$ when an indication of stoichiometry is required, but more simply and conveniently $\alpha1\beta2\gamma2$ in routine use. Further examples and a more detailed rationale are given in Collingridge *et al*. (2008) and Olsen and Sieghart (2008).

The primary motivation behind this letter is to alert members of the Society to a more radical proposal to rename the ionotropic glutamate receptor subunits (*i.e*. the NMDA, AMPA, and kainate families) for which multiple and sometimes illogical nomenclatures exist. The origins of these idiosyncratic schemes, which are likely to dismay all but experts, have been elegantly reviewed by Lodge (2008). In outline, the NC-IUPHAR ionotropic glutamate receptor subcommittee, whose members are listed in Collingridge *et al*. (2008), propose the naming of all subunits to commence with 'Glu', reflecting the abbreviation of the natural transmitter in conventional three letter code. This is then followed by the letter N, A, or K, to reflect membership of the **N**MDA, **A**MPA, or **K**ainate subunit families. Finally the subtype of subunit within a family is added to complete the name, this being either a single number or the combination of a number and letter. Hence, the AMPA receptor subunit that has most commonly been denoted as GluR1 (or GluRA) becomes GluA1, whilst GluR2 (or GluRB) changes to GluA2, with a similar conversion applying to the two remaining members (now GluA3 and GluA4). Happily, this renaming aligns subunit and gene names much more closely (*e.g*. GluA1 and *GRIA1*). Similarly, the NMDA subunit most commonly called NR1, or NMDA-R1, is renamed GluN1 (the gene being *GRIN1*) and that previously termed NR2A, or NMDA-R2A, becomes GluN2A (gene name *GRIN2A*). These changes should not prove too taxing to remember. However, the kainate receptor subunits, which have most commonly been termed GluR5, GluR6, GluR7, and KA1 and KA2, posed a special difficulty and were extensively debated by the subcommittee, with the eventual outcome that they will be renamed GluK1, GluK2, GluK3, GluK4 and GluK5 respectively. Such a scheme harmonises with the gene names, which are *GRIK1* through to *GRIK5* respectively. Although in the interim the conversion in numbering may require a degree of cerebral activity, perhaps involving kainate receptors, it will be worth the effort if a subunit nomenclature that is consistent and logical is widely adopted.

Graham Collingridge, University of Bristol, UK
Richard Olsen, University of California, USA
John Peters, University of Dundee, UK
Michael Spedding, Servier, France

Collingridge GL, Olsen RW, Peters J, Spedding MA (2008). A nomenclature for ligand-gated ion channels. *Neuropharmacology* doi:10.1016/j.neuropharm.2008.06.063.

Lodge D (2008). The history of the pharmacology and cloning of ionotropic glutamate receptors and the development of idiosyncratic nomenclature. *Neuropharmacology* doi:10.1016/j.neuropharm.2008.08.006

Olsen RW, Sieghart W (2008). International Union of Pharmacology. LXX. Subtypes of γ-aminobutyric $acid_A$ receptors: Classification on the basis of subunit composition, pharmacology, and function. Update. *Pharmacol Rev* doi: 10.1124/pr.108.00505.

The Pharmacological Network

Jeff Aronson,
President, BPS

"There is an urgent need to develop individuals who have the ability to combine a firm grounding in the principles of basic and clinical pharmacology with the most modern research technologies to address complex (patho)physiological questions" The Wellcome Trust, 2007

I have elsewhere portrayed clinical pharmacology as a spectrum, ranging from basic pharmacology in humans at one end to applied pharmacology at the other [1]; one version of this depiction [2] is reproduced in Figure 1. It reflects the current interest in how to link 'molecules to man' and go from 'bench to bedside' and beyond.

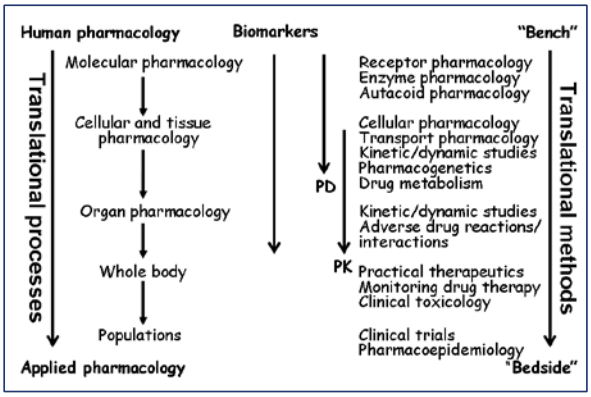

fig 1

However, this linear model of science, like the model that Vannevar Bush propounded in the aftermath of the Second World War as a strategy for the future of US scientific development [3], and which dominated scientific thinking for many years [4], is an incomplete account of what actually happens. It gives the impression that practical applications proceed in a direct line from basic discoveries and neglects the important feedback to basic research from clinical findings that informs further research. This to-ing and fro-ing is familiar to those who, whether clinical or non-clinical scientists, have experienced the intellectual stimulus of collaboration across the spectrum, and it prompts me to depict what we do in a different way—as a network (Figure 2).

In this representation I have identified four discrete systems. These four systems are subdivided into two pairs. The top two systems include the basic tools that clinical and non-clinical pharmacologists use and the bottom two include the practical applications of the findings that result. These systems all talk to each other. For example, understanding basic pharmacological principles, such as the nature and actions of receptors, informs the clinician in teasing out the pharmacodynamic actions of drugs, and pharmacokinetic-pharmacodynamic (PK/PD) studies provide one way in which feedback is achieved. Similarly, the results of clinical trials and observational studies in large populations inform clinical practice in the individual patient, and here the major feedback link is via evidence-based medicine, using techniques such as meta-analysis and teleoanalysis [5]. For the sake of simplicity I have omitted some arrows from the diagram, for example the to-and-fro link between basic clinical pharmacological studies and practical drug therapy. However, at the heart of all this, and providing the missing links, is the study of biomarkers, to which all aspects of pharmacology contribute. And drug development hovers invisibly over the whole structure.

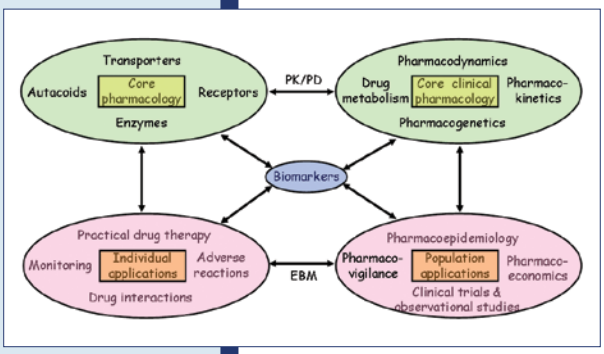

fig 2

These two models are not mutually exclusive. Each depicts an important aspect of what pharmacology means for both clinical and non-clinical scientists. The model in Figure 1 stresses the depths of the subject and informs the concept of 'translational medicine'. That in Figure 2 shows how scientific and clinical developments go hand in hand and talk to each other, information from one area informing research in another.

In his 1959 Reith lectures, Peter Medawar said that 'the bells which toll for mankind are—most of them, anyway—like the bells of Alpine cattle; they are attached to our own necks, and it must be our fault if they do not make a cheerful and harmonious sound.' His simile was not quite apt—Alpine cattle have no control over the sound of their bells—but we know what he meant. Adapting his imagery, we might say that our techniques and their applications are like church bells, and it is our fault as bell-ringers if they do not make a cheerful and harmonious sound when we ring out our message.

The major difference between clinical and non-clinical pharmacologists is that the former spend some of their time contributing directly to patient care in one way or another, implementing and monitoring practical drug therapy and teaching and developing policies about it. At other times they are largely indistinguishable—there are non-clinical pharmacologists whose research is clinical and there are clinical pharmacologists doing bench pharmacology in human or animal tissues. Recognition of the dual role that we all play, and close collaboration across the basic/clinical spectrum, will help us to win the translational bell-ringing competition.

Jeff Aronson, University of Oxford

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Classics from BJP: Gaddum & Picarelli (1957)

Humphrey Rang
BJP Editor-in-Chief

The study of chemical mediators and the effects that they produce has been at the heart of pharmacology ever since its inception. Where there was an anatomical gland, such as the thyroid, pancreas or adrenal, the focus was on identifying the hormone, understanding its relevance to human disease and devising ways to replace it when deficient. The discovery of neurochemical transmission in the 1920s and 1930s brought a fresh wave of understanding, focused particularly on acetylcholine and noradrenaline. The third leg of the tripod came from the study of active substances ('autacoids') derived from blood and tissues, among them histamine and 5-hydroxytryptamine. Classifying the numerous, and bewilderingly complex, actions of these substances became an engrossing task for many pharmacologists, notably the founding editor of the British Journal of Pharmacology and Chemotherapy, J H Gaddum, then Professor of Pharmacology in Edinburgh.

Gaddum's most highly cited paper (900 citations to date), published in BJP in 1957 with Z P Picarelli as co-author, is entitled simply 'Two kinds of tryptamine receptor'. It came at a time when the concept of receptors was coming to the forefront of pharmacological thinking after a long period in limbo (due in large part to Henry Dale's low opinion of theoretical ideas not grounded in solid evidence). Its revival stemmed largely from the work of A J Clark, H O Schild , and others, as well as that of A J Ahlquist, who first postulated the existence of two distinct (α & β) catecholamine receptors to account for the varied effects of different catecholamines.

Gaddum & Picarelli's classic paper is actually a follow-up of an earlier paper in BJP (Gaddum & Hameed, 1954) describing the effects of various antagonists, including dibenamine and LSD, on the actions of 5-HT on a range of tissues. They concluded: 'The effects of various 5-HT antagonists can be explained on the theory that there are two types of tryptamine receptor. One type is present in the smooth muscle of the uterus and ear and is specifically inhibited by low concentrations of…(LSD). The second type is present in the nervous tissues of the ileum, and is not inhibited by LSD.' Gaddum and Picarelli (1957) focused on the effects of two inhibitors, dibenzyline and morphine, on the effects of 5-HT on the ileum, concluding that responses mediated by M-receptors in the nervous tissue were blocked by morphine, while those of D-receptors in the smooth muscle were inhibited by dibenzyline. There is an element of confusion in Gaddum and Picarelli's paper about how morphine actually worked. They say at one point: 'The receptors which were blocked by morphine have been called the M receptors…….', but they later quote previous studies showing that morphine inhibits a variety of neurally-mediated responses of smooth muscle preparations evoked by different stimuli, and conclude in their final sentence '…..there is no proof that they (i.e. 5-HT and morphine) act on the same receptor as one another'. Despite the uncertainty, the world quickly adopted the M and D receptor terminology, although it later seemed to sit awkwardly alongside the classification into 5-HT_1 and 5-HT_2 subtypes derived from binding studies (Fillion et al, 1977; Peroutka et al. 1981). Confusion reigned for a while, until Bradley et al (1986) identified Gaddum's D subtype as the 5-HT_2 site detected in binding studies, and christened the neuronal M-receptor 5-HT_3. Finally in 1994, the combined wisdom of 8 distinguished experts was brought to bear (Hoyer et al, 1994), under the auspices of IUPHAR, to propose a new classification, including 13 distinct subtypes of G-protein-coupled 5-HT_1 and 5-HT_2 receptors and a single ligand-gated ion channel, the 5-HT_3 receptor. The ball that Gaddum and Picarelli started rolling, based on the very limited range of pharmacological agents available to them, engendered copious research on the functional, anatomical, and pharmacological properties of 5-HT receptors (see the recent review by Green 2008), from which has stemmed an exceptionally diverse range of therapeutic drugs (for example: cyproheptadine, buspirone, fluoxetine, ondansetron, sumatriptan, tegaserod), targeting many of the known receptor types and transporters. Among the chemical mediators, 5-HT can claim to have spawned, not only the greatest number of receptor subtypes, but also the greatest number of useful drugs. So far, we have reached 5-HT_4 with tegaserod, and agents targeted at 5-$HT_{5,6 \text{ and } 7}$ wait in the wings. Overall, a remarkable therapeutic cornucopia.

Humphrey Rang, Editor in Chief, BJP

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Writing Pharmacological History

Dick Barlow

Collecting pA_2s or Clark, Gaddum, Schild and pA2 and the binding of drugs to receptors

Dr R.B. (Dick) Barlow has worked in Oxford, Edinburgh, and Bristol and is a leader in the field of study relating to determination of mechanisms of drug receptor interactions. He became an honorary fellow of the BPS in 1995 and recently gave an oral communication at the Manchester EPHAR meeting remarkably, 60 years after his first communication (on decamethonium) to BPS at the Edinburgh meeting in 1948.

Here Dr Barlow writes a historical reflection on some of the problems encountered in the measurement of antagonist activity, concentrating on the importance of, and what can be done with, a collection of antagonist affinities.

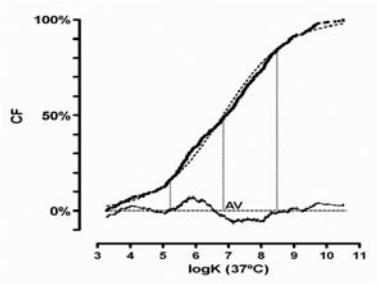

Figure 1 Distribution of values of logK (n=430). The broken line shows the curve for a single population with the mean, AV, AV-SD(16%) and AV+SD (84%) indicated. The difference between the experimental values of CF and the value for a single population is shown suitably magnified by the bottom line (with values below and above CF=0).

When the title of the BPS Bulletin was replaced by 'pA2' in 2003 the BPS former President, Graeme Henderson, found it necessary to explain 'pA2' for the benefit of 'members of the Society who have entered pharmacology from another discipline'. This stirred me to write an article 'The slopes of concentration-effect (dose-response) curves or Clark, Gaddum, Schild and pA2', which appeared in pA2online/Vol1 Issue2. In it I tried to put into perspective the developments between 1937 and 1946 which led to pharmacologists being able to measure the binding of competitive antagonists to receptors. These developments led indirectly to Stephenson's landmark paper 'A Modification of receptor theory' nearly 10 years later (Stephenson, 1956), because Schild's original paper (Schild, 1947) on the determination of antagonist activity included a description of how you could automate the experiments. Stephenson was able to make similar equipment, which made his work possible. With the recent introduction of a new title for the bulletin, Pharmacology Matters, it seemed appropriate to look again at antagonist affinities; this article describes the importance of collecting values of logK/pA2.

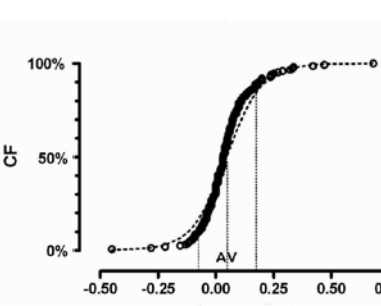

Figure 2 Cumulative frequency (CF) plotted against values of log.K(30°)-log.K(37°): n=150. The values of ΔH corresponding to AV-SD, AV and AV+SD are = -4.4, 3.1, and 10.6 kcal mol-1 (-18, 13 and 44 kJ mol-1) respectively.

Obtaining the collection of antagonist activities

Measuring the activity of antagonists had always been a problem for pharmacologists. Schild (1947) showed how you could measure their activity as a log equilibrium constant, dependent only on temperature. With agonists you could compare concentrations producing matching effects, but these depend on ability to activate receptors (efficacy) as well as on affinity. Although much is now known about the mechanisms by which agonists operate, if you want to understand the binding of drugs to receptors, it makes sense to start with competitive antagonists.

Like Schild's results, those described here were obtained with guinea-pig isolated ileum at 37˚C. The compounds tested were antagonists acting at muscarinic acetylcholine receptors, and the first work (Barlow, Scott & Stephenson, 1963) involved measuring the effects of the replacement of methyl groups by ethyl in the onium group, -N+Me3, of five series of antagonists (20 compounds). The effects on affinity appeared to be similar in all the series, a rise with one methyl group replaced by ethyl, a plateau with two, and a fall with the -N+Et3 compound.

Values of logK are directly proportional to the free energy of binding,-ΔG = RT lnK, where R is the gas constant and T is the absolute temperature (by convention the absorption of heat is considered positive). The results can be explained by supposing that the replacement of a methyl group by ethyl makes a contribution, a, to the free energy of binding, independent of the actual values of logK. If this applies also to the affinities of compounds that are agonists, it should be possible to calculate the effects of the change on their efficacy. When the series of antagonists was extended, however, it was clear that altering the onium group had different effects in different series (Abramson et al. (1969). When compounds were taken in pairs, with and without a particular group, the 'group effect', ΔlogK, varied widely. Over the years I have accumulated more than 400 values of logK/pA2 (means, se< 0.1 log unit). Each is a sounding of the receptor surface and combined with the geometry of the compound may make it possible to obtain a sort of chart.

The simplest hypothesis, that the values of logK all belong to a homogeneous population, can be tested by constructing a cumulative frequency curve. The values are arranged in order, and the cumulative frequency (CF) of the result ranked i out of n is i/n. For a single population the ranks should be distributed normally, with CF= 16% for AV-SD, 50% for AV, and 84% for AV+SD. The line is the integrated normal frequency curve. The distribution (Fig 1) shows that the population is not homogeneous and contains more than two components. This should not be surprising. It is likely that binding involves different handholds or footholds within the receptor area. It is also to be expected, because the free energy of binding depends on two independent properties, the change in enthalpy, ΔH, and the change in entropy, ΔS: ΔG = ΔH - TΔS. The enthalpy change is related to the effect of temperature on logK: ΔlnK/(Δ1/T) = -ΔH/R.

In a search for selective antagonists at muscarinic re-

ceptors, paired measurements were made on ileum at 30° and 37°C, and I had 150 sets of values of logK at these two temperatures. The distribution of the values of the difference between them, ΔlnK, gives some idea of the range of values of ΔH (Fig.2). Although the errors attached to estimates of temperature on logK make it difficult to put an exact value on the enthalpy of binding, the distribution indicates that this is an appreciable fraction of the energy involved in binding (if log K=10, ΔG = -14 kcal (-58kJ) mole^{-1}).

There must be a similar variation in the entropy of binding- compounds are interacting with different areas within the receptor. Entropy depends not only on the geometry of the drug and receptor but also on water. The binding of a drug with an ionic mass of 300 must involve the relocation of 15-20 water molecules. By taking compounds in pairs and calculating group effects (ΔlogK) they may have similar entropies. The distribution of group effects should be simpler than that of logK. Some effects, such as the difference between series of n-pentyl compounds and ethoxyethyl compounds (-CH_2- replaced by –O-), appear to come from a single population. For many there are two components and with some it is clear that there are steric constraints which limit binding. In a particularly interesting example it is possible to recognize three components. Two can be identified from the cumulative frequency curve (Fig. 3) for the difference between series of ethoxyethyl compounds and esters (-CH_2-O- and –CO-O-; n=24). The diphenylethyl ethers are much weaker than the diphenylacetyl esters, the cyclohexylethyl ethers are stronger than the esters, and the phenylethyl ethers are only slightly stronger than the esters. There are, in fact, significant differences between all three sets (Anova, P <0.05). Buchwald & Bodor (2006) suggested that differences in the activity of compounds of this type can be ascribed to differences in metabolism, but in these experiments the antagonist solution is replaced at least every 90 seconds. The differences must involve the interactions between drug and receptor and the explanation may well involve differences in effects on water. In aqueous solution the esters are slightly smaller than the ethers. The increment in apparent molal volume at infinite dilution, Δφov = 2.6 to 4.7 cm^{3}mol^{-1} (25°C): for the difference between n-pentyl compounds and the ethers, Δφov = 10.9 cm^{3}mol^{-1} (-CH_2- bigger than –O-).

Importance of collecting antagonist activity values

Values of logK/pA2 and of group effects, combined with knowledge of the geometry of suitable (preferably rigid) compounds, can go some way towards suggesting where there are pockets within a receptor area but it obviously makes sense to include any information that can be obtained about the structure of the receptor itself. The two approaches should be complementary. Models of receptor structure must be compatible with experimental values of logK, just as suggested steric restrictions from limits to group effects must be backed up by evidence from receptor conformation. A collection of information about receptors is kept in Edinburgh – though there does not yet appear to have been much work on muscarinic receptors in guinea-pig ileum, should there not also be a collection of values of logK/pA2? This would have the advantage of preserving useful information and making it possible to compare group effects for compounds acting at different receptors. The group effects of replacing hydrogen by an aromatic group in antagonists acting at nicotinic receptors in the frog rectus abdominis muscle, for instance, are less than 10% of the group effects of replacing hydrogen by phenyl in antagonists acting at muscarinic receptors in guinea-pig ileum, Schild's work included measurements of antihistamines as well as

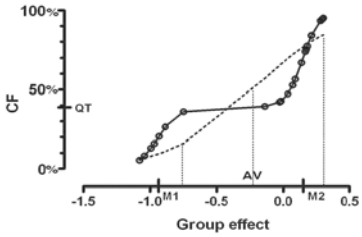

Figure 3 Cumulative frequency plotted against group effect, logK(-CH2-O-) - logK(-CO-O-): AV= -0.225, sd 0.53, n=24. The full line shows a least-squares fit for two populations with means M1 and M2 and the proportion of the lower component,QT=38%. In an analysis of variance the means are -0.941, 0.051 and 0.215 and the least significant difference between means is 0.102 (p=0.05). There are also significant differences (p=0.05) between the groups using a Kruskal-Wallis test.

antagonists of acetylcholine acting on guinea-pig ileum and of atropine, and it would be extremely interesting to compare group effects for the two types of receptor.

My collection of results consists of tables of logK/pA2 values and also apparent molal volumes, along with an appendix containing group effects and their analysis. These are in the form of word.doc files, and I should be happy to make them available to anyone interested. Perhaps these could form the start of a library such as I am suggesting. I think Schild would have approved of this idea! Pharmacology matters - receptor models must be checked against actual pharmacological results.

Anyone wishing to take up Dr Barlow's offer can contact Hazel O'Mullan (hom@bps.ac.uk)

PS The X-ray crystal structure of some of the compounds is available from the Cambridge Crystallographic Data Centre and the possibility of linking this with the collection is being explored.

Dick Barlow, Honorary Fellow BPS

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My sincere thanks to:

Susan Bond, Division of Neuroscience, School of Biomedical Science, Edinburgh University for help with the figures.

Younger Members News


Stephanie Francis

New Sub-Committee Members

This winter we welcome two new members to the younger member's sub-committee, James Dear (University of Edinburgh) and Sara Barnes (University of Cambridge). We hope they will enjoy being part of the team and will soon become actively involved in making decisions regarding our current issues, including the organization of forthcoming events.

EPHAR Manchester, July 2008

The younger members' committee were delighted with the success of the young persons networking event at EPHAR in July. Our thanks go to Professor Roger Corder for helping to make this evening an interesting and enjoyable event for all our guests. Our thanks also go to Tom, Annie and Sarah for all their hard work on behalf of the younger members' sub-committee (a more detailed account of this event went out in the July e-bulletin and on the EPHAR website).

Our congratulations go to the winners of the young pharmacologist prizes: Nimesh Patel (William Harvey Research Institute, London, UK) and Phillip Robinson (University of Manchester, UK) joint winners of the best oral presentation, and Sarah Pitkin (University of Cambridge, UK) and Chloe Young (University of Manchester, UK), joint winners of the best poster presentation.

Winter BPS-Brighton December 2008

After the success of our young person's event at EPHAR we have now planned a young pharmacologist social event on Tuesday 16 December. This will follow the welcome reception and will incorporate a team-based pub quiz and an informal buffet; there will even be a few team prizes up for grabs (the venue has been confirmed as 'The Latest Music Bar'.) All members are welcome, and we hope it will provide important networking opportunities in the Society. Please contact the BPS office to purchase your tickets.

The BPS, in collaboration with Trends in Pharmacological Sciences (TIPS) will be holding a Young Pharmacologist of the Year competition and prize symposium on Wednesday 17 December. We look forward to seeing our younger members presenting and hope that those not participating in presenting will support their fellow members by attending the symposium. We are confident that this will be an enjoyable and interesting session.

This year we are sponsoring 21 undergraduate students to attend the winter meeting. This will provide these students with the opportunity to present their work. All their posters will be presented on Wednesday 17 December to form part of the Younger Members' day.

Sponsored Student Society Pharmacology Talks

We are beginning to approach a number of University Pharmacology/Biomedical departments and student societies with the aim of starting to sponsor pharmacology related talks. Your attendance at such events will enable us to be in contact with undergraduate students, encouraging enthusiastic individuals to become involved with the Society as well as giving them an opportunity to hear talks from renowned scientists on interesting and relevant subjects.

Stephanie Francis, Younger Members Editor

Prizes and Awards the winners 2008

Gaddum Memorial Award
Professor Arthur Weston

Rang Prize GRAC editors:
Dr. Steve Alexander
Professor Alistair Mathie
Professor John Peters

J R Vane Medal
Dr. Pat Humphrey

Novartis Prize
Dr. Victoria Chapman

Bill Bowman Travelling Lectureship
Dr. David Wyllie

Aptuit Prize
Dr. Felicity Gavin

ASIF Awards: Vacation Studentships
Myrna Carlebur
Amanda Pugh
Elinam Gayi
Ben Samson
Will Owen

Research Collaboration Grant
Dr. Andrew Ramage

Post-Doctoral Support
Dr. Ross Corriden

AJ Clark Studentship
Sara Barnes

Schachter Award June 2008
Tim Funnell, University of Oxford, for his visit at the University of Bristol to learn artificial membrane-bilayer electrophysiology with Dr Rebecca Sitsapesan

The GlaxoSmithKline Prize for Research in Clinical Pharmacology
Dr. Michael Eddleston

Report from the AJ CLark Award Winner 2005: Nadia Luheshi

Nadia has spent the last three years studying as an AJ Clark funded PhD student at the University of Manchester, working alongside Prof. Nancy Rothwell and Dr. David Brough. Her PhD research focused on investigating the intracellular trafficking and actions of a key proinflammatory cytokine, interleukin 1 (IL-1).

I am really grateful to the British Pharmacological Society for its support during my PhD. It has been an invaluable learning experience, and I hope that the discoveries I have made during my studies provide a valuable contribution to our understanding of cytokine biology.

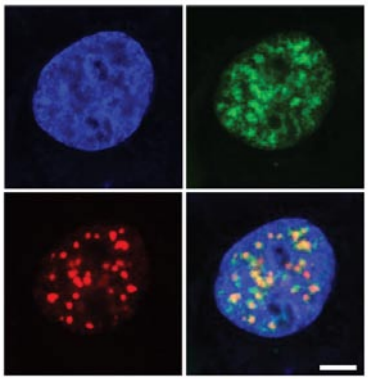

Image: The co-localisation of pro-IL-1α-GFP with SC-35 in ATP-epleted cells Pro-IL-1α-GFP (green) co-localisation with the nuclear speckle marker SC-35 (red) was analysed in ATP-depleted, immunostained COS-7 cells, co-stained with DAPI (blue). Scale bar represents 5 μm.

IL-1α and β: secreted cytokines that may also act inside cell nuclei

Inflammation is vital for host defence against infections and tissue injury. However, dysregulated inflammation contributes to the pathogenesis of major peripheral and brain diseases. IL-1 is a key proinflammatory cytokine and is implicated in the pathogenesis of many of these diseases. IL-1α and β, the best characterized IL-1 family members, are produced by cells as cytoplasmic precursors. Both proteins are assumed to act primarily following secretion, via activation of transmembrane IL-1 receptors on IL-1-responsive cells. All current anti-IL-1 therapeutic strategies target these extracellular IL-1 actions.

However, there is evidence that pro-IL-1α can act inside the nuclei of IL-1 expressing cells. These intranuclear actions remain a poorly understood, potentially important area of IL-1 biology. The objective of my PhD was therefore to investigate the intracellular trafficking and intranuclear actions of IL-1α and β.

Cell density-regulated IL-1 nuclear localization in microglia

While IL-1α is reported to have intranuclear actions in peripheral cells, it is not known whether it has similar intranuclear actions in brain cells. Therefore, we tested the hypothesis that IL-1α and β localize to the nuclei of microglia, the main IL-1-producing cells in the injured brain. Using immunocytochemistry and cell fractionation, we discovered that both pro-IL-1α and β produced by microglia in response to bacterial lipopolysaccharide localize to microglial nuclei. Nuclear localization of both cytokines was regulated by local cell density, a highly relevant factor in neurodegenerative diseases, where microglia experience profound changes in local cell density and microenvironment.

The dynamics and mechanisms of IL-1 nuclear import

While IL-1α is known to contain a nuclear localization sequence (NLS), allowing pro-IL-1α active nuclear import, the mechanism of IL-1β nuclear import remains unknown. Therefore, we tested the hypothesis that IL-1β nuclear import, like that of IL-1α, is an active process, dependent on a putative pro-IL-1β NLS. Using IL-1-β-galactosidase and IL-1-GFP chimeras (analysed by fluorescence recovery after photobleaching), we discovered that nuclear import of pro-IL-1α is exclusively active, dependent on its NLS and the small GTPase Ran, whilst pro-IL-1β nuclear import is entirely passive.

Intranuclear actions of IL-1

The current evidence for IL-1α intranuclear effects on cell proliferation, migration, gene expression, and RNA splicing is contradictory. Furthermore, since IL-1β is assumed to be primarily secreted, the effects of intranuclear IL-1β remain unknown. Therefore, we investigated the nature of pro-IL-1α and β intranuclear actions.

In contrast to previous reports, we found no evidence for a role of intranuclear pro-IL-1α in the regulation of proliferation, IL-6 expression, or Bcl-X alternative splicing. However, we found that ATP depletion led to immobilization of pro-IL-1α-GFP in nuclear speckles, storage sites for RNA splicing proteins, and to enhanced pro-IL-1α co-localization with the histone acetyl transferase, p300. This preliminary evidence suggests that intranuclear pro-IL-1α may interact with RNA splicing proteins and p300.

These data provide support for the hypothesis that IL-1α and β have intranuclear actions in IL-1 expressing cells, and provide new insights into the dynamic regulation of intracellular IL-1 trafficking.

Life as an AJ Clark Student

In addition to spending a lot of time in the lab, I have had the opportunity to present my findings at conferences, including Life Sciences 2007, the VIIIth European Meeting on Glial Cells in Health and Disease, and most recently at Toll 2008: Recent Advances in Pattern Recognition. I have also really enjoyed talking about science with Manchester school children during Brain Awareness Week.

During my PhD I have learnt a great deal from the various training courses I have been able to attend, at the University of Manchester and elsewhere. The Astra Zeneca Biosciences in Drug Discovery course in January 2008 was a real highlight. Learning more about how commercial companies pursue the discovery of new drugs provided a new perspective on the nature and role of pharmacological research. Presentations from academic collaborators with AZ also revealed how industrial-academic partnerships can develop. I am now about to take up a post doctoral position with Dr. David Brough, who has co-supervised me during my PhD. I will be continuing to investigate IL-1 biology, focusing on mechanisms of IL-1 processing and release.

Nadia Luheshi, University of Manchester

AJ Clark Award Winner 2008 Profile: Sara Barnes

Sara Barnes
University of Cambridge

Sara (pictured) grew up in a small village outside Louth on the east coast of Lincolnshire. In 2004 she enrolled in a 6-year Medicine course at Cambridge University. Part of the course involved studying a Natural Science or an equivalent subject in the 3rd year, and Sara chose Pharmacology. She was rewarded for her hard work through her achievement of a First-class Honours degree in Natural Sciences (Pharmacology) in June 2007. This completed the third year of a much longer six-year course. However, her achievements in Pharmacology emphasized her desire to pursue a career in Pharmacology and she soon realised that research in this field was the career path that she wanted to follow.

Why did you decide to embark on a PhD?

The final year of my undergraduate course really fired up my enthusiasm for Pharmacology – I enjoyed reading the literature and getting to understand a topic in depth, and I also liked learning new techniques in the lab and using them in my project. I felt stretched during that year and knew that I wanted to pursue a career in research.

However, my BA degree in Pharmacology formed the 3rd year of a much longer six-year Medicine course I was enrolled on at Cambridge. I was expected to move on to 3 years of Clinical Studies and then become a medical doctor, but after a few months of Clinical training I realised that it just wasn't for me – I was more at home in the lab than in a hospital.

How did you find out about the A J Clark Award and do you feel there are any advantages or disadvantages compared with other studentships?

One of the lecturers in the Pharmacology department informed me about the A J Clark Award when I was talking to people about wanting to do a PhD. The A J Clark studentship seemed a really good award for a budding pharmacologist to apply for, because it was funded by the organization representing pharmacologists in the UK and around the world and so would allow you to become part of this network of scientists. For example, I'll be attending the BPS Winter Meeting in December and am really looking forward to getting to know people who share an interest in Pharmacology.

Did you know who A J Clark was before your interview and can you explain his contribution to Pharmacology?

As an A J Clark Award candidate I thought that it was essential to know who the award was named after. After finding out about the award I was very quick to find out who A J Clark was and certainly knew about him before the interview. Alfred Joseph Clark was a British pharmacologist working at the beginning of the 20th century, who wrote the famous textbook *Applied Pharmacology*. His main contribution to the field was his work investigating concentration-effect relationships.

Where will you be studying your PhD?

In the lab of Dr. Ruth Murrell-Lagnado at the Department of Pharmacology, University of Cambridge. Dr Murrell's lab investigates purinergic signalling.

What is your PhD project title and can you explain what you will be studying in a sentence or two?

I'll be researching the regulation of the intracellular trafficking of P2X receptors, with possibly some work on the stoichiometry of heteromeric P2X receptor assemblies. P2X receptors are ionotropic receptors that respond to extracellular ATP and/or ADP. Seven subfamilies have been identified: $P2X_{1-7}$. Upon activation, P2X receptors are selectively permeable to cations and consist of three subunits (both hetero- and homotrimeric assemblies have been identified). They are expressed in a wide variety of cell types, including immune cells, smooth muscle and neurons. An interaction between P2X receptors and pannexin molecules has also been recently discovered, so there may be some scope for research in that direction as well. The current state-of-play of the purinergic signalling community and what other lab members are doing will affect which direction I decide to pursue.

What attracted you to this subject area?

I like to understand mechanisms behind processes, so how ion channels and G-protein coupled receptors affect the cell's activity interests me from that perspective. I decided to do a PhD on P2X receptors because I was intrigued by their role in the development of pain.

Can you briefly explain the involvement of P2X in the development of pain?

$P2X_4$ receptors are involved in pain pathways. When a rat damages a peripheral nerve it experiences pain hypersensitivity (tactile allodynia). $P2X_4$ receptors are upregulated in the spinal cord microglia of these rats, and preventing this upregulation, using oligonucelotides against the $P2X_4$ receptors, reduces the severity of tactile allodynia. This suggests that $P2X_4$ receptor antagonists may be of benefit in the treatment of pain disorders.

Do you think P2X receptors will provide a target for the development of future treatment?

There is much scope for modulating P2X receptor activity for therapeutic benefit. P2X receptors play roles in cancer, inflammation, stroke and pain, and it is hoped that drugs targeting P2X receptors may be useful as an adjunct to conventional treatments as well as being effective on their own. Now that ligands with increased receptor selectivity are available, our knowledge about the therapeutic potential of P2X modulation will accelerate.

Was the application and interview process difficult?

The interview process was challenging but rewarding. The panel asked some very specific questions about my PhD proposal and subject area, which gave me a chance to talk about the primary literature I had read and to show that I understood the methods I had written about in my proposal. They were also interested more generally in my motivation for doing a PhD and how I would achieve a work-life balance. It reminded quite a lot of my interview several years ago when applying to Cambridge: taxing, but very rewarding if you have prepared well.

Have you received any support from the BPS leading up to the start of your PhD?

Yes, I've become a member of the BPS Young Members Committee, which will help me to meet other PhD students from other universities.

How are you feeling about starting your PhD?

I'm feeling quite excited about beginning my PhD. I think it may be difficult initially, like starting anything new for the first time, but I can't wait to get back into the lab again.

Many of your friends will have finished their studies and already be working; what did they think about your starting a PhD?

Most people have said, "You're so lucky to be a student for another 3 years!" Others have said, "Why on earth would you want to spend even more time studying?" And the ones who are doing PhDs say, "Do you know what you're letting yourself in for?"

How do you expect to juggle your PhD and social life?

Cambridge is a small city, so it's quick and easy to get from one place to another by bike. This makes it easier to integrate your hobbies and social life with your studies, because you can leave the lab and within 5 minutes be back at college or at the cinema. However, I haven't been a PhD student before, so it remains to be seen what life will really be like! I like going hiking (which means getting out of the flat Fens) and I was planning to take up archery this year, so I'm just hoping there'll be enough time for these things.

What other interests/activities do you hope to pursue in Cambridge?

[See answer above also]. I also like going to see independent films, and plays at the student-run ADC theatre in Cambridge. In the past I've done French and German language courses while at university, so if I have enough time and energy left after being in the lab all day I will look into doing another one of those.

What is your career aim after the PhD?

At the moment my career aim is to become a post-doc in a laboratory and contribute original research to the field of Pharmacology. I think I would like to stay in academia, and I would also be interested in working in a university overseas for a few years if the opportunity arose.

Finally, is there any advice that you would give to an undergraduate student who intends to follow a career in Pharmacology?

I would say not to be daunted by the prospect of doing a PhD. Although it is undoubtedly hard work and very different from doing an undergraduate degree, if you enjoy reading the literature and working in the lab then you should seriously consider doing a PhD. If you are unsure, one option is to take a year out and find a job in a lab as a research assistant, which gives you the chance to find out what doing research is like without being committed to several years of study. Once I had decided to do a PhD the most helpful advice I received was to consider the supervisor and how they run their lab as much as the topic itself. Supervisors have different styles and personalities , and it's advisable to visit the lab to get a feel for whether that environment would suit you.

I would like to take this opportunity to thank Sara for her time and wish her good luck as she starts a new life as a PhD student.

Interview by Stephanie Francis

Prizes and Awards 2009

BPS A J Clark Studentship
Deadline for applications 12 December 2008

Schachter Awards
Deadlines for applications 30 January and 30 June

The J R Vane Medal
Deadline for nominations 31 January 2009
Designated area for the 2009 award will be Cardiovascular and Renal Pharmacology.
Deadline 31st March 2009:

The Wellcome Gold Medal
The Novartis Prize
Aptuit Prize (Self-nomination is acceptable)
The Bill Bowman Travelling Lecturership
BPS Teaching Prize: "The Rang Prize"
(Part of the ASIF Initiative)
Anniversary Strategic Initiatives Fund (ASIF) Awards
1. Vacation Studentships
2. Post-doctoral Support
3. Research Collaboration Initiating Grants

The Lilly Prize (Clinical Section)
Deadline for nominations 30 June 2009

Clinical Pharmacology Section Prizes for Medical Students
Deadline for nominations 25 July 2009

Schachter Award Winners:

Sarah Maher

The Schachter award was set up in 2002 using a donation from Ruth Schachter in honour of her late husband Dr Melville Schachter. Two grants each of £500 are awarded each year to be used as a contribution towards the visit of a postgraduate student to another laboratory. Sarah Maher won the award in 2007. Her work is described below, followed by a report from the first winner of 2008, Martina Fehler.

I should like to thank Mrs Schachter and the BPS for the Schachter award, which enabled me to spend 5 weeks learning a new technique in Professor Brad Undem's laboratory at Johns Hopkins Asthma and Allergy Center, Baltimore, USA. Professor Undem and his colleagues use a technique to record action potentials from single nerve fibres that innervate the larynx, trachea, and bronchi, and this has proven to be a great asset to my research.

My PhD research focuses on prostaglandin E2 (PGE2) as a potential therapy for airway inflammatory diseases. PGE2 is anti-inflammatory and bronchodilating, but it causes airway irritation and cough. I have been researching the prostanoid receptor responsible for PGE2-induced sensory nerve irritation, in the hope that an analogue of PGE2 could be developed that is anti-inflammatory and bronchodilating but devoid of the irritant adverse effects. In our lab at Imperial College I have been using an isolated whole vagus nerve preparation. While this is a useful technique, until now I have been unable to identify the effects of PGE2 on nerve fibres that innervate only the lungs.

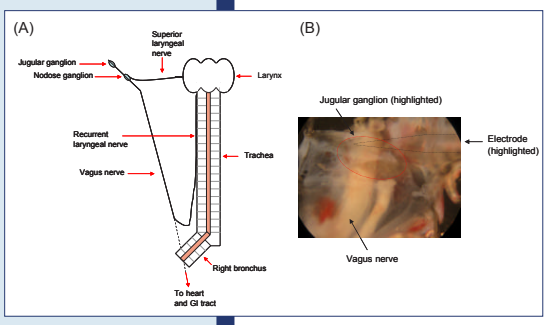

Figure 1: Anatomical diagram of the experimental setup (A) and a view down the microscope of the electrode positioned in the ganglion, recording nerve activity (B)

Professor Undem's experimental technique is an excellent model of airway nerve activity. An electrode is inserted into the vagal ganglion, which contains the cell bodies of the nerve fibres carried in the vagus nerve (see Figure 1). The mucosal surfaces of the guinea-pig larynx, trachea, and bronchi are then mechanically probed until a burst of firing can be detected. Stimuli (e.g. PGE2) are then applied directly to the area or perfused in the chamber and the activity is recorded from a single nerve fibre. As well as learning the technique, I was able to generate some results for my thesis, which was an added bonus to an extremely rewarding 5 weeks. Learning this technique has helped our group to be successful with a grant application to the Medical Research Council. The funding will enable us to set up the experiment in our lab, which will make the technique available not only to our university but to other researchers in the UK.

While living in Baltimore, I took the opportunity to explore the city as well as the nearby cities of New York and Washington DC. I gained valuable experience, not only in the experimental technique, but from working and living abroad in a new environment. It was an invaluable opportunity to meet new people and make contacts, and I also made some great friends. The Schachter Award is a unique award and I would highly recommend a visit to an overseas laboratory by other PhD students. I would like to thank Professor Undem and his team for welcoming me into the group and for their expert teaching and advice, and to Mrs Schachter for making this fantastic experience possible.

Sarah Maher, Imperial College London

Martina Fehler

Martina (pictured) is in her last year of a PhD under the supervision of Dr. Emma Kidd at the Welsh School of Pharmacy, Cardiff University.

The Experimental Biology (EB) annual meeting 2008 was held on 5-9 April in San Diego. The EB annual meeting is the most important international scientific meeting in the field of biology and pharmacology. This year the meeting involved important American societies, such as the American Association of Anatomists, the American Association of Immunologists, the American Society for Biochemistry and Molecular Biology, and the American Society for Pharmacology and Experimental Therapeutics.

My project has been investigating the effects of trace amines on the rat aorta, so being able to attend such an important and well-regarded scientific event in the field of biology and pharmacology was a great opportunity for me to get information on many aspects of vascular biology, physiology and pharmacology and also to get ideas regarding my future career in research. Also, attending career-orientated seminars and workshops from various companies and universities has given me a clear idea of how to pursue a career in research. My abstract was selected for a poster presentation in a session on general cardiovascular pharmacology. The presentation of my poster "Investigation of trace amine-associated receptors in rat aorta" was a success. I enjoyed discussing my results with in-

ternational experts in the field and also with people with different backgrounds. During my poster session people from the Oregon Health and Science University in Portland came to see me, as they were also working on trace amines. Furthermore, another poster regarding trace amines was presented by a group from the pharmaceutical company, Hoffman-La Roche in Switzerland. So far, trace amines and their effects on trace amine-associated receptors have not been investigated in great detail. Therefore, it was important for me to start networking with people working in the same field to exchange experiences, discuss results, and get some advice for future work.

By attending lectures during the conference on various fields of research, I made contact with many experts, who not only gave me the opportunity to exchange ideas, experiences, and knowledge, but also allowed me to gain advice and helpful suggestions. Referring to my PhD, I attended some very interesting lectures on G protein-coupled receptors and their signalling pathways. In this regard, well-known pharmacologists whose papers and books I have read, such as R.J. Lefkowitz from Duke University and A.G. Gilman from the University of Texas, presented the latest results of their research and also discussed possible future work in this field. Furthermore, I attended interesting lectures on topics regarding regulation of ion channels in cardiovascular diseases. These topics are closely related to my PhD and have helped me to understand better the background of the field.

Martina Fehler, Cardiff University

Anniversary Strategic Initiatives Fund (ASIF) Vacation Studentship

These awards, part of a series to be announced annually, have been made available from the BPS 75th Anniversary Strategic Initiatives Fund, set up to support and enhance the discipline of pharmacology. The Vacation Studentship is meant to encourage consideration of a pharmacology specialism for either school leavers entering a biomedical science degree or undergraduates studying biomedical science. Each studentship provides £900 support to the living costs of the student while they undertake a summer vacation research project in the host laboratory.

Elinam Gayi is one of the five students who won a vacation studentship in 2008. Here is her report on the summer project she undertook at the University of Bristol.

Project Title: Pharmacological characterisation of a novel animal model of cognitive affective processing using antidepressants

People are generally more sensitive to reward losses than reward gains. This sensitivity is influenced by emotional state and hence people with major depressive disorder (MDD) are particularly sensitive to reward loss (Burman *et al*, 2008). MDD patients exhibit symptoms such as low mood, lack of motivation, and anhedonia (inability to experience reward). A lack of animal models to quantify the altered cognitive function associated with this disease has led to the development of the cognitive affective bias operant model.

At the beginning of the project trained rats were tested for stability of performance following training in a forced choice serial reaction time task (FCSRTT). Half the animals were trained using one pellet reward, whereas the other half received four pellets. Once stability was achieved, successive negative contrast (SNC) was used. SNC 'stimulates reward loss by unexpectedly decreasing the size of the food reward which an animal has been trained to receive' (Burman et al, 2008). During SNC sessions, all of the animals only received one pellet; those who had previously received four responded more slowly to stimuli, and presentation of food indicating disappointment-like emotional state. There was an amplified effect of this slowing down during the subsequent SNC sessions. A drug study using the tricyclic antidepressant desipramine was done. The animals were trained for oral administration of the drug which was suspended in sucrose solution. Desipramine was administered to the animals on SNC sessions to try and reduce the effect of reducing the food reward. The results were not reliable, as the rats were less willing to drink the sucrose with the suspended drug.

Another group of animals was trained during the project to do the emotional tone discrimination task (ETDT); these were based on the cognitive affective bias model. The animals were trained to listen to tones that would predict where to respond to receive a reward or avoid a punishment. The animals were trained through the first three stages of the task. At the time of finishing the project, the rats had shown an ability to discriminate the tones. After the project, intermediate tones will be added to test whether the animals' responses was biased towards obtaining a reward or avoiding a punishment. Some of the rats were to be subject to unpredictable housing conditions, which would make them more biased to avoidance of punishment than the controls. They were likely to show 'reduced anticipation of a positive event.' This is similar to findings in depressed or anxious humans, who have reduced expectation of positive events (Harding et al, 2004).

Although most of the project focused on developing novel techniques to research MDD, there were other projects going on at the time, such as one into attention deficit disorder (ADD). This involved measuring impulsivity of the animals while using the FCSRTT.

Elinam Gayi, University of Bristol

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GRAC Editors Win the 2008 Rang Prize

Jude Hall, Education and Training Manager

The BPS Teaching Prize, The Rang Prize, was made available from the BPS 75th Anniversary Strategic Initiatives Fund to support and enhance the discipline of pharmacology. The prize is awarded in recognition of a contribution to the teaching of Pharmacology and to the maintenance and development of Pharmacology as a discipline. With the recent announcement of the 2008 prize winners, the Guide to Receptors and Channels (GRAC) editors Stephen Alexander, Alistair Mathie and John Peters, nominations are now open for the 2009 award. We felt that this edition of *Pharmacology Matters* represented an ideal opportunity for us to inform readers about the Rang Prize. In this article, Jim Ritter explains why the Rang Prize was so named and Steven Alexander describes the value and uses of GRAC as a teaching tool that led to the GRAC editors receiving this prestigious award.

Why the Rang Prize?

Humphrey Rang, BJP Editor-in-Chief

The BPS Executive Committee, chaired by the then president-elect Jeff Aronson, unanimously agreed that this prestigious teaching prize be named after Professor Humphrey P Rang (HPR). Here Jim Ritter, colleague and friend, reflects on the considerable contribution made by Humphrey to the discipline of pharmacology and to its teaching over his distinguished career.

The inception of the Rang Prize is a good moment to reflect on HPR's achievements as an educator during a career that has spanned academia (lectureship in Oxford, chairs in Southampton, St George's Hospital Medical School and University College London), industry (Sandoz/ Novartis) and "retirement" (author, biotech consultant etc). His main educational contribution , which has touched the lives of the greatest number of pharmacologists, medics and other biological scientists around the world is "Pharmacology", the textbook, first published in 1987, that he conceived from Schild's "Applied Pharmacology" and which he wrote in collaboration with Maureen Dale. (My own subsequent involvement - from the third edition - provides my excuse for writing this piece.) This book has been widely appreciated, perhaps because it manages to combine the rigour of a conventional scientific textbook with a readability and joie de vivre most unusual for that genre. It owes this combination to Humphrey's overall approach, which these brief reflections seek to illustrate via some personal recollections.

I first encountered HPR in the late 1960s, when I was a preclinical student in the Oxford Department of Pharmacology, where he was a newly appointed lecturer. The Oxford pharmacology course was legendary, with heavyweights such as Bill Paton (with whom Humphrey had done his DPhil, supported by a Burn studentship), Miles Vaughan-Williams, Hermann Blaschko, and Edith Bülbring among others, any or all of whom would often attend each others lectures. As the new kid on the block, HPR's teaching might have been pitched with at least half an eye to this peer group, as well as to us callow medical students, but far from it. Indeed for us his lectures were the stars of the show, witty, pithy, and crystal clear. The secret seemed to be to take difficult concepts and demystify them, and this desire to be helpful (as opposed to a desire to seem smart) has driven his approach to the textbook. As he wrote to me on reviewing one of my chapters (of which I had been really rather pleased): "Jim, this is supposed to be a textbook, not current controversies in...". The underlying motivation, it seemed to me, was an intense commitment to the importance of the subject, coupled with unaffected enthusiasm and a desire to explain. And what is "the subject" you may ask? Some pharmacologists agonize over defining their subject, but HPR took (and takes) a pragmatic line: pharmacology, with its basis in physiology, cell biology, biochemistry, molecular biology and (most importantly) chemistry, is about what drugs do and how they work. He was enthusiastic but sceptical. Drugs could be valuable probes of physiological function, certainly, but with limitations as to specificity that rendered experiments involving multiple drug cocktails highly suspect, if not positively misleading.

One of the best parts of the Oxford course was the rotating weekly practicals - three pairs of students to each station. The original stations had been devised while JH Burn was head of department, and some of them had become dated. Burn, still a frequent visitor to the department, used to enjoy debating with HPR a concept that he championed, namely that pharmacology could be defined via a group of core experimental "preparations", such as rat phrenic nerve/ diaphragm, Langendorff heart, and so on, several of which featured among the class practicals. The enjoyment may have been asymmetric, and certainly HPR did not ascribe to this view. He did, however, contribute new practicals. One was a comparison of the effects of a local anaesthetic on the compound action potential amplitude in frog sciatic nerve and its dependence on pH; a potential explanation of the observations in terms of effects of pH on drug ionization, and hence on drug distribution, was considered and its prediction tested by repeating the experiment in nerves that had been de-sheathed (by HPR rather than the students - these experiments were designed to work!) to eliminate a critical distribution barrier. It was a revelation for us in more ways than one: the use of an oscilloscope rather than a smoked drum, the importance of appropriate controls (eg for Ringer's solutions of different pH), the hypothesis based in physical chemistry, the neat test of its prediction, and the exhilaration of getting a totally convincing result. I think that this station replaced the guinea-pig vas deferens, which, with its anomalous anatomical distribution of postganglionic adrenergic neurons, had misled Burn to the ill-fated "cholinergic link" hypothesis of adrenergic transmission - a nice irony!

My next experiences with HPR were during a vacation project and subsequently as his (first) DPhil student:

he was the most demanding but most rewarding and generous of supervisors, always ready to point one in good directions, interactive and available. His advice could be simple and decisive yet permanently influence one's subsequent approach. On one occasion I had almost all the work ready for a submission, when a run of experiments showed that what had seemed a stable/ persistent phenomenon could in fact change over a period of 15 minutes or so. What should I do? "Describe the facts and include the worst example as a figure". He was also a great adviser when it came to writing up (did I appreciate this at the time? – which of us do?), helping me to express scientific ideas straightforwardly and unambiguously. (There is a general rule that whenever one is particularly pleased with a turn of phrase, it is almost certainly quite wrong; HPR is the man to get it right, usually in about half the words.) He has since of course supervised many doctoral and post-doc students, and this educational influence will persist down the intellectual generations.

I hope that these recollections, arbitrary and incomplete as they are, shed some small light on the characteristics that make HPR so remarkable an educator. Serious, focused, parsimonious in written style, dedicated to clarity rather than "elegancy" (in Fowler's pejorative use of that term); but also witty and charismatic. How do such diverse qualities come to be bedfellows? My guess is as a result of a unified philosophy rather than one based on silos. Problems are dealt with one at a time in order of importance (and a sailing commitment may be more important than a presentation to the BPS), but each part of life builds on and contributes to each other aspect: he is a hedgehog rather than a fox in the analogy quoted by Isiah Berlin. Thus, the search for clarity in explaining basic concepts to students helped define the research questions he so successfully addressed; his research output was used (with that of others) to illustrate general scientific principles in the textbook; artistic talents help him explain complex mechanisms visually; his love of anecdote gives an infectious leavening to the mix, and so on. Are there lessons to draw for lesser mortals? I suggest two: that we should do our best to maintain breadth of scholarship in these progressively specialized times, and always to remember that the best and most important things in life can also be fun.*

**A Russian folk tale of a fox that knows lots of small things and a hedgehog that knows one big one – don't ask why! Berlin's essay of this title is well worth the read.*

Jim Ritter, King's College London

The 2008 Prizewinners

The 2008 Rang Prize was awarded to the GRAC editors, Stephen Alexander (University of Nottingham), Alistair Mathie (University of Kent), and John Peters (University of Dundee). Here, Stephen Alexander explains the value of GRAC as a teaching tool.

We all know that the Human Genome Project has generated an abundance of information about the molecular nature of pharmacological targets. Most of the genome, however, is not yet exploited (or even exploitable) pharmacologically. There are probably about 2000 proteins that have potential for pharmacological exploitation. The current version of the Guide to Receptors and Channels (GRAC 2008, 3rd Edition) lists a large proportion of these in less than 200 pages, with 61 7TM receptor, 7 transmitter-gated channel, 14 ion channel, 6 catalytic receptor, 6 nuclear receptor, 6 transmitter transporter, and 15 enzyme tables. In addition, a number of orphan 7TM and nuclear receptors are listed, in an attempt to identify where future developments in pharmacology might arise. GRAC is available free from the BJP office and is also freely available on the internet, with active links to Ensembl (www.nature.com/bjp/journal/vgrac/ncurrent/index.html), the online database of vertebrate genomes. We compile records on these pharmacological targets, taking advice from many consultants, attempting throughout to co-ordinate information with Nomenclature Committees of the International Union of Pharmacology and Clinical Pharmacology (NC-IUPHAR), the primary arbiters for nomenclature of receptors and ion channels. When such guidance is lacking, advice from several prominent independent experts has been obtained, to produce an authoritative consensus, which attempts to harmonize with the general guidelines from NC-IUPHAR.

Our intention in producing GRAC has been to balance an authoritative but user-friendly publication, which allows a rapid overview of the key properties of a wide range of established, or potential, pharmacological targets. The aim is to provide information succinctly, with the majority of entries presented on a single page, so that a newcomer to a particular target group can identify the main elements 'at a glance'. It is not our goal to produce all-inclusive reviews of the targets presented; references to these are included in the Further Reading sections of the entries. In many ways, therefore, the Guide is of limited value to experts. People who have worked solely on glycine receptors for 20 years, for example, will have intimate knowledge of the field and will have no need for the Guide.

The primary aim, therefore, is to act as the starting point for educating novices. In many cases, reviews elsewhere describe agents that exhibit the highest affinity, or greatest selectivity, but which may not be available to the new worker. GRAC provides information on the best agents available (either commercially or by donation) to allow definition of a target for someone who is new to a particular research field and doesn't know which agonists, antagonists, activators, or inhibitors will allow the involvement of a particular receptor, channel, transporter, or enzyme to be identified. Thus, novices (or those furthering their education) are the major target of the Guide.

Steve Alexander, University of Nottingham.

A final word from the President

The Rang Prize is awarded "in recognition of [the prizewinner's] contribution to the teaching of Pharmacology and to the maintenance and development of Pharmacology as a discipline". The Committee considered that GRAC is both a research tool and a teaching tool, and that it has made an important contribution to the maintenance and development of Pharmacology as a discipline. The GRAC Editors were nominated for a prize by Humphrey Rang, who will present the award at the meeting of the Society in Brighton.

Jeff Aronson, President BPS

Nominations for 2009

The BPS Awards and Prizes Committee invites nominations for the 2009 Rang Prize of £1000 pounds in accordance with the criteria below. Please send nominations by March 31 2009 to ks@bps.ac.uk. Nominations will be considered by the Committee, chaired by the President, Jeff Aronson, and the winner will be announced in June 2009.

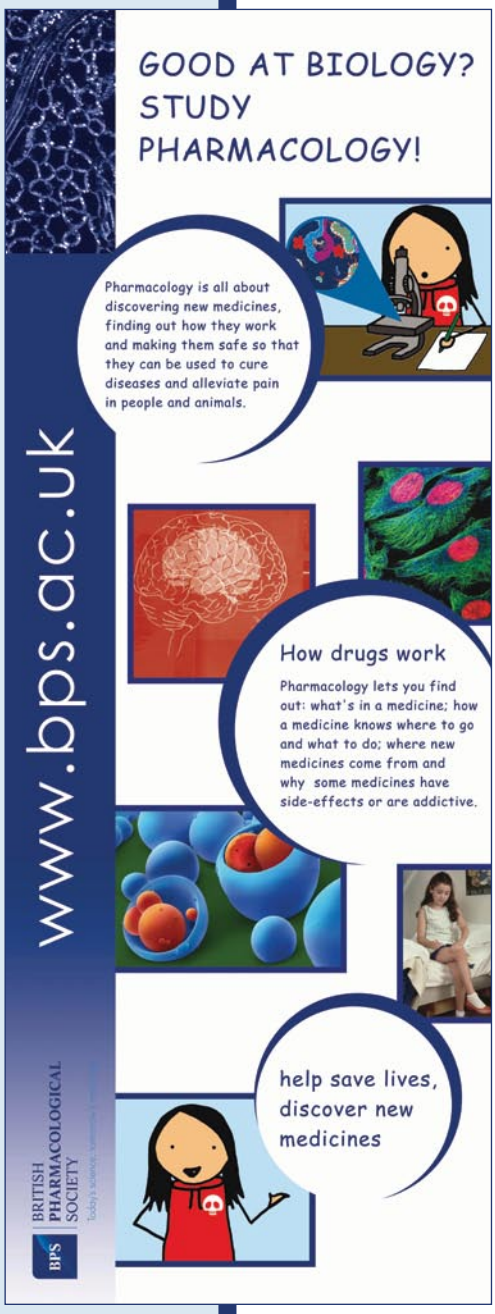
Eligibility: BPS members at any stage in their career. Nomination: Self-nomination or nomination by another BPS member The application: One page of A4 maximum outlining the candidate's significant contributions to the teaching of pharmacology Criterion: Significant contribution to the teaching of Pharmacology in past five years (i.e. it is not a lifetime award but a prize for initiating recent developments in teaching)

To download a promotional leaflet of the ASIF Prize and Awards, go to the Awards and Prizes section of the BPS website.

Examine your future

Julie Keeble

On 20 June 2008, Jude Hall (BPS Education and Training Manager) and I (Research Fellow, King's College London) represented the BPS at the Examine Your Future careers fair at the Business Design Centre in Islington, London. This UCAS event was sponsored by NHS Careers and was specifically targeted at school students in years 10, 11 (GSCE), 12 (AS level), and 13 (A2 level) with a serious interest in science and careers allied to medicine. We set up our stand armed with leaflets and DVDs on careers in pharmacology (plus, of course, the all-important chocolate, fluffies, and BJP/BJCP pens!). Approximately 5000 students from over 150 schools attended the event, and around 60 exhibitors were present, representing a very diverse range of scientific/ medical careers. For example, the BPS stand was shared with the Society for General Microbiology and was located next to the Royal Pharmaceutical Society of Great Britain. Opposite was the Armed Forces Medical Division and in the distance we could spot some odd-shaped objects, which turned out not to be freebies, but prosthetic limbs, displayed by the National Centre for Prosthetics and Orthotics.



Our position next to the Royal Pharmaceutical Society was highly fitting, considering the common misconception among school and sixth-form college students that pharmacy, pharmaceutical science, and pharmacology amount to the same thing, and that pharmacology is entirely a 'chemistry subject'. Once rectified on these points (the slogan of our newly designed BPS banner reads '*Good at biology? Study Pharmacology!*' certainly helped put right this latter misconception), students at all key stages were really interested to hear what a career in pharmacology could involve. Many questions were asked, including 'How long does it take to do a pharmacology degree?', 'Do I need to be good at chemistry?', 'How much do you earn?' (sometimes this was directed at me personally!), and 'Do you use animals?'. This last question was particularly appropriate for me, as I currently have a Fellowship at King's College London in the Centre for Integrative Pharmacology. An essential part of my Fellowship is to address the issue of *in vivo* science with school children and the wider community. My previous experience meant that I could comfortably discuss this issue with the students who attended our stand and experienced no negativity towards what I said. In fact, the students were frequently keen to hear about my job and personal experiences, and careers advisors were very keen to receive copies of the '*Animals in research: make up your own mind*' DVD kindly supplied by the Physiological Society.

One of the things that stood out from the day is the importance of communicating information on pharmacology to students at these levels, as ignorance of the subject was so prevalent; even students who intended studying medicine or dentistry were not aware of exactly what pharmacology is. I had to admit to them that at their age I had had a similar level of ignorance and my entry into pharmacology had more to do with luck than judgement. This needn't be the case, if schools are given sufficient information. We hope that we went some way towards doing this at the exhibition. In fact, I was approached regarding the possibility of giving talks in schools by a couple of people during the day.

Overall, our stand received an encouraging level of interest from both students and careers advisers. When the careers fair opened, we received a constant flow of visitors that did not relent for a good couple of hours. In the afternoon, it was slightly more laid back, but we were still quite busy. We happily wore our brightly-coloured fluffies all day, advertising BPS and encouraged as many people as possible to take them and with a bit of luck, BJP/BJCP pens are now being used in classrooms across the region.

We hope that, as a result of our hard work on the day at least some of the students will find their way on to a pharmacology or biomedical science course over the next few years.

Julie Keeble, King's College London

Examine your Future is one of several outreach conferences aimed at school children, undergraduates and post-graduates, teachers, and the general public at which BPS regularly exhibits. If, like Julie, you would be interested in supporting this or any other form of outreach for BPS, we'd be very happy to hear from you. Please contact Jude Hall (jmh@bps.ac.uk).

Why do we need them and what are we doing to support them?

The British Pharmacological Society (BPS) and The Physiological Society acknowledge the importance of practical biology teaching at all key stages in motivating and inspiring the next generation of scientists. In recognition of this, the two societies are working together in a joint venture to support the Biosciences Federation (BSF) and the Nuffield Curriculum Centre (NCC) in the development of a web-based resource of practicals for schools. The societies are jointly represented on the Steering Committee by Dr Jude Hall (Education and Training Manager, BPS).

Why we need to get involved

Concerns over the amount and quality of practical skills taught in schools and sixth-form colleges, particularly core laboratory skills, have been raised by employers, school inspectors, and colleges of higher education (www.bsf.ac.uk/responses/Enthusing.pdf); this is despite practicals being cited by students as one of the most enjoyable elements of studying science and the reason they choose to pursue a career in science. Some of the reasons suggested for the decline in practicals taught in schools include: health and safety concerns of teachers; cost; time restraints; a lack of technical support; league tables; and teacher confidence.

To address some of the shortfalls in practical biology teaching, the BSF/NCC is establishing a website (registered domain: www.practicalbiology.org) to help teachers in schools and colleges to deliver affordable and reliable practicals to pupils from key stage 3 to A-level. The biology website follows the launch of similar websites already up and running for chemistry (www.practicalchemistry.org) and physics (www.practicalphysics.org). Advice on content and contributions, including ideas for practicals for the site, are being sought from a wide range of stakeholders, including: teachers; learned societies, medical charities, and funding bodies; employers; authors; examiners; university and industrial scientists and lecturers.

The benefit of teaching a consistent quality and appropriate range of practicals in schools is clear.

Practicals:

- are core to teaching science; biology is an experimental subject
- aid development of problem solving and analytical skills
- stimulate original thought and creativity
- promote collaboration and discussion within and between peer groups
- foster a life-long interest in biology
- encourage a career pathway in science

The future

BPS and The Physiological Society hope this project will achieve the same level of success as the practical chemistry and physics sites. The physics site, launched in January 2004, has a bank of around 650 practicals and receives in excess of 30 000 unique visitors per month, typically viewing a total of 250 000 webpages - testament to the need for such a resource.

The practical biology website will be launched on 22 September 2008. BPS and The Physiological Society are keen to ensure that all biomedical disciplines are adequately represented on the site. If you have any recommendations for practicals for inclusion or any other suggestions please e-mail Jude Hall at jmh@bps.ac.uk she will forward ideas to the Steering Group.

Jude Hall, Education and Training Manager, BPS

Chrissy Stokes, Head of Education and Membership, The Physiological Society.

Practicals in Schools – a Teacher's View

Catherine Bleasdale, biology teacher

As a biology teacher I find that a number of students who take biology at A-level do so because they believe it is an easy option. However, A-level biology is not easy and students find the new vocabulary and practical classes challenging.

At GCSE, practical classes are limited by time, cost, and resources, and so teachers become constrained to teaching facts and figures, which the student can regurgitate without the need to understand the underlying concepts. As a result, students arrive in their A-level biology class with many misconceptions and it takes time to retrain them to think like scientists. Some misconceptions have developed through the repetition of experiments at Key Stages 2, 3, and 4. Each time a student is presented with the same experiment, they realize they have seen it before and rather than develop their understanding they recall the results and regurgitate the facts – this doesn't help with the independent thinking that we need to develop in our A-level science students.

As a former scientist, working in academia and in industry, I am only too aware of what these students are missing in terms of practical classes. After all, it is practical classes that will keep them motivated and wanting to carry on until university. And new and exciting practical classes and concepts will enable students to develop inquisitive, scientific minds.

Providing practical equipment for the whole class to undertake an experiment is expensive and, with prescribed practicals for the new type of coursework, it is even more difficult to justify spending money on consumables that can be used only once and will not contribute to coursework.

With improving IT and internet resources, it has become possible to show students videos of other scientists carrying out practicals; although this type of learning has its place, it should never be a substitute for hands-on experience. Students like science because it is a practical subject, and reducing practical work by allowing them to sit and watch videos is not a satisfactory solution. Interactive computerized virtual labs are a start but to keep students motivated and interested we need opportunities and ideas for cheap, easy, and effective experiments that can be done in school.

Practicals in Schools – a Student's View

Tom Carrington Smith, A-level student

As an A-level student who has just finished studying biology at a 6th form college I have always enjoyed the hands-on element of learning. Over the two years at college, I took part in a number of different practicals, which varied from simple experiments, like finding out my blood group, to more complex procedures, like studying the effects of different light wavelengths on the rate of photosynthesis.

In biology, I took part in a practical once every 2 weeks, maybe even less often. Being someone who learns better visually, I felt this was not enough and would have liked to have seen more practicals in biology.

I completed practicals in a number of different group sizes and also worked on my own for some practicals. I found group work more stimulating, as the experiments were normally more complex and allowed ideas to be bounced off each other.

I felt that experiments where I knew the outcome were not as enjoyable; as I already knew the answer, I had nothing to achieve or learn by doing the experiment. I found it far more exciting to discover answers myself or as part of a group.

The majority of practicals I completed when studying A-level biology were based on plants, which can become tedious after a while, and I would have liked to have studied more animal-based practicals.

For the coursework element of A-level biology, we had to complete an assessed experiment. One of my assessed experiments looked at the rate of reaction of two different sources of amylase on the hydrolysis of starch. I enjoyed the aspect of planning the experiment and then concluding and evaluating the results, but did not enjoy being assessed under practical conditions. I felt it put pressure on the procedure of the experiment and I also felt rushed to complete the experiment. More experiments where students are allowed to plan the experiment would help them to understand and remember the topic more clearly.

When I completed a practical in a certain area of biology, I understood and remembered the topic much better. Practicals helped me to create a picture of the biological processes and helped me revise for exams. I certainly enjoyed the practical side of the biology course the most and would have liked to take part in more practicals. The practical side of biology definitely motivated me to continue studying science and go to university. I am hoping to study sports and exercise at the University of the Bath, with the view of going into research on human physiology.

A version of this article will also feature in Issue 72 of Physiology News, The Physiological Society's magazine.

YOUNG PERSON'S DAY, BRIGHTON
Wednesday 17 December

Are you a young member of the BPS? Then come along to the 2008 Winter Meeting and enjoy a day of activities at the Winter Meeting by the seaside in Brighton (buckets and spades optional!)

- Poster presentations entered for the 2008 Clinical Pharmacology Medical Student Prize
- Tocris Lecture by Dr Andrew Kicman *"Anabolic drugs in the gym"* (organized by the Young Persons Committee)
- Aptuit Prize Lecture by Dr Felicity Gavins *"Intravital microscopy: Real time disease modelling"*
- TiPs 2008 Young Pharmacologist of the Year prize symposium
- Plus enjoy a glass of wine while viewing the poster presentations from twenty one nominated undergraduate students from across the country during the afternoon poster session
- Think you know your music and sport? Come early to show off your skills and do some networking at the Young Persons Pub quiz. Tuesday night at 8.30pm at the Latest Music Bar. Prizes for best and worst teams and best and worst individual. Young Members £5, others £10. All welcome!

Come along and get inspired! Free registration for members includes hot buffet lunch and refreshments. Register online before 21 November at www.bps.ac.uk

Interested in Pharmacology and Drug Discovery?

DAP BPS Diploma in Advanced Pharmacology

Sign up for the Diploma in Advanced Pharmacology!

The development of medicines has had a great impact on disease treatment and quality of life for a whole host of diseases. But if you're a clinician or a research scientist where can you find out (and learn) about the science underlying the discovery and development of medicines and get a recognized qualification in the process? The short answer is that it is really difficult… unless you enrol on the Diploma in Advanced Pharmacology (DAP) run by the BPS.

Pharmacology is one the key foundations of the drug discovery process. Pharmacology is primarily concerned with studying the actions of molecules on receptors and the influence they have on physiology and pathophysiology. Pharmacologists are concerned with discovering new receptors and the potency/affinity and receptor selectivity of molecules. Classic examples testify to this: the discovery of α, β1 and β2 adrenoceptors by Ahlquist and Lands and the subsequent development of molecules selective for activating β2 (salbutamol for asthma) or blocking β1 (atenolol for hypertension).

Although basic pharmacology is at the core of the Diploma, many other disciplines are pivotal to drug discovery, such as drug metabolism, *in vivo* biology, molecular biology, safety sciences, and clinical development. Scientific advances have had a great impact on how potential medicines are designed and tested. For instance, advances in molecule biology have allowed cloning and expression of receptors of humans and animals aiding translational biology and safety testing. Polymorphisms can also influence how people respond or metabolise molecules and this can have a great impact on the design and interpretation of clinical trials.

To this end the Diploma in Advanced Pharmacology has been set up, with the intent of teaching and training people in pharmacology and allied and emerging disciplines and areas involved in the discovery and development of medicines.

The Diploma today

The Diploma programme was launched two years ago; how has it gone? There are now over 40 registered for the Diploma, including research scientists from industry and post-docs and clinicians from both the UK and overseas. Several of those enrolled for the Diploma are near to completing their six workshops, dissertation, and two communications that make up the Diploma programme, and BPS looks forward to announcing the first graduates in the near future.

Feedback

The feedback for the Diploma has been very positive indeed.

Some quotes from a recent survey exemplify the above:

"I am aware of the potential issue related to each kind of assay: previously when I have to develop an assay, I did choose the technique (b-lac, cAMP…) only by the practical knowledge I had about it. Now I also know the bias I have to take in account for each of them (receptor reserve, equilibrium…) and what kind of information we can get from them. This really helps me to choose the best option."

"The writing of the reflective account for the Drug Discovery workshop has been really educational as had to perform literature searches on field I do not know anything about. Now I feel more confident to do this type of searches for my own projects."

So, if you are a basic scientist or clinician and need to increase your knowledge of pharmacology and drug discovery, sign up for the BPS Diploma in Advanced Pharmacology. It will be fun and hard work but very rewarding

Mike Trevethick, BPS Diploma in Advanced Pharmacology, Steering Committee, Sandwich Labs, Pfizer Global Research and Development

BPS Workshops—all welcome

The Diploma programme involves attending six workshops run by BPS. Some members may not be aware that these workshops are also available to those who are not enrolled in the Diploma programme. In 2008, so far, BPS has held workshops on *Applying Receptor Theory to Drug Development*; *Statistics*; *Pharmacokinetics*; and *Molecular Biology Techniques in Pharmacology*, and will re-run the popular two-day workshop on *General and Advanced Receptor Theory* (CPD=9 credits) at the winter BPS meeting at Brighton. For 2009, we have workshops planned on *Integrative Pharmacology; Statistics; Drug Discovery and Early Phase Trials*.

Pharmacokinetics Workshop—Sabih Huq, Non-Diploma participant

The BPS Advanced Diploma workshop in Pharmacokinetics was a one day event held in the appropriately named New Frontiers Science Park, a retro-futuristic complex originally built by BP in 1966, and now home to a small GlaxoSmithKline city on the outskirts of the Essex new town of Harlow. Organized by a capable team from GSK, and guided by the thoughtful hand of Jude Hall, it drew a mixture of academic, clinical, and industry participants from as far away as Belgium.

Workshop Format

It consisted of a series of lectures interspersed with tutorial exercises, some undertaken in a computer lab, all with the aim of introducing basic pharmacokinetic concepts and parameters, and briefly exploring how these affect modern drug development. For those taking the full diploma, the workshop was followed up with a 2000 word "reflective account" containing calculations and critical appraisal.

The range of prior experience, and future needs, in the workshop audience was wide, from jobbing physicians to dedicated pharmaceutical scientists. Catering for this heterogeneity was sometimes difficult, and while this occasionally led to a lack of dynamism in communal activities, it did allow a diverse group of participants to interact and learn from each other. On the whole, it would appeal to anyone wanting to get to grips with fundamental pharmacokinetic principles with a view to using these in their future work, whether at the bedside or in the lab.

What worked well?

For most clinicians, pharmacokinetics normally engenders a response more akin to being stuck in a room with Gordon Brown, an amalgam of incomprehension, boredom, and juvenile scoffing. The most worthwhile achievement of the workshop was to make sense of the whorl of equations, even for those not mathematically minded. This was done by keeping things simple to start with and gradually introducing more advanced concepts as the day went on. The impact of pharmacokinetics on compound development was also stimulating and made the theoretical constructs immediately more relevant.

The workshop was well organized, predominantly via a handy and useful Google Group, and we were well looked after by all concerned.

What could be improved?

From a pedagogical point of view, a more explicit formulation of what I would be physically able to do at the end of the day would have helped me frame my activities, both before and during the workshop. It may also have helped workshop facilitators to move along at an appropriate pace. I thought the task in the reflective account, of listing personal learning outcomes and opportunities for future application, was a good one. I would have liked to have heard others' views, both to shed more light on the myriad uses of pharmacokinetics, and to bring the audience together through mutual understanding.

The workshop provides a good basic introduction to modern pharmacokinetics. I would recommend it as a foundation module, to be supplemented by further work in more applied contexts, especially for practicing clinicians. If the Advanced Diploma program were to offer a 'Clinical Applications of Pharmacokinetics', I would happily sign up.

Sabih Momenul Huq, Specialist Registrar in Clinical Pharmacology & General Medicine

Statistics Workshop—David Winpenny, Diploma participant

It was an early start from East Kent to get to Guy's Campus for 9.30 am. As usual, I got lost coming out of London Bridge station, but a policeman pointed me in the right direction and I found our venue for the day without further mishap. The workshop was held in the Gordon Museum, which is a curious amalgamation of a teaching space with a bizarre collection of human parts stored in jars.

The workshop was delivered single-handedly by Domenico Spina from King's College London. This is a departure from the norm usually a crack team of pharmacologists are let loose on us. It must have been a fairly demanding day for our sole teacher, but Dom coped admirably and even found the strength to join us in the pub for a drink at the end of the workshop.

Pfizer have a group of statisticians focused on supporting research and who offer training on the appropriate use of statistics in experimental design and analysis. So I thought I would know the ground we would cover and it would be a fairly straightforward day. As usual we had been provided prework consisting of presentations, reviews, and research papers, which taught me that I still had a lot to learn.

Workshop Format

The day was split into a series of alternating lectures and tutorials, which took us through why we use statistics, good experimental design, t tests, F tests, ANOVA, and *post hoc* tests. I was familiar with some of the concepts and had used them in my research but the lectures and the tutorials gave an excellent introduction to the use and abuse of statistics in pharmacological research.

The tutorials helped embed the concepts raised during the lectures and gave us a chance to analyse and report data appropriately. For the tutorials we used Graphpad Prism™ to perform statistical tests. I have been using this package for years to fit data but I had never used its statistical analysis functions. It was very straightforward to use and I can now perform repeat measures ANOVA and an appropriate *post hoc* test with a few clicks.

Reflective Accounts

A key part of any workshop is the reflective account, and I feel it's only in writing this that you become fully familiar with what you have been taught. As part of the reflective account I re-analysed some work I had performed 3 years ago, this time using Graphpad Prism™. It was far simpler to do and more powerful than the analysis I had conducted initially. In addition, it revealed significant differences that strengthened the conclusions of the work.

Workshop Benefits

I routinely use the learning gained from this workshop to help me design my experiments and to analyse and present my data, and I can thoroughly recommend both the workshop and the Diploma to anyone who wants to increase their understanding of pharmacology.

David Winpenny, Research Scientist

Pfizer Global Research and Development.

If you are interested in applying for the Diploma or attending any of the workshops, please contact Jude Hall, Education and Training Manager (jmh@bps.ac.uk).

BPS Diploma in Advanced Pharmacology

General and Advanced Receptor Theory Workshop

Date: Thursday 18–Friday 19 December
Venue: Hilton Hotel, Brighton, UK.
In association with BPS Winter meeting 16-18 December
Registration: contact: sm@bps.ac.uk
Eligibility: BPS members and non-members are eligible to attend
Further information: www.bps.ac.uk

Provisional Programme

Note this programme is subject to change

Thursday 18 December

Welcome and Introduction
Classical approaches to the study of drug-receptor interactions
Discussion and problem solving exercise I
Introduction to the principles of radioligand binding
Discussion and problem solving exercise II
Excel spreadsheet tutorial exercise I – non-linear least-squares curve fitting and the analysis of radioligand binding data

Dinner at 7:00 pm

Friday 19 December

Competitive and non-competitive antagonism
Discussion and problem solving exercise III
Partial agonists, agonist efficacy, receptor constitutive activity
Inverse agonism
Discussion and problem solving exercise IV

Lunch

Excel spreadsheet tutorial exercise II
Discussion and problem solving exercise V
Workshop discussion and feed-back

Cost: £75 (academia) £150 (industry)

Prestigious Award for Mandy MacLean

Mandy MacLean and Bob Grover

We would like to congratulate Professor Mandy MacLean (BPS Vice-President (Meetings)) on winning the prestigious Estelle Grover Lecture Award. The award was given by the American Thoracic Society for her research into the life-threatening condition, pulmonary arterial hypertension (PAH). Professor MacLean is the first woman to receive the accolade, which was presented to her by Bob Grover (pictured). Bob established the Grover conference 28 years ago in memory of his late wife Estelle.

In her award lecture at the 2008 Grover Conference in Sedalia, Colorado, Professor MacLean revealed findings that explain how PAH develops, how the chemical serotonin is involved, why recreational amphetamines can bring on this dangerous condition, and how better drugs could be designed to treat what is invariably a fatal disease. A summary of the work is described below.

The serotonin hypothesis of PAH arose after a number of cases of pulmonary arterial hypertension (PAH) were linked to taking diet pills that were indirect serotonergic agonists; these include aminorex and dexfenfluramine. Mandy has been studying the role of serotonin in the control of pulmonary arterial tone, and how this changes in PAH, for some 15 years.

Recently, her group (pictured below) demonstrated that serotonin is required for the development of both hypoxia-induced and dexfenfluramine-induced PAH in mice (Morecroft et al., Hypertension 49: 232-6; Dempsie et al., Circulation, 117: 2928-2937). They have previously demonstrated that serotonin can activate 5-HT_{1B} receptors to mediate both pulmonary vascoconstriction and pulmonary artery smooth muscle cell (PASMC) proliferation in human preparations. Uniquely, serotonin-induced proliferation of PASMC and pulmonary arterial fibroblasts can be via the serotonin transporter, and the group have shown co-operation between the transporter and 5-HT_{1B} receptors in mediating both proliferation and contraction.

Left to right: Kevin White, Neil McRitchie, Ian Morecroft, Mandy MacLean, Marta Baranowska, Yvonne Dempsie and Margaret Nilsen

Among other topics, current work in the lab investigates the interaction of serotonin with the BMPR2-activated Smad signalling pathway (in collaboration with Nick Morrell, Cambridge), novel *in vivo* gene transfer techniques targeting tryptophan hydroxylase and miRNA studies (in collaboration with Nick and Andy Baker (Glasgow), the effects of sex and oestrogens on the pulmonary serotonin system, and the role of mts1 and RAGE in PAH. Mandy is also PI on the Glasgow/Strathclyde Universities Integrative Mammalian Biology £3M award of 2007, funded by BBSRC, BPS, Pfizer, GSK, AstraZeneca, KTN, MRC, and SFC. She is on the BBSRC Animal Science Committee and the BBSRC Animal Physiology Working Group.

BPS Prescribing Sub-Committee

Simon Maxwell Prescribing Sub-Committee Chair

I'm very pleased to have been asked to chair the Prescribing Sub-Committee (PC), having been a member of the group over the last two years. I would like to start by paying tribute to the work of my predecessor, Professor Helen Leathard, who set up the group, led the planning of two successful BPS symposia, and did so much to make connections with respresentatives of non-medical prescribing groups. Her energy and enthusiasm will be greatly missed, but she has laid the foundations for future progress.

The main purpose of the PC is to provide a focus for developing BPS policy and responses to developments in this particularly high-profile area of medicines activity. It's not hard to find challenges ahead in the field of prescribing: adverse effects of prescribed medicines continue to be a leading cause of illness; prescribing errors are still easily identified in most hospital wards; newer expensive medicines are stretching drug budgets; electronic prescribing systems are being rolled out; communication with the public about medicines often leads to misunderstanding; numbers of trained prescribers from non-medical backgrounds have grown substantially; and, amid all of this, the level of access to adequate prescribing education remains questioned. The PC can't expect to overcome all of these problems but aims to provide a BPS response and, if possible, some action. The future PC work programme will include:

- Developing a brief BPS statement on safe prescribing practice;
- Overseeing and advising on the development of the Department of Health e-Learning for Health initiative in Clinical Pharmacology and Prescribing;
- Coordinating some research activities relevant to prescribing which might depend on input from BPS members;
- Updating guidance on education for safe prescribing, taking into account the statements by the GMC/ Medical Schools Council Safe Prescribing Working Group and the new version of Tomorrow's Doctors;
- Looking at the feasibility of developing a BPS 'Prescribing Certificate';
- Fostering links between the BPS and those representing new prescribing groups (eg BPS; RCN; GMC; RPS; AHP; NMC).

Through these and other activities we hope to try to raise the profile of the BPS as a relevant stakeholder in the process of improving prescribing in the health service.

Although Angel Gate will host occasional face-to-face meetings, the PC will largely work as a 'virtual group' meeting by teleconference, to make it as accessible as possible. Although the PC has an established membership, if you feel that you would like to make a contribution to the initiatives above, please feel free to contact me.

Simon Maxwell, University of Edinburgh

BJP's Future Impact

This is an interesting time to be setting out to lead the BJP team and to carry on Humphrey Rang's excellent stewardship. In January 2009, we will have the same publisher for BJP and BJCP, Wiley-Blackwell. This will allow the two journals to work together covering the whole of Pharmacology. Historically, the journals have been perceived as covering a narrow spectrum of pharmacology, we now have an opportunity to broaden this. We can also make more use of editorial content, drawing on expertise from across the whole spectrum. The intention is both to expand the reach of our publications and to provide a real showcase for Pharmacology and the BPS.

The editorial teams on both journals are fully committed to these goals and the publishers are enthusiastic about facilitating them, for example, having joint tables of contents and "virtual themed issues" that can cover both journals. Pushing the translational agenda, 'Bench to Bedside', will become much easier. The thematic concept and the increased use of reviews that we have developed in the last couple of years will be used to the full, and will be the bait to draw in related original papers. It will also allow better integration with the BPS meetings programme. It would be a drawcard if the editorial board could better reflect the diversity of pharmacologists, and we will work on this too. They should include a wider range of skill bases and viewpoints, such as more international experts, more women and more people from industry. We would welcome suggestions.

The BJP team and the publishers are moving towards a seamless transition to Wiley-Blackwell's system for the January 2009 issue. The BJP office team at Angel Gate have been exemplary in achieving this and have put us in a position to proceed to a "relaunch" later in the year. There will be a number of innovations revealed at that time, but a sneak preview, and one close to my own heart, will be the free availability of full colour, which, I believe, will prove a boon, and an incentive to publish in BJP for those of us using imaging and other visual technologies.

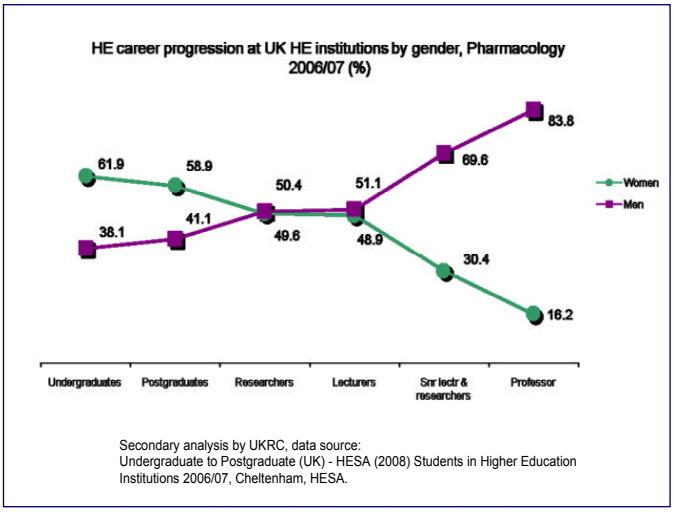
However, the journal's success depends only partly on what our team do. It will mainly depend on our authors submitting their best work. Our job is to encourage them to do that.

If every member of The Society submitted one of their best papers every year or so, the journal would benefit greatly. The trouble is that most of us submit our best papers to either non-specialist general journals, or to narrow specialist journals, with "high impact factors" according to the Thomson-ISI Citation Reports. This seems quite rational because many of our bosses, who know nothing about academic publishing, judge us by this criterion. Which is, of course, barmy because the important point about citations is how many times our own article is cited over its life, be it one year or twenty, not the average for the journal in the two calendar years after publication year (the basis of the commonly used "impact factor"). It looks as if the use of this particular "output measure" may be shifting because, as governments of countries and universities move towards metric-based assessment (e.g. in UK, Australia), they are realising that the actual piece of work is the important thing. For example, they are now looking at such things as the "H-factor", which evaluates the individual scientist by the citations of their work. Of course there will always remain an element of Kudos in the journals in which the articles appear. In this respect, BJP retains a reputation for high standards that we should be proud of.This is a long preamble to a plea to all of you to submit at least one of your best papers to BJP in the next couple of years. If a good proportion of you do so, and you are still obsessed about the "impact factor" of the journal, you can calm down because it will have rocketed.

Ian (JC) McGrath, BJP Editor-in-Chief elect

BPS Tackles the Gender Gap

Most senior pharmacologists will recognize this scenario: although they teach and may supervise a majority of female undergraduate and postgraduate students, there are frequently few women on committees, interview panels, or symposium programmes. In fact, this is not unique to Pharmacology and is representative of most of the science and engineering disciplines, with typically 50-60% representation of women amongst undergraduates, dwindling to only 12% representation amongst the Professorship; and overall, under 20% of SET (science, engineering, and technology) employees are women. The reasons are complex, from obvious factors like career breaks due to caring responsibilities to the less obvious (but nethertheless important) cultural and structural barriers, stereotyping, and unconscious bias. Whatever the reasons, such an attrition rate of highly trained personnel clearly represents loss of a valuable resource.



Secondary analysis by UKRC, data source:
Undergraduate to Postgraduate (UK) - HESA (2008) Students in Higher Education Institutions 2006/07, Cheltenham, HESA.

Collaboration with UKRC

In 2004, the BPS, represented by Professor Amrita Ahluwalia, started to tackle this issue in Pharmacology. As a first step, they embarked on a mentoring scheme for women to try to address the gender gap identified in the society's membership. This scheme was established with the support of the UK Resource Centre for Women (UKRC) in SET (science, engineering, and technology). Mentors are women who hold senior positions in academia, in industry, or in medicine. They are pharmacologists and clinical pharmacologists who have successfully progressed their careers while experiencing, to varying degrees, the issues that more typically affect women - career breaks, short-term contracts, juggling career and family commitments, and the challenges that these pose. Many of these women are motivated to take part in the scheme because of their own positive experience of mostly informal mentoring that they received from senior male and female colleagues during the earlier stages of their own careers. Mentees are typically at an early post-doctoral stage of their career, seeking encouragement and advice on how to move their own careers forward. To date over 30 junior female BPS members have been paired with a mentor, and the feedback from both mentees and mentors has been excellent. If you would like more information on the BPS women's mentoring scheme look out for our 'Women in Pharmacology' stand and leaflets at BPS meetings, or check out our pages on the BPS website. The next training session for mentors and mentees will take place soon; if you think that you might benefit from mentoring or if you feel that you could use your own experience to give advice to younger women at the beginning of their careers, get in touch (info@bps.ac.uk).


Amrita Ahluwalia &
Isla Mackenzie
WIP Committee Members

BPS's Women in Pharmacology Committee

In 2007 the growing success of the mentoring scheme led to the formation of a 'Women in Pharmacology' (WIP) committee, chaired by Amrita, with representation from early career stage members (currently Fliss (Felicity) Gavins, Imperial College); clinical pharmacology (currently Isla Mackenzie, University of Dundee), and academic pharmacology (currently Gillian Gray, University of Edinburgh). We are in the process of recruiting a woman from industry, so that we have representation from all interested and relevant groups. The remit of the committee is to continue to work with the UKRC to ensure successful administration of the mentoring scheme, but also to consider other ways of promoting women's careers in pharmacology.

Women in Leadership

In 2008, with the help of the UKRC, the WIP hosted a 'Women in Leadership' seminar. Surrounded by inspirational photographs of successful women nominated for UKRC's 'Women of Outstanding Achievement in SET', 44 women, mostly BPS members but also physiologists, neuroscientists, and endocrinologists from around the country, gathered on 25 September at the People's Palace at Queen Mary University of London. The event started with a tour-de-force from Professor Beverley Alimo-Metcalf, University of Bradford School of Management (www.realworldgroup.com), reviewing research on 'Gender & Management'. We were all encouraged to hear that women

are clearly good for organizations, with increased success deriving from increasing numbers of women on company boards. However, it was disappointing to learn that most organizations are still set up, perhaps unintentionally, to reward more typically male leadership values and behaviours preventing more women from reaching senior roles. One of the underlying reasons for this appears to be the fact that appointment systems were traditionally set up by men for men and that we are left with the relics of this system even today. There is a natural tendency for people to appoint others like themselves, and this may perpetuate the lack of senior women when appointment committees remain largely male-dominated. A similar principle exists in selection of fellow committee members, and even chairpersons and speakers at meetings. In the afternoon of the Leadership seminar Professor Teresa Rees, Pro-Vice Chancellor for Research, Cardiff University, made the point that women need to remain true to themselves and their own values while trying to change institutions by promoting equality and diversity, something which she has done to amazing effect. The UKRC (Annette Williams, UKRC Director) is clearly making progress in educating institutions about the need for change, identifying barriers to advancement and helping to break them down. Academic credibility remains the principle key to advancement for all, male and female. Professor Dame Nancy Rothwell, Deputy President and Vice Chancellor, University of Manchester, discussed this among other factors required for successful leadership in academia. While recognizing that there are relatively few female role models, she felt that leadership behaviours seen as effective in higher education are more common in women and that women are not necessarily disadvantaged. In fact she saw being in a minority as a positive factor that had given her the opportunity to participate in many events from which she might not otherwise have benefited. Professor Jackie Hunter (Senior VP Science Environment Department GlaxoSmithKline) fittingly finished the day by highlighting the importance of networking and self-promotion skills in personal and business development. A quick straw poll of the audience revealed that while many recognized the importance of these skills, tellingly few had the confidence to put them into practice effectively. The day was certainly a success on the networking level, bringing together senior BPS members from all parts of the country. The speakers gave us plenty of food for thought and more than a little inspiration.

Terry Tetley, Sissie Wong & Deborah Clarke, networking at the BPS Leadership Seminar

The Future for Women Pharmacologists

Increasing the visibility of successful women scientists as role models is another important item on the WIP agenda. Despite no lack of skill or merit, women are typically poorly represented amongst symposia speakers or winners of prestigious prizes in all fields of science. This issue has been the topic for a series of articles in Nature (www.Nature.com), including a contribution from Professor Annette Dolphin, UCL, highlighting the lack of female winners of prestigious Biochemical Society prizes. This situation might be improved by encouraging female pharmacologists to nominate themselves and each other for existing awards and as symposia speakers. Alternatively, the BPS could consider following the path of other professional bodies and societies and recommend more positive action, e.g. awarding a specific prize for women, such as the Royal Society's prestigious Rosalind Franklin Award (www.royalsociety.org).

Jackie Hunter

Recent government research suggests that women will not reach equal pay and recognition in the UK until 2095 (www.equalityhumanrights.com). However, things are looking optimistic for women in Pharmacology, with the most recent data on BPS membership showing an increase in female representation among members and senior fellows, in comparison to our statistics of 2004 (see www.pa2online) A quick look through 'Pharmacology Matters' also reveals that more female members are taking on senior roles in running the Society, and the WIP committee feels that the appointment of a women as its Chief Executive is a positive step by the BPS towards increasing the representation and influence of women in senior positions. The WIP committee aims to build on these signs of success by equipping women with the skills necessary to fulfil their potential in pharmacology and clinical pharmacology.

If you are a women interested in promoting your career, a woman or a man who wants to promote the careers of women working with you, or if you are interested in participating in mentoring or networking, look out for our stand and leaflets at BPS meetings and events advertised on the BPS website or contact info@bps.ac.uk. New faces are always welcome.

BPS Women in Pharmacology Sub-Committee

Useful Links

UKRC (UK Resource Centre for Women in SET);
www.ukrc4setwomen.org

The Greenfield Report (resulted in the formation of the UKRC)
www.set4women.gov.uk/set4women/research/the_greenfield_rev.htm

UKRC for Women in SET'S Annual Conference, Pharmacology Matters, Volume 1 Issue 1, 16-17, 2008
www.bps.ac.uk/uploadedfiles/PharmacologyMatters/PMJune08.pdf

A Mentoring Scheme for Female BPS Members
http://www.pa2online.org/articles/article.jsp?volume=3&issue=11&article=44

uk resource centre for women in science, engineering & technology

Computer Assisted Learning (PharmaCALogy) series—Asthma Update

Roger Small
Honorary Reader,
University of
Manchester

pharma-CAL-ogy is the product name for a range of over 50 software and Teachers' Workbooks titles produced by pharmacologists and distributed by the British Pharmacological Society.

Areas covered include:

Drug Metabolism; Drug Targets; Neuropharmacology; Cardiovascular System; Simulations; Clinical Development; Asthma and Inflammation

The products are designed to meet identified teaching needs and can be implemented in various way. A tutor's guide is available for each product and explains the variety of ways in which the material can be used to meet various learning objectives. See also Teaching and Learning Resource Packs. TLRPs contain, in editable format, the materials teachers will need to properly integrate particular CAL software packages into their courses.The materials are delivered as interactive software supplied on CD-ROM for Windows stand alone, network and in many cases inter/intranet delivery A full list of the materials available with comprehensive product descriptions and pricing information can be found on the BPS website

Programme development and recommended method of use

Clive Page and David Dewhurst were the principal authors of the original pharmaCALogy programme entitled "Asthma". This programme has now (2008) been updated and expanded by Roger Small. "Asthma" is a highly interactive programme that has been written mainly for use by undergraduate students of dentistry, medicine, nursing, pharmacology, and pharmacy. However, it could also be of value as a revision aid for postgraduate students (e.g. medical postgraduates preparing for their Royal College examinations). The programme is suitable for independent study (primary learning or revision). It is divided into a number of topic-based sections. These are listed in a main menu, from which the student can choose a particular topic for study. Each section is followed by a series of multiple-choice questions so that the student can perform some self-assessment. Within each topic section an "Options" button gives the student access to other facilities, such as a list of the aims and objectives of the programme, the "Help" pages (an explanation of how to use the programme), a glossary of terms, and some useful references.

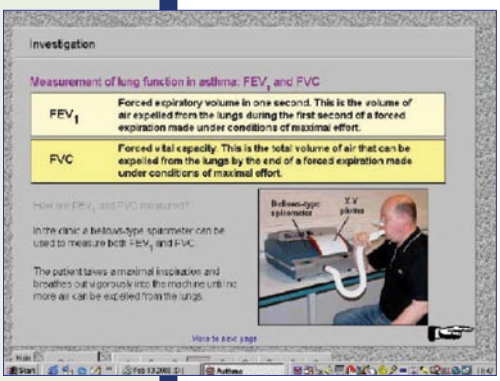


fig 1

To obtain maximum benefit from a CAL programme it is essential that it be integrated with other teaching/learning material. Students do not gain maximum benefit if provided with a piece of software and told to "use it to help you learn". Teachers who do not fully integrate CAL material will generally be disappointed with the effectiveness of CAL and students' responses to it. Students are expected to refer to library sources in the normal way, and only a few key references have been included in the programme. To study the whole programme in detail might take 3-4 hours. However, it is strongly recommended that students use the programme in separate sessions of about 30-40 minutes duration.

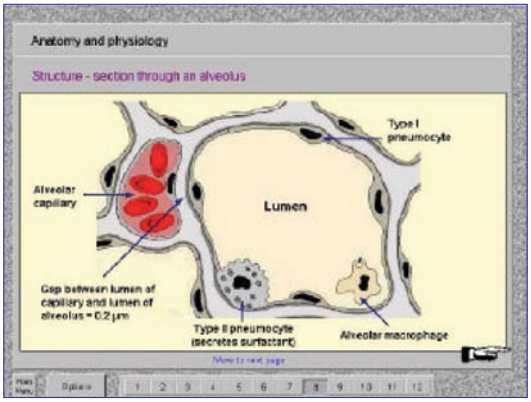


fig 2

Aims and objectives of the programme

A principal aim of "Asthma" is to enable students to learn the signs, symptoms, pathophysiology and pharmacological treatment of bronchial asthma. On completion of this programme students should be able to:

1. Outline the structure and normal physiology of the airways;
2. Explain how some aspects of respiratory function are measured;
3. Describe the pathophysiological changes that occur in asthma;
4. Understand the principles underlying the use of drugs to treat the causes and symptoms of asthma;
5. Describe the various devices used to administer drugs by the inhaled route;
6. Understand some of the clinical consequences of asthma.

Introduction

The programme begins by testing the student's knowledge of the epidemiology of bronchial asthma in the UK. The student is invited to estimate the

annual costs incurred by the NHS in treating asthma and the annual costs of asthma in terms of lost production. The student's prior knowledge of the pathophysiology, signs, and symptoms of asthma is also put to the test.

Anatomy and physiology (fig 2)

The student is asked to estimate the surface area for gas exchange in the lung. By means of an interactive, animated diagram the student is next invited to identify various parts of the respiratory tract. Each of these structures is then illustrated in more detail. Interactive, animated diagrams are used to describe not only the innervation of airways smooth muscle but also the neurotransmitters involved and the postjunctional receptors on which they act.

Investigation (fig 1)

This section of the programme opens with a definition of PEFR and a description of its measurement using a peak flow meter. The influence of asthma on PEFR is demonstrated by an interactive diagram and is placed in a clinical context by reference to patients' use of peak flow diaries in the self-management of their condition. FEV_1 and FVC, are defined and their measurement by a bellows-type spirometer is described. Interactive diagrams are used to illustrate the effects of asthma on FEV_1, FVC and FEV_1/FVC ratio. The student is informed that the low FEV_1/FVC ratio seen in asthma indicates an obstructive ventilatory disorder. Further interactive, animated diagrams show the effects of some anti-asthma drugs on FEV_1, FVC, and FEV_1/FVC ratio.

Pathophysiology (fig 3)

The chronic airway inflammation associated with asthma is illustrated by a diagram, in which the features of the healthy airway wall are compared with those of the airway in asthma. This diagram is supported by appropriate photomicrographs. Mediators of the inflammatory changes that occur in the airway wall are listed in a table. Interactive, animated diagrams are used to define bronchial hyper-responsiveness (BHR), to show how BHR functions as an index of asthma severity and to illustrate the possible mechanisms underlying BHR. Further interactive, animated diagrams are used to illustrate the early and late phases of an attack of allergic asthma. The morphology of a mast cell is shown in an electron micrograph. The role of mast cells in the early phase of airway smooth muscle contraction (release of preformed mediators and mediators synthesized *de novo*) and their role in promoting the migration of eosinophils and neutrophils into airway tissue are illustrated using interactive diagrams. The role of mononuclear cells and platelets in the early phase of an attack of allergic asthma is discussed, along with their ability to activate eosinophils and other inflammatory cells, thereby initiating the late phase response. A series of interactive, animated diagrams shows how allergen exposure causes the release of cytokines from activated Th2 cells and how these cytokines activate eosinophils and mast cells, thereby triggering the release of mediators responsible for the late phase in an attack of allergic asthma. The role of cytokines and growth factors in causing long-term structural changes in the airway wall is illustrated in a diagram.

Pharmacology

This major section of the programme initially classifies anti-asthma drugs as bronchodilator/relievers or preventer/prophylactic agents. Students are then offered a menu from which they may choose to study any one of the principal types of anti-asthma drug. The section on agonists at β_2-adrenoceptors opens with an account of how the agonists selective for β_2-adrenoceptors were developed from adrenaline (epinephrine). The many locations of β_1- and β_2-adrenoceptors in the body and the effects that such receptors mediate are listed. The chemical modifications to the adrenaline molecule that yield selectivity for β_2-adrenoceptors together with an adequate duration of drug action are described. Salbutamol, terbutaline, formoterol, and salmeterol are used as examples. The structure of the β_2-adrenoceptor forms part of a sequence of interactive, animated diagrams that outlines the biochemical cascade triggered by β_2-adrenoceptor activation in airways smooth muscle. Effects other than relaxation of airways smooth muscle that may contribute to the anti-asthma action of agonists at β_2-adrenoceptors are listed. A series of diagrams is used to illustrate and explain the unwanted effects of β_2-agonists. Finally, the place of β_2-agonists in the British Thoracic Society (BTS) guidelines for the treatment of asthma is shown in the form of a table.

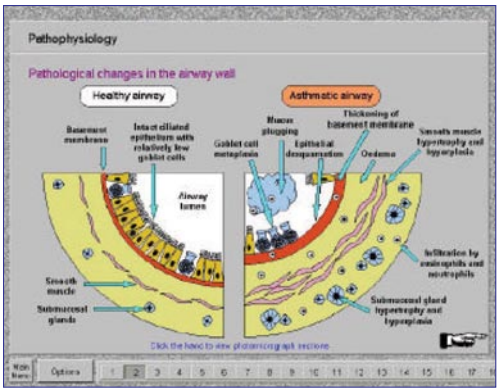


fig 3

The section on ipratropium opens with a discussion of the peripheral effects mediated by muscarinic M_2 and M_3 receptors. The chemical structures of acetylcholine, atropine, and ipratropium are compared in a table. The selectivity of inhaled ipratropium for muscarinic receptors located in the lung is explained in terms of selective administration (inhaled route) and selective distribution (quaternized nitrogen atom yielding poor absorption across mucous membranes). This section concludes with discussion of the unwanted effects of ipratropium and its usefulness as an anti-asthma drug.

The section on alkylxanthine bronchodilators opens by comparing the chemical structures of theophylline and caffeine and by pointing out that strong cups of tea and coffee can contain alkylxanthines in doses sufficient to have a therapeutic effect in asthma. The pharmacological effects of theophylline are listed, and an interactive, animated diagram is used to illustrate the effects of inhibiting the various isoforms of cyclic nucleotide phosphodiesterase (PDE) in the lung. The roles of PDE inhibition and adenosine antagonism in mediating the anti-asthma effects of theophylline are discussed, along with the unwanted effects of this drug. The pharmacokinetic factors that influence the use of theophylline as an anti-asthma drug and its place in the BTS guidelines are described. The section concludes with a brief account of aminophylline, a water-soluble complex of theophylline and ethylenediamine.

The glucocorticosteroid section describes the various zones of the adrenal cortex, the steroids produced by each zone, and the biological effects of these steroids. The rationale for the development of glucocorticosteroids suitable for inhalational administration in asthma is provided. Beclomethasone dipropionate, budesonide, and fluticasone are used as examples and an interactive screen allows the student to obtain further details for each agent. Prenisolone and hydrocortisone are used as examples of glucocorticosteroids that can be administered by the oral and intravenous routes respectively. A series of interactive, animated diagrams is used to explore the nuclear mechanism of the anti-inflammatory action of the glucocorticosteroids. Further screens illustrate the useful effects of glucocorticosteroids on cells,

enzymes, and mediators involved in inflammation of the lung. The beneficial effects of glucocorticosteroids on the expression of β_2-adrenoceptors in the lung are also discussed. The unwanted effects of inhaled and orally-administered steroids are illustrated by means of diagrams and photographs. The way in which abrupt withdrawal of orally-administered steroids can lead to adrenocortical insufficiency is demonstrated by means of an interactive, animated diagram. The section concludes with a table showing the place of the glucocorticosteroids within the BTS guidelines for the treatment of asthma.

The chemical structures of sodium cromoglicate and nedocromil are used to introduce the section on cromones. Further screens list the possible mechanisms of the anti-asthma action of the cromones and the unwanted effects of these drugs. This section concludes with discussion of the use of the cromones as anti-asthma drugs.

The section on montelukast and zafirlukast (antagonists at the *Cys*LT$_1$ receptor) includes an animated diagram showing the synthesis of cysteinyl leukotrienes. The effects of *Cys*LT$_1$ receptor activation that may contribute to the pathogenesis of asthma are listed. The section concludes with an outline of the unwanted effects of montelukast and zafirlukast, together with an indication of their place in the BTS guidelines for the treatment of asthma.

Inhaler devices

In this section the advantages of drug administration by the inhaled route are outlined, together with the effect of inhaled particle size on drug deposition in the lung. The metered dose inhaler (MDI) is described by means of a labelled photograph and mention is made of the importance of CFC-free propellants. Methods of compensating for poor technique in the use of MDIs are discussed in terms of breath-activated MDIs and spacer devices. The distribution of the inhaled drug dose within the body is illustrated by a diagram. Various devices used for inhalation of drugs as dry powders are described by means of labelled photographs. These devices include the Diskhaler®, Accuhaler®, and Turbohaler®. Benefits of the colour coding of inhalers are mentioned. Nebulizer devices are described and shown in action by means of photographs. The importance of nebulizer use in severe asthma is discussed.

Clinical case study

The final section of the programme comprises a case study of a patient with atopic asthma.

Two clinical scenarios are entertained – an initial consultation and an emergency visit. If the scenario of an initial consultation is chosen from the menu, the student can call up the patient's medical history and presenting symptoms. Medical notes can be called up to explain the presenting symptoms. The student can also choose to be tested on occupations that are known to trigger asthma or the clinical investigations that might be appropriate to the initial consultation. If the scenario of an emergency visit is chosen from the menu, the student can call up the presenting symptoms and is then asked a series of questions relevant to those symptoms. Choosing "Investigation" from the menu outlines two tests that give a indication of the severity of the asthma attack while choosing "Examination" from the menu reveals that the patient might exhibit tachycardia, tachypnoea, cyanosis, or bradycardia. Definitions of each of these terms can be called up. Finally, under "Treatment" the student is asked to choose the correct level of treatment within the BTS guidelines.

Roger C. Small, BSc, MSc, PhD, DSc, FRPharmS, Honorary Reader, University of Manchester

How the BPS supports *in vivo* Pharmacology in the UK

Mike Collis
Industrial Liaison Officer

Integrative *in vivo* studies form an essential component of many research programmes. They are often the key factor in translating information from the genome into advances in the understanding and treatment of disease. Experiments using animals must always be conducted to the highest standards of welfare, encapsulated in the principles of the "3Rs" (reduction, replacement, and refinement), and we can be justifiably proud that the standards of animal welfare in the UK are the highest in the world. As a consequence, UK pharmacologists and physiologists undertaking research involving animals must be trained by experts, so that they have a clear understanding not only of the technical issues, but also of the ethical and welfare aspects of *in vivo* work. Thus, education and training needs to include instruction in experimental design, to ensure that the appropriate number of animals are used in each experiment. It should also include consideration of the alternative experimental approaches that might replace the need for an animal experiment. Unfortunately, there is an abundance of evidence available that the opportunities for expert training and education in *in vivo* pharmacology (and physiology) have diminished over the last two decades in UK universities (1,2).

In response to this problem, the BPS has taken the lead in supporting high quality *in vivo* training and education in the UK. In fact there are currently three distinct BPS funds that support high quality *in vivo* training and education. These funds have developed at different times and with differing objectives. The steering groups that manage the three funds, however, interact closely and have members in common. The existence of three distinct funds supporting *in vivo* training, can be confusing and the purpose of this article is to explain the differences between them.

The **BPS *in vivo* Pharmacology Training Group** has been in existence the longest and was set up to provide small grants to support Pharmacology Departments that provide *in vivo* education to undergraduate students. The grants are scaled to the number of students being trained and were originally introduced to cover the costs of obtaining a Home Office licence for the students. The grants are not intended to cover the full costs of training. Approximately eight grants are made each year and the money is donated by a number of pharmaceutical companies. During the years, the Training Group has noted a gradual decline in the number of departments applying for these grants, which is indicative of the decline in the opportunities for this type of education and training. It is very encouraging to note that last year there was an increase in applications, perhaps a sign that more academic institutions are recognizing the importance of this type of training.

Despite indications of an upturn, the number of universities that offer *in vivo* training at undergraduate level is still small. Many undergraduate and postgraduate students of pharmacology and physiology cannot access this training at their home institutions. In response to this problem, the BPS and The Physiological Society joined together 7 years ago to launch **Short Courses on Integrative *in vivo* Pharmacology/ Physiology.** These courses are aimed at both undergraduates and postgraduates. Three residential courses, of one week duration, are currently run each year at Bristol University, Kings College London, and Glasgow University. Funds are provided for the students selected for the courses to cover travel, accommodation, attendance at a Home Office modules 1-4 training course, and the subsequent *in vivo* training course. The costs of running the university courses are also covered. This is achieved by a combination of grants from the Wellcome Trust, the BBSRC, the two Societies, and the Pharmaceutical Industry. The cost of putting on these courses is approximately £1500 per candidate and the competition for places is strong (calls for nominations go out via Heads of Departments in the 4th quarter of the year preceding the course). The feedback from students lucky enough to attend the courses is very positive; many of them decide to continue *in vivo* research in their academic or industrial careers because of these courses.

The most recent BPS initiative to support *in vivo* training is the BPS Integrative Pharmacology fund (IPF), which was founded in 2004. The three largest pharmaceutical companies with research and development operations in the UK - AstraZeneca, GlaxoSmithKline, and Pfizer - committed £1 million a year for a four-year period to support research in UK universities in the fields of Pharmacology, Physiology, and Toxicology. The aim of this fund is to build UK capacity for high-quality *in vivo* animal research relevant to the discovery of new medicines, through the training and development of scientists in this field. The strategy behind the fund is to make flexible grants to institutions in the academic sector with the greatest expertise in this area, and which demonstrate the highest standards of animal welfare. As the BPS was already supporting undergraduate training (see above) when the IPF was established, it has concentrated on postgraduate training and support.

BPS Initiative	Educational Level	Objective	Calls for Applications	Grants	Donors
In vivo pharmacology training group **	Undergraduate	Partial support for departments that offer *in vivo* training	Contact BPS	< £10 K to departments	Pharmaceutical Industry
BPS/Physiological Society Short Courses	Undergraduate and Postgraduate	Practical courses for those who cannot get *in vivo* training at home institution	Autumn each year via HODs	£25-30K per course	Pharmaceutical Industry, Wellcome Trust, BBSRC, BPS, Physiological Society
BPS Integrative Pharmacology Fund	Will support at all levels but generally Post graduate	Build capacity and sustainability for *in vivo* research and training	New funding opportunities will be advertised widely, when they become available	£18K(PhD support) – £500K (Capacity Building Awards)	Pharmaceutical Industry, BBSRC, MRC, HEFCE,SFC, DIUS

Early after its formation, the IPF Steering Group decided that its strategy should be to seek co-funding opportunities with Government and charity funders of research. In addition, to "swelling the coffers", the strategy of co-funding has the potential to influence Government funders and policy makers to give higher priority to *in vivo* sciences. This has proved a very effective approach, and the £4 million donated by the three companies has facilitated about £17 million of new money to support *in vivo* research, education, and training. The activities of the IPF have been reviewed in a recent pA2 article (3) and I shall not repeat them in detail here, but in brief it has supported PhDs, Academic Research Fellows, and Capacity Building Awards in Integrative Mammalian Biology. The steering group is currently liaising with other funders on new potential co-funding opportunities. These will be advertised widely to society members when they become available.

As pharmacologists we all know that (at the present time) research cannot translate advances in knowledge about disease into new drugs and improved health care without *in vivo* animal studies. Members of the BPS can feel proud of the very significant support the society is giving to the training and development of *in vivo* pharmacologists (4) to perform these essential studies to the highest standards of science and of animal welfare.

Mike Collis, Industrial Liaison Officer

** The *in vivo* pharmacology training group has recently introduced a new scheme to fund the costs of Home Office training and the acquisition of personal licences for final year undergraduate pharmacologists undertaking final year *in vivo* research projects. See the BPS web-site for details.

References

(1) A survey of integrative physiology/pharmacology teaching undertaken by the BPS and the Physiological Society. 2004; pA2. 3:10-11.

(2) *In vivo* sciences in the UK: sustaining the supply of skills in the 21st century. 2007; http://www.abpi.org.uk/Details.asp?ProductID=325.

(3) The British Pharmacological Society Integrative Pharmacology Fund – 2 years on and still growing. pA2 2006; 4: 8-16.

(4) Collis MG. Integrative pharmacology and drug discovery--is the tide finally turning? Nat Rev Drug Discovery 2006; 5: 377-9.

Meetings Report

Mandy MacLean
Vice President
(Meetings)

Greetings from Meetings! Well we are gearing up for Brighton 2008 and encourage everyone to check out the really exciting programme on the BPS web-site. As always there also will be a stimulating programme for the Young Pharmacologists, beginning with the Young Person's pub quiz on Tuesday evening, which all are welcome to attend. The following day will be 'the Young Persons' Day, which will include poster presentations for the CPS Undergraduate Medical Prize and the TiPs Young Pharmacologist of the Year prize symposium. Members of the Young Persons' Committee will also be chaperoning a group of undergraduates who are attending the meeting for the first time and they will also be presenting posters. (See pg 10 and the advert on pg 20). As Arthur Weston's article said (July PM E-bulletin), EPHAR was a huge success. It was not all plain sailing, however (we may have looked like the proverbial graceful swan but we were all paddling like fury under the water!), and there was an ominous start to the meeting when the Meetings Manager Luisa dropped a table on her foot -thanks Luisa for an excellent job done and for soldiering on regardless! Arthur gave us all a very strict lecture on how to behave at BPS meetings at the Civic reception! We were, however, grateful that a mistake had been made on the official invitations to this event and we were not to be entertained by the 'Manchester Gay and Lesbian Choral Society' after all!! Arthur also managed to save face when he almost nicked the Lord Mayor's camera in error! We also had a memorable display of 'Where's Wally', when one delegate tried in vain to identify old friends by holding up photos with faces circled at every opportunity. It all added to the flavour of the meeting, which seemed to leave everyone with a very good taste in their mouths. The main feedback I received (all positive!) from many many people was 'thanks' for an excellent, dynamic meeting, which was very reminiscent of BPS meetings of old with a great deal of discussion and interaction. We can promise you all that Brighton will taste just as good!

The 6th James Black conference was held on 16-17 August in St Andrews and was on 'New pain concepts and future treatments'. It was an excellent meeting with an extremely high-quality programme. It retained the flavour of a 'Gordon Conference' and many delegates said it was the best 'Pain' meeting they had been to for a while. I think it helped that the speakers (and Ivor!) were invited for a round of golf on the new 'Castle Course' the day before. Apparently, playing this course was more challenging, exhausting and frustrating than getting grant funding—surely not! It seemed appropriate that it was not painless. A very big thank you to Roger Whiting and Praveen Anand for organizing this excellent meeting. The 7th James Black Meeting will be 1-3 September 2009 in London, it will be on 'Integrative

Back from left: Hakan Alfredsson and Rolf Karlsten.
Front from left: Roger Whiting and Ivor Williams

Mammalian Biology' and will bring together all the PhD students, Fellows, and Lecturers funded by the Integrative Mammalian Biology awards and the BPS IPF fund. Next year we have a programme of meetings brimming over with variety. We will have an excellent meeting on 'Ion channels as therapeutic targets' which will be co-hosted with the Royal Society of Chemistry and will be held at Novartis, Horsham, 5-6 Feb. Thanks to Ian McFadzean for co-ordinating this on behalf of the BPS. There will also be another 'Cell Signalling' meeting on 20-21 April in Leicester, which promises to be just as exciting and successful as previous meetings, organized by Andrew Tobin and John Challis. In May (7-9) there will be a joint meeting with the two German Pharmacology Societies in Dresden on 'New drugs in cardiovascular research'. Check out the BPS website for details of all these meetings.

See you all in Brighton.

Mandy MacLean, Vice-President Meetings, University of Glasgow

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

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For more information visit **www.brjpharmacol.org**

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Future Meetings

2008

16-18 December—BPS Winter Meeting
Brighton, UK. E-mail: meetings@bps.ac.uk

18-19 December— General and Advanced Receptor Theory Workshop
Brighton, UK. E-mail: meetings@bps.ac.uk

2009

5-6 February—Joint Meeting with the Royal Society of Chemistry 'Ion Channels as Therapeutic Targets'
Novartis Horsham Research Centre, UK

Spring 2009; date TBC— Integrative Pharmacology Workshop
Bristol University

Spring 2009; date TBC—Statistics Workshop

20-21 April 2009—3rd Focused Meeting Cell Signalling
University of Leicester, Leicester, UK

7-9 May—Joint Focused Meeting with DGPT 'New Drugs in Cardiovascular Research'
Dresden, Germany

25-29 June—Royal Society of Chemistry Medicinal Chemistry Summer School
University of Nottingham, UK. E-mail: hart1@rsc.org

8-10 July—BPS Summer Meeting
University of Edinburgh, UK. E-mail: meetings@bps.ac.uk

12-15 July—EACPT Congress of the European Association for Clinical Pharmacology and Therapeutics
Edinburgh, UK

12 July— A symposium hosted by The British Pharmacological Society, in association with the 9th Congress of the European Association of Clinical Pharmacology and Therapeutics (EACPT) 'Clinical Pharmacology: Working with Patients'
Edinburgh, UK. www.bps.ac.uk

1 September— Early Phase Trials of New Drugs Workshop
King's College, London

1-3 September—7th James Black Conference 'Integrative Pharmacology and Physiology'
King's College, London, UK

15-17 December—BPS Winter Meeting
E-mail: meetings@bps.ac.uk

2010

17-23 July- WorldPharma 2010 (IUPHAR Congress)
Copenhagen, Denmark

For further information about any of these meetings please email meetings@bps.ac.uk or visit www.bps.ac.uk

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