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PHARMACOLOGY MATTERS

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Nutrition Special Issue

In this Issue:

Pg 4. Eat Your Beets!

Pg 6. Wine and Cardiovascular Health Beyond Antioxidant Properties

Pg 9. Dietary Supplements: a Source of Regulatory Confusion

Pg 11. An Introduction to Parenteral Nutrition

Pg 14. The Importance of Nutrient-Gene Interactions in Health: an example from the micronutrient selenium

Pg 16. Vascular Protection Afforded by Isoflavones

Pg 24. Pharmacologists in the Oxford Dictionary of National Biography

Pg 33 Preserving Clinical Pharmacology in the NHS?

PHARMACOLOGY MATTERS

Editorial

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

Front cover Image:
The obese Tuscan General Alessandro del Borro, died fighting the Ottoman Empire in a naval battle of the coast of Corfu in 1656. His portrait, attributed to the French artist Charles Mellin (1597-1649), hangs in the Kunsthistorisches Museum in Vienna.

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Hazel O'Mullan
Managing Editor

This issue of Pharmacology Matters is focused to complement a series of articles due for publication in the British Journal of Pharmacology (BJP) later this year. The themed issue entitled "Advances in Nutritional Pharmacology", edited by Cherry Wainwright, focuses on the value of dietary components to cardiovascular health:

> *Understanding the pharmacological mechanisms by which nutritional elements confer their health benefits enables us to keep the public informed, but also aids in the identification of new targets for drug development. In recent years there has been significant progress in this field, for example the identification of a receptor for niacin and the subsequent development of selective agonists as lipid lowering agents, the development of new Vitamin D analogues and greater insight into the mechanisms underlying the beneficial cardiovascular effects of omega-3 fatty acids and resveretrol. The themed issue on "Advances in Nutritional Pharmacology", aims to provide a valuable and timely update on progress in these areas. Cherry Wainwright*

The value of good nutrition as preventive medicine is crucial to health. We strongly suspect that our cover-boy, Alessandro del Borro, had both diabetes mellitus and hypertension. [He may actually have had Cushing's syndrome, and overeating may have been nothing to do with it, but that is only supposition.]

Much of this issue centres on cardiovascular protection afforded by, amongst others, wine and beetroot. Other chemicals originally considered to be nutritional supplements, are now used therapeutically, for example, folic acid is taken to prevent neural tube defects in babies. The interaction of nutritional supplements, and foods, and the effects they have on therapeutic drugs is an area of mass media interest and research. Examples include: grapefruit juice and certain calcium channel blockers: warfarin and vitamin K.

You will also find our regular meetings report, a profile of Emily Davies, (*in vivo* short course participant) and other articles of interest, including, 'Preserving Clinical Pharmacology in the NHS?'. All comments and/or questions about any articles in this issue, should be referred to the Managing Editor, hom@bps.ac.uk.

Contents:

Themed Articles

Eat Your Beets! 4

Wine and cardiovascular health beyond antioxidant properties 6

Dietary Supplements: a Source of Regulatory Confusion 9

An Introduction to Parenteral Nutrition 11

The Importance of Nutrient-Gene Interactions in Health: an example from the micronutrient selenium 14

Vascular Protection Afforded by Isoflavones 16

Features

BPS Media Update 21

BPS Diploma 23

Biotechnology YES: A Contestants Perspective 23

Pharmacologists in the Oxford Dictionary of National Biography 24

Biology in the Real World brought the Curriculum to Life! 30

The BSF Education Colloquium: Supporting Outreach and Enrichment in Schools 31

Life Sciences Career Conference 2008 32

Preserving Clinical Pharmacology in the NHS? 33

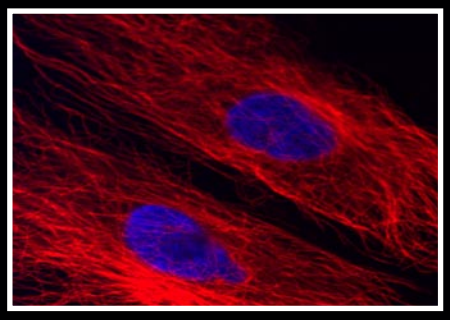
Regular Features

BPS Meetings Report 22

BPS Diploma Workshop Report: GART 26

Profile: Emily Davies 29

Future Meetings 35



Institute of Cancer Therapeutics

The Institute of Cancer Therapeutics (ICT) is based in the science quarter at the heart of the University of Bradford campus. The Institute's MSc courses reflect the growing need to address the short fall in specific areas of expertise and have endorsement from major pharmaceutical companies and The Medical Research Council.

The following courses are available:

All courses start in September and are full-time only

MSc in Cancer Pharmacology
MSc in Safety Pharmacology
MSc in Drug Discovery

Students who undertake the Masters in Cancer Pharmacology will focus on developing a fundamental understanding of the actions of anti-tumour drugs on cancer processes at a molecular level. Those undertaking the Masters in Safety Pharmacology will gain expertise in identifying potential adverse effects of potential new medicines and the significance of these effects in terms of clinical development, a modern and exciting discipline central to the pharmaceutical industry. Whether you are a chemist or biologist who has elected to undertake our Masters in Drug Discovery you will draw benefit from our expertise in medicinal chemistry and translation pharmacology which will provide you with the tools necessary to design and develop new treatments for disease.

All our taught courses and research degrees draw on the expertise in chemistry, chemical biology, toxicology and molecular pharmacology embedded in the Institute as well as appropriate experts from the School of Life Sciences, Pharmacy and from Industry.

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Entrance Requirements

Candidates for MSc in Cancer Pharmacology and Safety Pharmacology should normally have a first degree in a science subject at Honours level or equivalent, with a classification of 2:2 or above. For the MSc in Drug Discovery applicants should normally have a first degree in a chemical or biological sciences subject at Honours level, with a classification of 2:2 or above. Applications are welcome from candidates with non-standard qualifications, who have significant relevant experience; each case will be considered on its merits, and such applicants should contact the relevant MSc Course & Admissions Tutor.

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www.cancer.brad.ac.uk'

Eat Your Beets!

Andrew. J. Webb and Alexandra. B. Milsom

Beetroot, regarded as a panacea by the ancients, has long been considered beneficial to the blood, the heart and the digestive system (Grieve 1931). It has been used as a herbal remedy for constipation, a cure for bad breath, coughs and headaches, and even as an aphrodisiac (Nottingham 2004). Now a recent study performed at Barts and The London School of Medicine & Dentistry has shown it can also lower blood pressure (Webb et al, 2008).

Healthy subjects received 500ml beetroot juice or an equivalent volume of water in a cross-over study and had their blood pressure monitored over a 24 hour period. A peak difference in systolic blood pressure was achieved at 2.5 hours after ingestion in the beetroot juice arm of the study with a drop of 10.4±3.0 mmHg compared to the water arm of the study. Peak differences in diastolic blood pressure and mean arterial pressure were further observed at 3 hours after ingestion, with changes of 8.1±2.1 mmHg and 8.0±2.1 mmHg respectively. In addition to a reduction in blood pressure, the study also showed that beetroot juice could reduce platelet aggregation and also protect against ischaemia-reperfusion induced endothelial dysfunction (Webb et al, 2008).

These effects were attributed to nitrate, a metabolite found at high concentration in beetroot. Nitrate (NO_3^-) can be reduced to nitrite (NO_2^-) by commensal bacteria in the oral cavity and re-enter the stomach in the saliva (Lundberg et al, 2004). Following ingestion of beetroot juice, plasma nitrite levels increased over time and correlated with the reduction in blood pressure. This reduction was abolished if the subjects spat out their saliva for the first 3 hours of the study.

Nitrite and nitrate are oxidative products of nitric oxide (NO). In the cardiovascular system endothelium-derived NO is a potent vasodilator and plays a pivotal role in the control of blood pressure (Moncada et al, 1991). The pathway of nitrite reduction to NO has been attributed to chemical acidification and a nitrite-reductase activity of various endogenous proteins including endothelial nitric oxide synthase (eNOS), xanthine oxidoreductase, deoxy-haemoglobin and -myoglobin, and certain mitochondrial enzymes (Lundberg et al, 2008). A reduction in NO bioavailability is thought to be a key event in endothelial dysfunction, the presence of which has been implicated in the pathology of cardiovascular disease (Le Brocq et al, 2008). Constitutive NO production in the vasculature by eNOS is also reduced during hypoxia, a condition under which the nitrite reduction pathway is enhanced. Indeed, nitrite has been used successfully to protect against ischaemia-induced tissue damage in a number of ischaemia/reperfusion models (Sinha et al, 2008).

Following the discovery in the 1980's that NO acted as a physiological messenger in mammalian cells (Furchgott and Zawadzki 1980; Ignarro et al, 1987; Palmer et al, 1987), nitrite and nitrate were viewed as inert end products of the NO pathway. An indifference to nitrite and nitrate was not however shared by our ancestors and their historical role in medicine, explosives, and food preservation make for a fascinating read (Butler and Feelisch 2008). Pedanius Dioscorides (40CE-90CE) in his five volume book, De Materia Medica (a precursor to modern pharmacopoeias) recommends the juice of beetroot (due to the high potassium nitrate) combined with honey as a cure for headache and earache. He also recommends rubbing the roots and leaves on to the scalp to prevent hair loss and on the loins for digestive or procreative purposes (Gunther 1959). A recipe from the medieval period suggests placing a mix of potassium nitrate and arsenic sulphide under the tongue for a sure treatment of acute heart pain, cold in the hands and feet, and if one is struck by evil. In the second half of the nineteenth century amyl nitrite was the favoured treatment for angina, however due to its volatile nature it was replaced by chemically related but less volatile compounds including glyceryl trinitrate (GTN or nitroglycerin), interestingly a highly explosive compound that is a key component of dynamite. In the second half of the twentieth century however, the use of nitrite and nitrate fell out of favour. Animal studies reported a possible link between dietary nitrate and nitrite intake and the carcinogenic formation of nitrosoamines - a stigmatism that has been the source of much scientific debate (Butler and Feelisch 2008; van Grinsven et al, 2006).

Trials have shown that diets rich in fruits and vegetables reduce blood pressure and adverse cardiovascular events. The greatest protection against coronary heart disease afforded by a change in diet is that associated with the consumption of green leafy vegetables (e.g. spinach, lettuce) (Joshipura et al, 1999). Such vegetables, also including beetroot, commonly have high nitrate content. The protective pathways involved in a healthy diet are not fully elucidated and the reduction of nitrate to nitrite and NO may play a role in these beneficial effects.

The ability to increase NO bioavailability by modulating the nitrate-nitrite-NO pathway could offer a number of exciting therapeutic avenues in the treatment of cardiovascular disease and other pathological conditions associated with hypoxia. Future research into this pathway will hopefully elucidate whether secondary NO products (e.g. nitroso/nitrosyl products) are involved and whether this pathway is ubiquitous or tissue and condition specific.

The medicinal remedies of the past may seem humorous to us in the present but they may provide a hint to the future. As one author summarised the findings so eloquently, "Mother was right: Eat your vegetables and don't spit!" (Wink and Paolocci 2008).

References:

Butler AR and Feelisch M. Therapeutic uses of inorganic nitrite and nitrate: from the past to the future. Circulation 2008; 117: 2151-9.

Furchgott RF and Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980; 288: 373-6.

Grieve M. A Modern Herbal. Ed. Leyel, C. F. 1931. London: Penguin, 1931.93-94.

Gunther RT (editor). The Greek Herbal of Dioscorides. New York: Hafner, 1959.

Ignarro LJ, Buga GM, Wood KS, Byrns RE and Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proc Natl Acad Sci USA 1987; 84: 9265-9.

Joshipura KJ, Ascherio A, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, Hennekens CH, Spiegelman D and Willett WC. Fruit and vegetable intake in relation to risk of ischemic stroke. JAMA 1999; 282: 1233-9.

Le Brocq M, Leslie SJ, Milliken P and Megson IL. Endothelial dysfunction: from molecular mechanisms to measurement, clinical implications, and therapeutic opportunities. Antioxid Redox Signal 2008; 10: 1631-74.

Lundberg JO, Weitzberg E, Cole JA and Benjamin N. Nitrate, bacteria and human health. Nat Rev Microbiol 2004; 2: 593-602.

Lundberg JO, Weitzberg E and Gladwin MT. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. Nat Rev Drug Discov 2008; 7: 156-67.

Moncada S, Palmer RM and Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol Rev 1991; 43: 109-42.

Nottingham S. Beetroot (ebook). 2004. http://ourworld.compuserve.com/homepages/Stephen_Nottingham/beetroot6.htm

Palmer RM, Ferrige AG and Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 1987; 327: 524-6.

Sinha SS, Shiva S and Gladwin MT. Myocardial protection by nitrite: evidence that this reperfusion therapeutic will not be lost in translation. Trends Cardiovasc Med 2008; 18: 163-72.

van Grinsven HJ, Ward MH, Benjamin N and de Kok TM. Does the evidence about health risks associated with nitrate ingestion warrant an increase of the nitrate standard for drinking water? Environ Health 2006; 5: 26.

Webb AJ, Patel N, Loukogeorgakis S, Okorie M, Aboud Z, Misra S, Rashid R, Miall P, Deanfield J, Benjamin N, MacAllister R, Hobbs AJ and Ahluwalia A. Acute blood pressure lowering, vasoprotective, and antiplatelet properties of dietary nitrate via bioconversion to nitrite. Hypertension 2008; 51: 784-90.

Wink DA and Paolocci N. Mother was right: eat your vegetables and do not spit! When oral nitrate helps with high blood pressure. Hypertension 2008; 51: 617-9.

Alexandra. B. Milsom and Andrew. J. Webb, William Harvey Research Institute, Barts & The London School of Medicine and Dentistry, Queen Mary University of London

Highlights from the BPS Winter Meeting

Pic 1: Pat Humphrey receives the JR Vane Medal from Ray Hill

Pic 2: Arthur Weston receives the Gaddum Award from Ray Hill

Pic 3: Winners of the Clinical Pharmacology Section Prizes for Medical Students

BPS Prizes and Awards 2009

Schachter Awards
Deadlines for applications 30 June

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

Clinical Pharmacology Section Prizes for Medical Students
Deadline for nominations 25 July 2009
Email - ks@bps.ac.uk

Wine and Cardiovascular Health Beyond Antioxidant Properties

Ramaroson Andriantsitohaina

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A number of epidemiological studies reported an inverse relationship between alcohol consumption and cardiovascular disease risk. Indeed, moderate alcohol consumption, defined as 1 to 2 drinks per day, is thought to increase survival in a number of different population subgroups. The minimum all-cause mortality occurs for middle-aged and older individuals especially those who are at increased risk for cardiovascular disease. Although the beneficial effect of moderate alcohol use appears to be independent of the complex lifestyle confounders associated with alcohol consumption, no randomized controlled trials of alcohol have been performed with cardiovascular events as the end point. Coronary heart disease (CHD) risk decreases with increasing alcohol consumption, but hypertension, cardiomyopathy, atrial fibrillation, possibly hemorrhagic stroke, and many noncardiovascular diseases are associated with increased use [1]. Thus, high intake of alcohol leads to increased morbidity and mortality. Therefore, alcohol consumption presents the U- or J-shape alcohol mortality relation, a modest intake is beneficial and either no intake or an increased intake is harmful. Also, epidemiological evidence confirms an association between moderate alcohol intake and a reduced risk of CHD regardless of the type of alcoholic beverage consumed [2, 3]. The lower risk of CHD in moderate drinkers has been observed in a variety of patient populations, including healthy adults, patients with a history of myocardial infarction, diabetic patients and in healthy postmenopausal women. Light to moderate alcohol consumption may also be protective against stroke and peripheral arterial disease. On the basis of clinical and experimental data, the favourable effect of moderate intake of alcohol results in its action on lipid profile, hemostatic parameters, and reduction of inflammation markers.

St Leger et al. [4] first reported an inverse relationship between red wine consumption and mortality from ischemic heart disease in 18 different European and American countries. Since then a greater reduction in cardiovascular risk and greater vascular protection has been associated with wine, and especially moderate red wine consumption, compared with other alcoholic beverages. It should be pointed out that other studies have failed to see a major additional protection associated with red wine compared to other beverages [5-7]. Explanation for the probable dominant effects of red wine on other alcoholic beverages may be due to risk factor patterns among drinkers, the pattern of alcohol consumption or the presence of confounding life style. Red wine is more commonly consumed with meals. Consumption of red wine may be a specific marker for other lifestyle confounders. Indeed subjects who drink wine tend to be of a higher socioeconomic class, are more attentive to their health, and have fewer cardiovascular risk factors [8]. In this case the cardiovascular data with de-alcoholized red but not white wine and studies on isolated tissues or organs give decisive mechanistic insights that strengthen the case already made for randomized prospective controlled trials with cardiovascular endpoints [9]. The first trial should simply compare alcohol with red wine with abstinence, for example in postinfarct patients [10]. Nevertheless, the most probable explanation for the additional benefit from red wine consumption is linked to its components comprising alcohol itself, which is present in up to 15% of the volume of red wine, and red wine polyphenolic compounds (RWPC) which represent approximately 1.8 g/L of total polyphenol for a typical commercial bottle of wine.

RWPC exert numerous effects including antioxidant and free radical properties, anti-aggregatory platelet and anti-thrombotic activities. Moreover, RWPC are powerful vasodilators and contribute to the preservation of the integrity of the endothelium and inhibition of smooth muscle cell proliferation and migration. All these effects of red wine might interfere with atherosclerotic plaque development and stability, vascular thrombosis and occlusion. These properties of red wine might explain the prevention of ischemic heart disease, stroke and metabolic diseases in different experimental models [11-13].

Red wine contains a wide variety of polyphenols, which derives mainly from grape solids (skin and seeds) and can be divided in two classes, flavonoids and non-flavonoids. Flavonoids can be divided into flavanols, flavonols (quercetin, myricetin), anthocyanidins (cyanidin, delphinidin), proanthocyanidins and condensed tannins. The non-flavonoids compounds include stilben (resveratrol), hydroxinnamic acids, phenolic acids and other polyphenols like tannins. The detailed mechanisms by which RWPC exert cardiovascular protection have been described elsewhere.

As reviewed by Middleton [14], polyphenols exert antioxidant activities. With regard to red wines, they exhibit a stronger antioxidant capacity than white wines. Polyphenols like catechin or quercetin can directly scavenge reactive oxygen species (ROS), such as superoxide, hydrogen peroxide, or hypochlorus acid, which can be very deleterious by damaging lipids, proteins and DNA. Furthermore, polyphenols, quercetin particular, can chelate metals like iron involved in free radicals formation. Indirectly, RWPC can interfere with the cellular detoxification systems, such as superoxide

dismutases, catalase or glutathione peroxidases [15, 16]. Beside, polyphenols can inhibit enzymes generating ROS as xanthine oxidase and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [17, 18]. Antioxidant potential of polyphenols has been reviewed by Rice-Evans and Miller [19], and among all the polyphenols, quercetin and myricetin exert the most potent free radical scavenger activities. RWPC may also reduce the LDL-peroxidation both from experimental and clinical studies. RWPC may help to reverse hyperlipidemia or alter the atherogenecity of the LDL particle. The antioxidant effect on LDL is also linked to increased expression of paraoxonase-1 gene [20]. This is in harmony with studies in hypercholesterolaemic postmenopausal women with red wine complementation. Indeed, consumption of red wine also reduce LDL oxidation in human leading to limited plaque formation [21, 22]. Although many studies have shown inhibitory effects of polyphenols including RWPC on LDL oxidation, there have been an equal number of studies that showed a null effect on this variable. Although there are contrasting view points on the effects of polyphenols on LDL oxidation variables, there is increasing evidence that these compounds possess additional protective function including altering hepatic cholesterol absorption, triglyceride assembly and secretion, the processing of lipoprotein in plasma in order to improve plasma lipid profile [23].

Inflammation plays an important role in cardiovascular diseases and it starts with activation of circulating cells such as leucocytes and endothelial cells. Activation of the endothelium is marked by increased expression of adhesion molecule-1 (VCAM-1), secondary to nuclear factor-kB (NF-kB) transcriptional activity. RWPC act on different pathways, involved in the release of inflammatory cytokines and increased adhesion molecules. Indeed, red wine inhibits NF-kB activation in peripheral blood mononuclear cells and in human endothelial cells, resulting in down regulation of VCAM-1. NF-kB signalling pathway can be evoked by oxidative stress and is in turn inhibited by wine polyphenols including resveratrol. Wine further limits monocyte migration into arterial intima by inhibiting the expression of monocyte chemotactic protein-1. Beside, RWPC components, quercetin in particular, have been shown to inhibit cyclooxygenase and lipoxygenase known to be involved in the release of arachidonic acid leading to the release of cytokines by inflammatory cells.

With regard to vascular protection, RWPC can act on different cells including vascular smooth muscle cells (SMC) and endothelial cells by mechanisms linked directly or indirectly through their antioxidant properties. Several studies have shown that RWPC inhibit proliferation, hypertrophy and migration of vascular smooth muscle cells in culture [24-26]. These effects might retard the appearance intimal hyperplasia involved in the formation of atherosclerotic plaque. The mechanism involved delayed cell cycle progression, DNA strand breakage, decreased cyclin A and subsequent inhibition of transcription factor expression. In line with this property, administration of red wine in the hamster reduces the neointimal hyperplasia associated with a decrease of a protein implicated in the monocyte recruitment in the vascular wall, which is one of the mechanism observed in restenosis [27]. Oral administration of RWPC reduces in-stent neointimal growth, lipid deposition in association with its anti-inflammatory property in iliac arteries from hypercholesterolemic rabbits [28].

In animals, several studies performed on isolated vessels from different species like the aorta, the mesenteric or coronary artery show that RWPC are able to induce an endothelium-dependent relaxation [29, 30]. The effects of RWPC on the endothelium are mainly due to NO production [30] although it can cause EDHF-mediated relaxations of coronary arteries involving a pro-oxidant mechanism [31]. . Endothelial NO release is associated with an increase of both $Ca^{2}+$ through an extracellular Ca^{2+}-dependent mechanism and tyrosin phosphorylation of intracellular proteins, leading to the regulation of eNOS in endothelial cells [32]. Another study has shown that RWPC may also promote the release of endothelial NO through the redox sensitive PI3/Akt pathway [86]. French red wines are among the most potent to increase endothelial NO synthase mRNA, protein, and activity in cultured human umbilical vein endothelial cells [33]. Low concentrations of RWPC are sufficient to strongly inhibit one of the most potent vasoconstrictor, endothelin-1, release and transcription of prepro-endothelin-1 in bovine aortic endothelial cells. Indeed, oligomeric procyanidins inhibit endothelin-1 synthesis at concentrations similar to those in some red wines, with some correlations between the procyanidins activity of the wine varietal and longevity [34]

One can advance the hypothesis that the beneficial effects of wine and especially red wine partly rely on its components among of which resveratrol, delphinidin and quercetin appear to give most of the biological protection. It has to keep in mind that all these molecules might act on synergistic ways in addition to their antioxidant properties by acting as an agonist to sirtuin [13], to oestrogen receptor [35], on adenosine-activated protein kinase, NO synthase [29] and endothelin-1 [34].

In summary, *in vitro* and *in vivo* experimental data support epidemiological studies relating the beneficial effect of moderate alcohol use (1-2 drink daily for men, 1 drink daily for women and the elderly) including red wine on cardiovascular morbidity and mortality. Both ethanol and RWPC components of red wine are potent inhibitors of atherosclerosis process part of which can be attributed via their antioxidant properties. Red wine may promote the maintenance of a healthy endothelium and inhibit atherosclerotic plaque formation, progression and rupture. Although, the available evidence indicates that red wine might be of therapeutic benefit for cardiovascular protection, prospective controlled clinical trials are still lacking. Thus, there is insufficient evidence to recommend that abstainers initiate consuming red wine as a part of a strategy to reduce cardiovascular risks at present.

References:

1. Thun MJ, Peto R, Lopez AD, Monaco JH, Henley SJ, Heath CW Jr, Doll R. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. N Engl J Med 1997; 337:1705-14.

2. Corrao G, Rubbiati L, Bagnardi V, Zambon A, Poikolainen K. Alcohol and coronary heart disease: a meta-analysis. Addiction 2000; 95:1505-23.

3. Szmitko PE, Verma S. Antiatherogenic potential of red wine: clinician update. Am J Physiol Heart Circ Physiol 2005; 288:2023-30.

4. St Leger AS, Moore F, Cochrane AL. Factors associated with cardiomortality in developed countries with particular reference to consumption of wine. Lancet 1979; 1:1017-20.

5. Klatsky AL, Armstrong MA, Friedman GD. Red wine, white wine, liquor, beer, and risk for coronary artery disease hospitalization. Am J Cardiol 1997; 80:416-20.

6. Gaziano JM, Hennekens CH, Godfried SL, et al. Type of alcoholic beverage and risk of myocardial infarction. Am J Cardiol 1999; 83:52-7.

7. Lindberg ML Amsterdam EA. Alcohol, wine, and cardiovasculae health Clin Cardiol 008; 347-51.

8. Naimi TS, Brown DW, Brewer RD, Giles WH, Mensah G, Serdula MK, Mokdad AH, Hungerford DW, Lando J, Naimi S, Stroup DF. Cardiovascular risk factors and coufounders among nondrinking and moderate-drinking US adults. Am J Prev. Med 2005; 28:369-73.

9. Freiberg MS, Samet JH. Alcohol and coronary heart disease : the answer awaits a randomized controlled trial. Circulation 2005; 61:107-15.

10. Goldberg DM, Yan J, Soleas GJ. Absorption of three wine-related polyphenols in three different matrices by healthy subjects. Clin Biochem 2003; 36:79-87.

11. Ritz MF, Ratajac P, Curin Y, Cam E., Mendelowitsch A., Pinet F., Andriantsitohaina R. Chronic treatment with red wine polyphenols compounds mediates neuroprotection in a rat model of ischemic cerebral stroke. J Nutr 2008; 138:519-25.

12. Ranaivo HR, Diebolt M, Andriantsitohaina R. Wine polyphenols induce hypotension, and decrease cardiac reactivity and infarct size in rats: involvement of nitric oxide. Br J Pharmacol 2004; 142:671-8.

13. Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, Prabhu VV, Allard JS, Lopez-Lluch G, Lewis K, Pistell PJ, Poosala S, Becker KG, Boss O, Gwinn D, Wang M, Ramaswamy S, Fishbein KW, Spencer RG, Lakatta EG, Le Couteur D, Shaw RJ, Navas P, Puigserver P, Ingram DK, de Cabo R, Sinclair DA. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 2006; 444:337-42.

14. Middleton E Jr, Kandaswami C, Theoharides TC: The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. Pharmacol Rev 2000; 52:673-51.

15. Sies H. Oxidative stress: from basic research to clinical application. Am J Med 1991; 91:31S-38S.

16. Krinsky NI. Mechanism of action of biological antioxidants. Proc Soc Exp Biol Med 1992; 200: 248-54.

17. Nijveldt RJ, van Nood E, van Hoorn DE, et al. Flavonoids: a review of probable mechanisms of action and potential applications. Am J Clin Nutr 2001; 74:418-25.

18. Orallo F, Alvarez E, Camina M, et al. The possible implication of trans-Resveratrol in the cardioprotective effects of long-term moderate wine consumption. Mol Pharmacol 2002; 61: 294-02.

19. Rice-Evans CA, Miller NJ, Paganga G. Structure-antioxidant activity relationships of flavonoids and phenolic acids. Free Radic Biol Med 1996; 20:933-56.

20. Gouedard C, Barouki R, Morel Y. Induction of the paraoxonase-1 gene expression by resveratrol. Arterioscler Thromb Vasc Biol. 2004; 24:2378-83.

21. Nigdikar SV, Williams NR, Griffin BA, Howard AN. Consumption of red wine polyphenols reduces the susceptibility of low-density lipoproteins to oxidation in vivo. Am J Clin Nutr 1998; 68: 258-65.

22. Maxwell S, Cruickshank A, Thorpe G. Red wine and antioxidant activity in serum. Lancet 1994; 344:193-4.

23. Zern TL, Fernandez ML; Cardioprotective effects of dietary polyphenols. J. Nutr. 2005; 135: 2291-4.

24. Moon SK, Cho GO, Jung SY, et al. Quercetin exerts multiple inhibitory effects on vascular smooth muscle cells: role of ERK1/2, cell-cycle regulation, and matrix metalloproteinase-9. Biochem Biophys Res Commun 2003; 301: 1069-78.

25. Yoshizumi M, Tsuchiya K, Suzaki Y, et al. Quercetin glucuronide prevents VSMC hypertrophy by angiotensin II via the inhibition of JNK and AP-1 signaling pathway. Biochem Biophys Res Commun. 2002; 293:1458-65.

26. Iijima K, Yoshizumi M, Hashimoto et al. Red wine polyphenols inhibit proliferation of vascular smooth muscle cells and downregulate expression of cyclin A gene. Circulation 2000; 101:805-11.

27. Feng AN, Chen YL, Chen YT, Ding YZ, Lin SJ: Red wine inhibits monocyte chemotactic protein-1 expression and modestly reduces neointimal hyperplasia after balloon injury in cholesterol-fed rabbits. Circulation 1999; 100:2254-9.

28. Elbaz M, Roul G, Alvès A, Andriantsitohaina R: Provinols, a polyphenolic extract of red wine inhibits in-stent neointimal growth in cholesterol-fed rabbit (Abstract). Arch Mal Coeur Vaiss 2005; 98:406.

29. Andriambeloson E, Kleschyov AL, Muller B, Beretz A, Stoclet JC, Andriantsitohaina R. Nitric oxide production and endothelium-dependent vasorelaxation induced by wine polyphenols in rat aorta. Br J Pharmacol 1997; 120:1053-8.

30. Fitzpatrick DF, Hirschfield SL, Coffey RG. Endotheliumdependent vasorelaxing activity of wine and other grape products. Am J Physiol 1993; 265:H774-8.

31. Ndiaye M, Chataigneau T, Andriantsitohaina R, Stoclet JC, Schini-Kerth VB. Red wine polyphenols cause endothelium-dependent EDHF-mediated relaxations in porcine coronary arteries via a redox-sensitive mechanism. Biochem Biophys Res Commun 2003; 310:371-7.

32. Martin S, Andriambeloson E, Takeda K, Andriantsitohaina R. Red wine polyphenols increase calcium in bovine aortic endothelial cells: a basis to elucidate signalling pathways leading to nitric oxide production. Br J Pharmacol 2002; 135:1579-87.

33. Ndiaye M, Chataigneau M, Lobysheva I, Chataigneau T, Schini-Kerth VB. Red wine polyphenol-induced, endothelium-dependent NO-mediated relaxation is due to the redox-sensitive PI3-kinase/Akt-dependent phosphorylation of endothelial NO-synthase in the isolated porcine coronary artery. FASEB J 2005; 19:455-7.

34. Corder R, Mullen W, Khan NQ, Marks SC, Wood EG, Carrier MJ, Crozier A. Oenology: red wine procyonidins and vascular health. Nature 2006: 444;566.

35. Klinge CM, Wickramasinghe NS, Ivanova MM, Dougherty SM. Resveratrol stimulates nitric oxide production by increasing estrogen receptor alpha-Src-caveolin-1 interaction and phosphorylation in human umbilical vein endothelial cells. FASEB J 2008; 22:2185-97.

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Dietary Supplements: a Source of Regulatory Confusion

Ruth Kava

Ruth Kava, Ph.D., R.D. has served as Director of Nutrition for the American Council on Science and Health since 1995. The ACSH's goal is to provide consumers and the media with up-to-date, scientifically sound information on the relationship between human health and environmental factors, food, nutrition, lifestyle, and chemicals. As nutrition director, Dr. Kava has authored or directed production of educational materials on a variety of health and nutrition-related topics, including vitamin and mineral supplementation, biotechnology and food, functional foods, vegetarianism, dietary supplements, food irradiation, nuclear energy and health, and coverage of nutrition topics by popular media.

Dr. Kava holds a B.A. from the University of Kansas, a master's degree and doctorate in human nutrition from the Graduate School of Arts and Science of Columbia University in New York City. Her post-doctoral training and research in nutrition at Vassar College focused on developing an animal model of obesity-related type 2 diabetes mellitus. Subsequently, she completed the qualifications to become a registered dietitian, including a clinical internship at the New York Hospital.

Dr. Kava's research interests focused on nutrition during pregnancy and on animal models of genetic obesity and type 2 diabetes. She has authored and co-authored research papers in scientific journals, including Diabetes, the Journal of Nutrition, and the American Journal of Physiology. Her professional memberships include the American Society for Nutrition, American Society of Clinical Nutrition, the American Dietetic Association and the North American Association for the Study of Obesity.

As part of her responsibilities at ACSH, Dr. Kava has testified before the New York City Department of Health in hearings related to banning trans fatty acids and requiring listing of calories on menu boards. She also has participated in numerous interviews exploring issues around nutrition and food safety, and presented talks about organic foods, safety of intense sweeteners, and discussions of appropriate interpretation of scientific studies.

The market for dietary supplements is enormous, reaching an estimated-$24-25 x 10^9 in the U.S. (Thurston, 2008), and £335 x10^6 in the UK (Eberhardie, 2007). This is a remarkably robust market for a wide variety of compounds that are neither foods nor medicines, and it continues to expand. Consumers often regard supplements as more "natural," or traditional and therefore safer than pharmaceutical products—a conclusion that is often without merit. Dietary supplements occupy unique positions in the U.S. and EU regulatory schemes—positions that are often not well understood by consumers. This misunderstanding can lead to unfortunate consequences for individuals' health.

In the United States, dietary supplements were defined in the 1994 Dietary Supplements Health and Education Act (DSHEA) (www.fda.gov/opacom/laws/dshea.html#sec3) as products (other than tobacco) that:

- Are intended to supplement the diet;
- Contain one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents;
- Are intended to be taken by mouth as a pill, capsule, tablet, or liquid; and
- Are labeled on the front panel as being a dietary supplement.

This legislation also created an Office of Dietary Supplements within the National Institutes of Health, which is responsible for conducting and coordinating supplement-relevant research within the NIH. (ODS: http://ods.od.nih.gov/About/about_ods.aspx).

Similarly, in the EU, "food supplements" include foodstuffs intended to supplement the normal diet. The EU definition is more detailed about the forms supplements may take than about the actual content. It states that they are concentrated sources of nutrients (vitamins and minerals) or other substances with a nutritional or physiological effect. These substances may be marketed in capsules, pastilles, tablets, pills, pastilles, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities. (Eberhardie, 2007)

The US Food and Drug Administration (FDA) is responsible for oversight and regulation as specified in the DSHEA. In the US, supplements are regulated as foods, not as food additives or pharmaceuticals. This is more than a semantic distinction, as this categorization determines the extent to which manufacturers or suppliers must test products before they may be offered to the public.

Pharmaceutical products must undergo rigorous testing to determine first, safety, and second efficacy for the treatment of the particular health condition for which they are intended. Further, post-marketing surveillance is a source of ongoing safety information.

Purveyors of new food additives, substances such as colorants or preservatives, in contrast, must present data to the FDA demonstrating the safety of the compounds before they are added to the public food supply (such a substance that has been in long term safe use, such as salt, sugar or spices would be excluded from this requirement, and categorized as "Generally Recognized as Safe" or GRAS). (Rados, 2004) They do not have to undergo the extensive efficacy trials required of pharmaceutical products.

In contrast, dietary supplement manufacturers or suppliers do not have to present any premarketing safety or efficacy data to the FDA. Manufacturers supposedly will have such data to present, but are not compelled to do so before they sell their products.

If there is any question about the safety of a supplement once it is available to consumers, it is the responsibility of the FDA to show that the item is not safe when used as intended. This requirement is very difficult if not impossible to accomplish, since supplement marketers are not required to report the results of any post-marketing surveillance, and thus the FDA must rely on voluntary reports of adverse health events.

This lack of a surveillance requirement has led to a situation in which adverse effects and interactions between various supplements or between supplements and pharmaceuticals are discovered serendipitously. For example, St. John's Wort, a popular herbal product for treatment of depression, can interact with oral contraceptives, anticoagulants, and immunosuppressive drugs. (ACSH, 2000.; Markowitz et al. 2003)

Similarly, there are concerns about the appropriate regulation of supplements in the European Union. The Medicines and Healthcare products Regulatory Agency (MHRA. 2002) lists numerous areas of public health risk associated with herbal medicines. The European Food Safety Authority is responsible for the safety of food supplements under EU Directive 2002/46/EC. This Directive specifies a 'positive' list of nutrients and sources. (Eberhardie, 2007) There are further directives relating to traditional herbal medicines—only those with a known efficacy which have been used for 30 years, half of which have been in the EU—are approved under EU Directive on Medicinal Products for Human Use (Eberhardie 2007; EC, 2004).

In both the EU and the United States, the categorization of dietary supplements (or "food" supplements) seems to be an obstacle to regulatory clarity. In the U.S., regulating supplements as foods means there is little oversight of safety or manufacturing processes.

In the EU, the definition of food supplements based on a description of their form rather than content seems to make it difficult to determine exactly which set of regulations should apply. As Eberhardie (2007) notes, garlic may be sold as a plant, a food, or an herb; it may also be produced and sold as an herbal medicine.

Until there is clarification of how supplements should be described, regulation will likely continue to be confusing, and will not adequately protect the public health.

References:

American Council on Science and Health (ACSH). Drug-Supplement Interactions. Available at: http://www.acsh.org/publications/pubID.515/pub_detail.asp.
Accessed February 3, 2009.

Eberhardie C. Nutritional supplements and the EU: is anyone happy? Proc Nutr Soc 2007; 66:508-511.

European Commission (2004) Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. Official J EU L136, 34–57.

Markowitz JS, Donovan JL, DeVane CL, Taylor RM, Ruan Y, Wang JS, Chavin KD. Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. JAMA 2003; 290(11):1500-1504.

MCA. Safety of herbal medicinal products. 2002. Available at: http://www.mhra.gov.uk. Accessed February 4, 2009.

Office of Dietary Supplements, National Institutes of Health. Dietary supplements: background information. http://ods.od.nih.gov/factsheets/dietarysupplements.asp.
Accessed January 29, 2009.

Rados C. GRAS: Time-tested, and trusted, food ingredients. FDA Consumer magazine. March-April 2004; http://www.fda.gov/fdac/features/2004/204_gras.html.
Accessed January 30, 2009.

Thurston C. Dietary supplements: the latest trends and issues. Nutraceuticals World. http://www.nutraceuticalsworld.com/articles/2008/04/dietary-supplements-the-latest-trends-issues.
Accessed February 1, 2009.

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An Introduction to Parenteral Nutrition

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This article looks at how nutrition can be provided intravenously when a patient cannot be fed via the gastrointestinal tract (GIT).

Parenteral nutrition (PN) is a means of providing food intravenously when oral or enteral (tube) feeding is not possible, or does not provide adequate nutrition, for example in patients with Crohn's disease or short-bowel conditions who may suffer malabsorption. Total parenteral nutrition (TPN) is the term used when the intravenous route (i.v.) is the sole method of nutritional support. Indications for TPN include:

- GIT obstruction (tumours, adhesions)
- Dysmotility e.g. scleroderma
- Gut ischaemia
- Complications of GI surgery
    - enterocutaneous fistula
    - anastomotic leak
    - ileus – absence of peristalsis

Such patients must remain nil-by-mouth until the underlying problem is resolved.

The National Institute for Health and Clinical Excellence (NICE 2006) published guidelines on the provision of nutritional support to adult patients, following consultation with the British Association for Parenteral and Enteral Nutrition (BAPEN). They indicate which patients should receive PN and recommend daily requirements based on weight, height, nutritional history and co-morbidity.

Energy (calories) provided by PN come from glucose, lipid and amino acids, a typical regimen containing:

- Glucose provides 4kcals/g and is available in a range of concentrations from 5% to 50%. Solutions of 10% and above are hypertonic and may need to be infused via a central vein.

- Lipid is calorie dense at 9kcals/g, a small volume providing a high number of calories allowing PN to be formulated in lower volumes than if dextrose was the sole source of energy. Addition of lipid to PN reduces the osmolality allowing peripheral administration and may reduce the need for a central line. Lipid emulsions were traditionally soya - oil based, consisting of long chain fatty acids and providing essential fatty acids. Recent formulations of mixed long and medium chain fatty acids are thought to reduce liver complications (Grau et al 2007). Newer developments of lipid emulsions based on olive oil and more recently fish oils are being marketed as "healthier alternatives" although there is little evidence to support their improved beneficial effects. Fish oils contain omega 3 fatty acids which are thought to be immunomodulatory and may benefit patients with cancer cachexia.

- Amino acid preparations provide nitrogen and are necessary for plasma protein synthesis and cell growth. They are available in a range of combinations providing essential amino acids. Some contain higher concentrations of specific non-essential amino acids such as glutamine which becomes conditionally essential and has been shown to improve morbidity in critical care patients. (Novak et al 2002).

- Electrolyte requirements vary. Some patients require sodium restriction, for example those patients with oedema or renal failure; others need supplementation of potassium and magnesium to replace excessive GI losses. The concentration of each electrolyte and the ratio of phosphate to magnesium and calcium are critical, as precipitation can occur if the stability threshold is exceeded resulting in an increased risk of thrombosis.
- Micronutrients
  - Water soluble vitamins especially ascorbic acid and B group vitamins are essential in all PN regimens. They are prone to photo and oxidative degradation so must be protected from light and extremes of temperature. Thiamine deficiency has serious consequences and must be provided before PN is commenced. It is required for carbohydrate metabolism and deficiency can cause neurological damage.
  - Lipid soluble vitamins A, D, E and K are stored in the tissues. In patients with kidney disease they can accumulate and may only be required once or twice a week.
  - Trace minerals are cofactors for the utilisation of protein, fat and carbohydrate. Selenium is antioxidant and protects organ function, zinc promotes wound healing, and iron and copper prevent microcytic anaemia.

Intravenous nutrition in the 1960s was provided as separate infusions of dextrose, amino acid solutions and lipid emulsions. This practice was superseded in the 1990s when multi-chambered "all-in one" bags were pioneered. These often contain electrolytes but do not contain micronutrients. A recent national alert advises that additions to PN bags must not be made outside an aseptic compounding unit (NPSA 2008). "All-in one" bags have a long shelf life at room temperature but after addition of the vitamins must be refrigerated and used within a week. A range of multi-chambered bags are available but these are not suitable for all patients so those with specific needs can be provided with a "bespoke" regimen.

Examples of typical PN patients' requirements

Complications of PN

Daily requirement	Energy (kcals)	Nitrogen (g)	Volume (ml)	Potassium (mmol)
Male 60kg chronic kidney disease requiring fluid restriction	1600	11	1000	zero
Male 90kg vomiting and diarrhoea requiring additional fluid and electrolytes	2000	16	3000	100
Elderly 40Kg female (low requirements)	1200	7	2000	40

1. Biochemical disturbance.

Significant unplanned weight loss, little or no nutrition for a week or longer and specific at-risk groups can suffer a re-feeding syndrome if nutrition is re-introduced too quickly. Intracellular electrolyte shifts result in hypophosphataemia, hypokalaemia and hypomagnesaemia which can cause cardiac complications, muscle weakness and respiratory problems and in severe cases death. Refeeding complications are minimised by introducing very low calorie regimens in at-risk patients and by providing water soluble vitamins especially thiamine prior to feeding. Patients may require as little as 5-10kcals/kg/day if at severe risk of re-feeding problems (NICE 2006). This can provide difficulties for the pharmacist in formulating a regimen with so few calories but requiring additional potassium, phosphate and magnesium, and it may be necessary to infuse electrolyte solutions separately if stability issues mean insufficient are provided by the PN.

2. Risk of sepsis is increased as PN is an ideal substrate for bacterial growth. Monitoring temperature, CRP and white cell count can identify possible catheter-related infection allowing PN to be stopped and early antibiotic treatment instituted.

3. Thrombophlebitis with pain and redness when infusing PN peripherally can be reduced by applying a glyceryl trinitrate patch producing vasodilatation. PN solutions with an osmolality above 1000 mOsm/kg water must be infused into a central vein.

4. Hypertriglyceridaemia is caused by infusing too many calories from lipid. This is corrected by reducing PN lipid concentration, changing to a mixed medium / long chain triglyceride emulsion or providing lipid-free PN. Short term pharmacological treatment with a fibrate or statin may be considered.

5. Metabolic complications can be improved by reducing total energy provision. Overfeeding in critical illness can cause:

- hyperglycaemia with impaired wound healing
- hypercapnia - respiratory problem due to excess carbon dioxide production
- derangement of liver function tests (LFT) - fatty liver, cholestasis

- azotaemia - increased urea due to excess nitrogen

6. Fluid overload or dehydration – Biochemical markers such as sodium and urea cannot be interpreted without full clinical assessment. Fluid restriction may be desirable for patients with cardiac or renal failure, and fluid from intravenous medication such as antibiotics and analgesia must be factored when deciding what volume of PN is required. Fluid balance charts provide information on oral or intravenous fluid intake versus losses from urine, vomiting, diarrhoea, surgical drains and stoma (colostomy or ileostomy). Blood pressure measurement and physical examination can also help identify a dehydrated or fluid overloaded patient.

Role of Nutrition Support Team (NST)

In hospital PN is often prescribed and monitored by a multidisciplinary nutrition team comprised of a dietician, pharmacist, doctor and nurses. Team members are specialist in their own professional areas but have broad nutritional experience and are able offer advice in their colleagues' absence. They meet daily to review new referrals and monitor existing PN patients as requirements can change, and clinical improvement allows increased energy and nitrogen provision. In the early stages of feeding daily blood electrolyte, kidney and liver function monitoring is required.

The dietician calculates macronutrient (calorie, protein) requirements based on the body mass index (BMI), nutritional history and whether the patient is critically ill or in a recovery stage. The pharmacist reviews drug therapy, as medication such as diuretics and ACE inhibitors may alter electrolyte requirements, and is responsible for formulating a stable regimen based on calculated macronutrient, micronutrient, electrolyte and fluid requirements. Specialist gastroenterology nurses are responsible for intravenous line placement, advice on line care and alternative methods of enteral feeding (nasogastric, nasojejunal and gastrostomy tubes). The doctor clinically examines the patient and advises on avoiding metabolic complications. Until recently the doctor traditionally prescribed the PN but recent legislation allows specially trained pharmacists and nurses to prescribe in their area of expertise. Each member of the team respects and considers the opinions of their colleagues and this team approach ensures all factors are considered when formulating PN regimens

Figure 1 - PN being compounded in an Aseptic Unit isolator

Figure 2 - A compounded PN bag and worksheet

A PN pharmacist's perspective

Improved nutrition helps the body fight infection, reduces muscle loss and aids wound healing. Providing PN can be a complicated process as standard feeds often need daily manipulation. Once PN macronutrient requirements are decided by the NST, the pharmacist uses specialist knowledge on product availability and stability issues to formulate and produce a worksheet allowing compounding of the regimen.

In recent years the role of a nutrition support pharmacist has become more clinical as pharmacists with appropriate training can now prescribe licensed medicines. PN is an unlicensed product and hence cannot be prescribed independently. However a supplementary prescribing partnership between a doctor and pharmacist allows management of a PN patient to an agreed clinical management plan. A prescribing nutrition support pharmacist spends a significant part of the day reviewing patients. This involves ordering and reviewing a range of blood tests and using supplementary prescribing skills to adjust the formulation. Licensed medicines which can be prescribed independently by the pharmacist include anti-emetics, fluids, vitamin preparations and acid suppression drugs. Specialist pharmacists must keep their knowledge up to date by literature review and attending study days or national conferences. They may be involved in training other pharmacists and health professionals in aspects of nutritional support. Many pharmacists find being part of a multidisciplinary team an enjoyable and fulfilling role. It provides opportunity to improve knowledge base and consider not only pharmacological issues but other aspects of patient care.

References

British Association for Parenteral & Enteral Nutrition. Current Perspectives on Parenteral Nutrition in Adults (ISBN 1 899 467 203). BAPEN Publications.

Grau T et al. Liver dysfunction associated with artificial nutrition in critically ill patients. Critical care 2007; 11:R10.

National Institute for Health and Clinical Excellence, Clinical Guideline CG32 Nutrition Support in Adults: oral nutrition support, enteral tube feeding and parenteral nutrition. London: NICE and the National Collaborating Centre for Acute Care. February 2006.

NHS National Patient Safety Agency (NPSA). Patient safety alert 20: Promoting safer use of injectable medicines. March 2007.

Novak F, Heyland D, Avenell A, et al. Glutamine supplementation in serious illness: a systematic review of evidence. Crit Care Med 2002; 30: 2022-2029.

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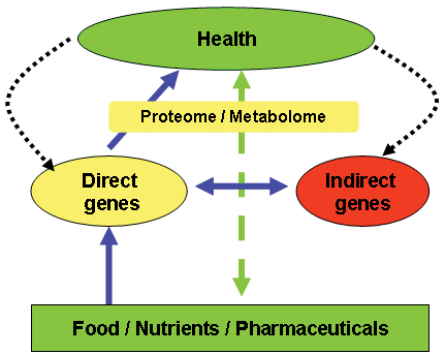
The Importance of Nutrient-Gene Interactions in Health:

an example from the micronutrient selenium.

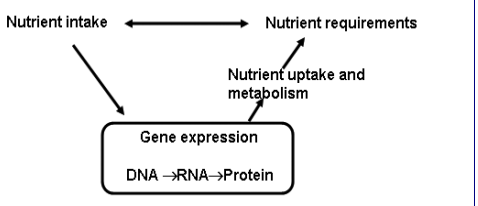
Fig 1: Nutrigenomics blueprint



"Leave your drugs in the chemist's pot if you can heal the patient with food" (Hippocrates)

The involvement of nutrition and the role of specific nutrients in health maintenance and disease prevention and treatment has been the subject of centuries of debate and research. The pioneering work of pharmacologists Garrod, Williams and Pauling, at the turn of the 19th century, identified the therapeutic use of substances native to human physiological chemistry to support health and, more recently, nutritional pharmacology has witnessed the discovery of many potential roles for several nutrients (e.g. vitamins, minerals, amino acids and fatty acids) (Bland, 2008). In parallel, nutritional science has defined many of the necessary constituents of an adequate diet in terms of both macro- and micronutrients. Nutritionists have demonstrated that the feeding of identical diets to two different individuals or to the same individual under different circumstances can give rise to different metabolic and even clinical effects. For example, on an identical energy intake one individual may become obese whereas another does not. Additionally, different individuals have varying requirements for micronutrients to maintain optimal health.

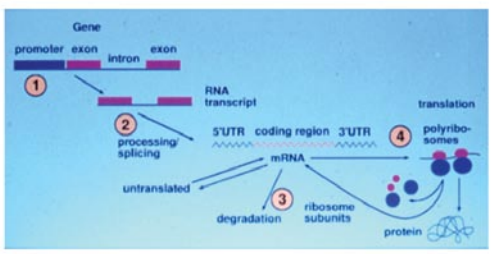
Fig 2: Inter-relationship of nutrients and gene expression



Adapted from Hesketh et al., 1998

A major challenge to modern nutrition and to nutritional pharmacology is to understand the basis for differences in nutrient requirements between individuals and ethnic groups, and the role of nutrients as therapeutics in order to achieve optimal health and or treatment of disease. This requires an appreciation not only of the traditional links between nutrients and endocrine status, but also of the less well-defined links between nutrition/intake of specific nutrients and gene expression.

Fig 3: Regulation of gene expression



Key stages of gene expression regulation: 1 DNA transcription, 2 pre-mRNA processing, 3 mRNA degradation, 4 mRNA translation.

In response to this, a new science, Nutrigenomics, has been developed in order to study nutrient-gene interactions. It allows researchers to examine how alterations in nutritional status affect single parameters or biochemical pathways and to investigate how genetic factors influence nutritional requirements (Fig 1).

The ability to define the interactions between nutrients and gene expression will enable scientists to explore at the functional and mechanistic levels how nutrients affect gene expression and subsequent cell function and physiology, and to identify individuals with particular needs. In a broad sense, this entails understanding how the role of nutrients in health and metabolism are linked to biochemical events that lead to gene expression. As shown schematically in Fig. 2, this can be reduced to two inter-linked processes: the influence of nutrient intake on gene expression and protein synthesis, and the influence of gene expression on nutrient requirements. In specific terms, it involves addressing important fundamental questions: which genes, particularly those involved in the control of metabolism, growth and differentiation are regulated by nutrients; how do nutrients regulate the expression of specific genes; and how is the expression of specific gene products involved in metabolism and channelling of nutrients? Potentially, the expression of any gene can be regulated at different steps between its transcription and synthesis of the final active protein product. In addition to regulation of transcription itself, many genes are regulated post-transcriptionally during the processing, transport and translation of the mRNA. It is important to emphasize that nutrients may alter the amount of functional protein expressed by a specific gene through a range of transcriptional, post-transcriptional and post-translational mechanisms (Fig. 3) (Hesketh et al., 1998; Clarke, 2004).

In this article, the micronutrient selenium (Se) is used as an example of how the intake of this trace element affects gene expression and how genetic factors influence Se metabolism and how this relates, potentially, to nutritional requirements for Se and optimal health. Se is an essential micronutrient for human health and low Se intake has been linked to a number of diseases including cardiovascular disease (e.g. Keshan disease) and cancer (e.g. colon and prostate cancer). It is, therefore, important to understand the interactions of sub-optimal Se intake with gene expression and genetic factors, and subsequently the link between Se intake and susceptibility to disease. Se exerts its biological function through selenoproteins that contain Se as the amino acid Seleno-cysteine (Sec). The incorporation of Se occurs during mRNA translation and specific UGA codons are recognized not as stop signals but for insertion of Sec from selenocysteine-tRNA; this requires specific sequences in the 3'untranslated region (3'UTR) of the mRNA that form stem-loop structures (SECIS). The best characterized selenoproteins are the glutathione peroxidases (GPx 1, 2, 3 & 4) which prevent the formation of reactive oxygen radicals and protect the cell against oxidative stress; thioredoxin reductases (TR 1, 2 & 3) which play a key role in the modulation of the cellular redox state; deiodinases (IDI 1, 2 & 3) which are involved in thyroid hormone metabolism; and selenoprotein P (SEPP) which has a key function in the transport of Se to extra-hepatic tissues.

The pattern of selenoprotein expression is the functional outcome of dietary Se intake. Potentially, both Se intake (nutrition) and genetic factors (e.g.single-nucleotide polymorphisms (SNPs)) could influence this pattern.

Animal and cell culture studies have shown that Se intake influences the level of activity of several selenoproteins and in some cases induces changes in mRNA levels for selenoprotein genes. However, the effect of Se intake on selenoprotein gene expression is different within and between tissues. A hierarchy of effects exists such that synthesis of some proteins is maintained more than others (Fig. 4) (Bermano et al., 1995; Hesketh, 2008). The 3'UTR of selenoprotein mRNAs appear to play a role in determining this hierarchy. Translational efficiency studies showed that the efficiency of the 3' UTRs in permitting Sec incorporation is similar in normal Se conditions but, when Se is limiting, the 3' UTR of GPx 1 is less efficient than the 3' UTR of GPx 4. The different sensitivity of the 3' UTRs could explain the differential effect that Se deficiency has on GPx 1 and GPx 4 activity and mRNA levels, stability and translation (Bermano et al., 1996). As changes in the pattern of selenoprotein expression are directly related to the physiological and functional effects of modifications in Se intake, it is important to obtain a clear picture of how all the selenoproteins respond to altered Se intake. Further studies are, therefore, needed to understand the precise mechanism involved in selenoprotein gene regulation by Se. The ability of the different transcripts to bind the proteins necessary to form the Sec incorporation complex are likely candidates.

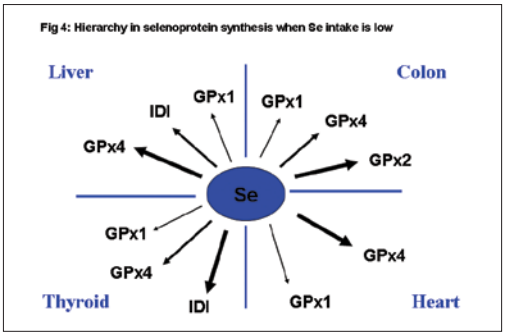


Fig 4: Hierarchy in selenoprotein synthesis when Se intake is low

Selenoprotein synthesis and functional activity is the result of the combined influences of Se intake and the genetic information in selenoprotein genes. When considering the role of Se intake and genetic factors in determining susceptibility to disease, the major questions are whether there are common genetic variations and if they are functional per se, or only in combination with dietary factors. Several SNPs have been discovered in selenoprotein genes that could potentially influence the Se intake required to achieve optimal functional activity and consequently optimal individual Se requirements. When Se intake is limiting, it is possible that genetic variations may induce differences in the ability of selenoproteins to function and therefore compromise their ability to protect cells from oxidative stress or affect thyroid hormone and Se metabolism (Hesketh, 2008). In particular, a SNP in the 3'UTR region of GPx 4 (rs713041) has been found to have functional significance: homozygous CC individuals were found to differ from TT homozygotes in the level of lymphocytes 5'lipoxygenase metabolites (Villette et al., 2002). Reporter gene studies in which the two variants of the 3'UTR were linked to the IDI coding region and transfected into colon cancer cells (Caco2), have shown, under both Se adequate and Se deficient conditions, that the C variant produced a higher level of deiodinase reporter activity (Bermano et al., 2007). Moreover, two association studies have shown that the variant T is associated with a lower risk of colon cancer and ulcerative colitis (Bermano et al., 2007; Qatatsheh et al., 2005). Taken altogether, the data collected from several studies have suggested that this mutation has functional consequences and it is linked to changes in GPx 1 and GPx 4 expression as well as possibly inflammatory changes and cancer susceptibility (Hesketh, 2008).

The reported experiments are a small example of the work carried out to date and that contributed to the increased understanding of the interaction between the micronutrient Se and selenoprotein gene expression (for a more comprehensive review of the literature see Hesketh, 2008). A major challenge still remains and it involves a more comprehensive understanding of how genetic variations in all selenoprotein genes, combined with Se intake, influence selenoprotein function, its downstream targets and susceptibility to disease.

It is very important to address this issue as the association between Se status and disease in different populations has identified Se intake as a potential public health problem. Nutrigenomics provides ways, via mechanistic and SNP analysis studies, to tackle issues related to nutrient-gene interactions and health and, in the future, more studies in this field will prove the original statement of Hippocrates and the concepts of Garrod, Williams, and Pauling to be correct, especially if the right dose of the right nutrient is used for the right patient.

References:

Bermano G, Nicol F, Dyer JA, Sunde RA, Beckett GJ, Arthur JR, Hesketh JE. Tissue-specific regulation of selenoenzyme gene expression during selenium deficiency in rats. Biochem J. 1995; 311 (2): 425-30.

Bermano G, Arthur JR, Hesketh JE. Role of the 3'untranslated region in the regulation of cytosolic glutathione peroxidase and phospholipid hydroperoxide glutathione peroxidase gene expression by selenium supply. Biochem J. 1996; 320 (3): 891-895.

Bermano G, Pagmantidis V, Holloway N, Kadri S, Mowat NA, Shiel RS, Arthur JR, Mathers JC, Daly AK, Broom J, Hesketh JE. Evidence that a polymorphism within the 3'UTR of glutathione peroxidase 4 is functional and is associated with susceptibility to colorectal cancer. Genes Nutr 2007; 2(2): 225-32.

Bland J. The future of nutritional pharmacology. Altern Ther Health Med. 2008; 14 (5): 12-14.

Clarke SD. The multi-dimenasional regulation of gene expression by fatty acids: polyunsaturated fats as nutrient sensors. Curr Opin Lipidol. 2004; 15 (1):13-18.

Hesketh JE. Nutrigenomics and selenium: gene expression patterns, physiological targets and genetics. Annu Rev Nutr 2008; 28: 157-177.

Hesketh JE, Vasconcelos MH and Bermano G. Regulatory signals in messenger RNA: determinants of nutrient-gene interaction and metabolic compartmentation. Br J Nutr 1998; 80: 307–321.

Qatatsheh A, Seal CJ, Jowet SL, Welfare MR, Hesketh JE. Patients with ulcerative colitis show an altered frequency distribution of a single nucleotide polymorphism (SNP) in the gene encoding phospholipid hydroperoxide glutathione peroxidise (GPx4). Proc Nutr Soc 2005; 64: 20A (Abstr.).

Villette S, Kyle JA, Brown KM, Pickard K, Milne JS, Nicol F, Arthur JR, Hesketh JE. A novel single nucleotide polymorphism in the 3'untranslated region of human glutathione peroxidase 4 influences lipoxygenase metabolism. Blood Cells Mol Dis. 2002; 29 (2): 174-178.

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Vascular Protection Afforded by Isoflavones

Activation of the redox sensitive Nrf2-Keap1 defence pathway in vascular cells by dietary soy isoflavones

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Keywords: Nrf2; Antioxidant response element; Oxidative stress; Redox signalling; Phytoestrogens; Isoflavones, Nitric oxide; Heme oxygenase; extracellular signal regulated kinase; endothelium; vascular smooth muscle

Abbreviations: ERβ, estrogen receptor β; Cav1, caveolin-1; eNOS, endothelial nitric oxide synthase; NOX, NAD(P)H oxidase; Hsp90, heat shock protein 90; sGC, soluble guanylyl cyclase; GPCR, G-protein coupled receptor; HO-1, heme oxygenase-1; NQO1, NAD(P)H:quinone oxidoreductase-1. Adapted from [4;5;47;51;57]

Increased oxidative stress in vascular diseases leads to endothelial dysfunction and reduced nitric oxide (NO) bioavailability. Epidemiological evidence suggests that diets containing high amounts of natural antioxidants afford protection against cardiovascular disease (CVD). Although the potential health benefits of isoflavones contained in soy products and other polyphenols contained in red wine, tea and dark chocolate have been the focus of recent research, supplementation trials have largely reported only marginal health benefits. The molecular mechanisms by which soy isoflavones (genistein, daidzein, equol) afford protection against oxidative stress in CVD remain to be investigated in larger scale clinical trials. Studies in animal models and vascular cells have established that isoflavones increase endothelial nitric oxide synthase (eNOS) activity and activate the Nrf2-Keap1 defence pathway, leading to an upregulation of detoxifying and antioxidant genes. We here review recent advances in our understanding of mechanisms by which dietary isoflavones activate eNOS and Nrf2-Keap1 mediated antioxidant gene expression.

Cardiovascular diseases (CVD) such as coronary heart disease, hypertension, atherosclerosis and diabetes are associated with increased generation of reactive oxygen radicals (ROS) and compromised endogenous antioxidant defenses [1-3]. CVD is more common in men than age-matched pre-menopausal women [4;5], and the loss of cardiovascular protection after menopause has been attributed to estrogen deficiency [6]. Differences in the regulation of blood pressure and vascular reactivity between males and females have been investigated extensively, with estrogen implicated in the protective effects of gender on the vasculature [7] and expression of longevity associated genes [8].

Epidemiological basis for isoflavone supplementation trials

The preferential affinity of genistein, daidzein and equol for estrogen receptor (ER) β [9;10] has precipitated studies of their vascular actions with minimised risk for stroke and breast cancer associated with prolonged hormone replacement therapy (HRT) [11;12]. In addition to reported antioxidant properties of the phenolic group in their steroid structure [13], estrogen and isoflavones activate intracellular kinase signaling pathways and gene transcription [4;5] and inhibit NAD(P)H oxidase superoxide production [14;15].
The current interest in the health benefits of isoflavones is largely based on epidemiological observations that an increased intake of soy isoflavones is associated with a lower incidence of CVD in Far Eastern populations [16]. Soy products contain significant amounts of the isoflavones genistein and daidzein, and plasma concentrations of genistein can reach 4μM in Japanese consuming a traditional soybean rich diet [17;18].

Initially the Framingham Offspring Study highlighted a favourable cardiovascular risk profile in postmenopausal women receiving isoflavone supplements [19], however, the American Heart Association subsequently attributed health benefits of isoflavones to the high content of polyunsaturated fats, fiber, vitamins, minerals and low content of saturated fat in soy products [20]. Several of the randomized trials included in the AHA prospective analysis were unfortunately based on small cohorts receiving varied anti-hypertensive therapy and/or isoflavone formulations. More importantly, many of these clinical trials failed to consider that only 30-50% of the population are able to metabolise daidzein to equol ('equol producers)' [21], which may have affected the metabolic fate, bioavailability and efficacy of isoflavone supplements. In postmenopausal women receiving synthetic alternatives to estrogen, arterial stiffness was found to be lower in 'equol-producers' compared to 'non-producers', however, soy supplementation had negligible effects on vascular function [22]. Notably, in this study endothelial reactivity was highly variable at baseline and following soy supplementation in both 'equol-producers' and 'non-producers'.

Rapid non-genomic actions of isoflavones in vivo

Physiological concentrations of isoflavones evoke acute endothelium-dependent increases in forearm blood flow [23-27] most likely mediated via NO [28]. A recent study in healthy postmenopausal women has shown that feeding an isoflavone enriched/low fat meal increases endothelium-dependent relaxation *in vivo* [29]. Our previous studies in rodents established that feeding a soy isoflavone deficient diet from conception and throughout adult life (10-12 months) leads to elevated blood pressure and endothelial dysfunction in male offspring [30;31]. Endothelial dysfunction in soy deficient adult male rats was associated with decreased glutathione and mRNA levels for MnSOD, and both vascular reactivity and blood pressure were restored to normal values upon refeeding an isoflavone rich diet for

4 months [30]. Since feeding a balanced isoflavone diet to younger rats for up to 4-6 months has marginal benefits for endothelial function [32], supplementation may only modulate vascular function in aged animals or subjects with CVD. We recently reviewed the evidence that isoflavones can also evoke rapid endothelium-independent relaxation of arterial rings *in vitro* involving modulation of ion channels [4,5]. Thus, in addition to acutely stimulating endothelial NO production [5], isoflavones, xenoestrogens and estrogen antagonists can directly modulate vascular smooth muscle tone by inhibiting L-type Ca^{2+} channels or activating Maxi K+ channels [33-35].

Acute activation of eNOS by isoflavones

We have previously reported that the dietary isoflavones genistein, daidzein and equol (1-100 nM, 2 min) rapidly stimulate endothelial NO production at basal cytosolic Ca^{2+} levels [28]. It is worth noting that higher concentrations of genistein (>10 μM) inhibit tyrosine kinase activity [36], and thus any vascular actions are likely to reflect non-selective inhibition of kinase activity. Our experiments with human umbilical vein endothelial cells established that the daidzein metabolite equol induces eNOS Ser1177 phosphorylation via activation of ERK1/2 and PI-3 kinase/Akt and independent of estrogen receptors [28]. Similar studies in bovine aortic endothelial cells have implicated PKA in eNOS phosphorylation [37].

Genomic actions of isoflavones: activation of the Nrf2-Keap1 defence pathway

Increased generation of ROS and accumulation of oxidized LDL in the vessel wall is linked with hypertension and CVD [38]. Under physiological conditions, ROS are eliminated efficiently by intracellular antioxidant defence systems [39], yet oxidative stress occurs when ROS production exceeds the capacity of antioxidant defences. The redox sensitive transcription factor nuclear factor-erythroid 2 (NF-E2-related factor 2, Nrf2) serves as a key regulator of cellular defences against oxidative or electrophilic stress [40-44]. Nrf2 forms heterodimers with small Maf proteins with subsequent binding to the antioxidant/electrophile response element (ARE/EpRE) in the promoter region of antioxidant and phase II detoxifying enzymes leading to gene transcription. Keap1 (Kelch-like ECH-associated protein 1) negatively regulates Nrf2 by targeting it for proteasomal degradation [45] . Oxidative or electrophilic stress induced alterations in the Nrf2-Keap1 complex prevent proteasomal degradation, enabling newly synthesized Nrf2 to accumulate in the nucleus and activate ARE-mediated gene expression[46].

Although few studies have addressed the molecular targets of dietary isoflavones in vascular endothelial and smooth muscle cells, non-genomic and genomic mechanisms of action include activation of intracellular kinases and eNOS, inhibition of NAD(P)H oxidase and transcriptional activation of phase II defence and antioxidant genes such as heme oxygenase-1 [4;5;47]. HO-1 protects cells against oxidative stress by degrading the pro-oxidant heme to biliverdin, which is subsequently converted to the radical scavenger bilirubin[48;49]. Since Nrf2-null mice exhibit an increased susceptibility to oxidants [50], this transcription factor may serve as potential target for dietary isoflavones [4;5]. As summarised in Figure 1, we hypothesize that generation of NO, O_2^- and peroxynitrite in endothelial cells (and other vascular cell types) in response to isoflavones may lead to Nrf2/ARE mediated transcriptional activation of antioxidant genes [47]. Under physiological conditions, low concentrations reactive oxygen and nitrogen species generated in response to isoflavones may serve as important 'second messengers' to activate intracellular signaling pathways linked with the induction of phase II and antioxidant defence genes [47;51].

Estrogen, isoflavones and shear stress

Exposure of the endothelium to laminar shear stress is associated with an upregulation of ARE-regulated genes, implicating the Nrf2/ARE pathway in atheroprotection [52-55]. Studies in cultured endothelial cells have shown that laminar flow, but not oscillatory flow, stimulates Nrf2/ARE mediated expression of antioxidant genes. Moreover, recent studies in mice *in vivo* suggests that Nrf2 is activated by 'atheroprotective' flow, with activation affected differentially in atherosclerosis-resistant and atherosclerosis-susceptible regions of the mouse aorta [56]. Thus, an upregulation of antioxidant defences in regions exposed to 'atheroprotective' flow may serve as a protective mechanism against transient increases in oxidative stress. As pre-menopausal women have a lower incidence of CVD compared to age-matched men, this raises the question whether cross-talk between shear stress and estrogen (or isoflavones) activated pathways in part accounts for the lower incidence of CVD in pre-menopausal women which is lost after the onset of menopause due to estrogen deficiency.

Future perspectives

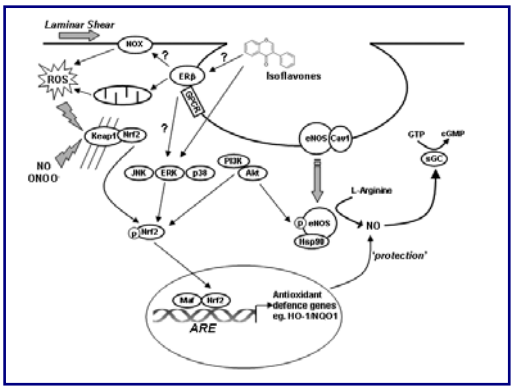
The molecular mechanisms by which isoflavones upregulate antioxidant gene expression in vascular cells certainly merits further investigation. Our ongoing studies of the actions of isoflavones on endothelial cells, isolated arterial rings and arterial blood pressure *in vivo* [28;30] have identified eNOS and the Nrf2-Keap1 pathway as a potential therapeutic targets for dietary isoflavones. However, it is worth noting that isoflavones and other polyphenols may also combat oxidative stress by modulating redox sensitive gene transcription via other transcription factors such as NF-κB [57].

Figure 1

Transcriptional activation of redox sensitive genes by isoflavones via the Nrf2-Keap1 defence pathway. Isoflavones and other polyphenols activate intracellular kinase cascades, leading to the acute activation of eNOS and NO release and/or generation of reactive oxygen and nitrogen species. Increased NO, ROS or peroxynitrite levels will modify cysteine residues on Keap1 leading to nuclear accumulation of the redox sensitive transcription factor Nrf2. Nrf2 binds to the antioxidant response element (ARE) or electrophile response element (EpRE) in the promoter region of target genes (e.g. phase II defense and antioxidant enzymes NQO1, HO-1). Induction of other antioxidant genes such as MnSOD may involve rapid phosphorylation of ERK1/2 and I-κB and translocation of the p50 subunit of NF-κB to the nucleus and transactivation of MnSOD expression.

Isoflavones have emerged as potential alternatives to HRT, yet there are still conflicting reports on their benefits for cardiovascular health [20]. Nevertheless, postmenopausal women supplemented with genistein for 6 months exhibit significant improvement in glycemic control and endothelial function compared to a placebo group [58]. These investigators emphasized that an individual's pre-existing metabolic status may affect responses to isoflavone therapy. Future, large-scale clinical studies evaluating the health benefits of isoflavones will need to consider the ability of intestinal bacteria to metabolize daidzein to equol as well as an individual's metabolic status. As studies in rodent models have shown that dietary isoflavones increase the expression of eNOS and antioxidant genes [30], further clinical studies of the effects of dietary isoflavones on gene expression in the vasculature are warranted. In summary, cardioprotective actions of dietary isoflavones may reflect their ability to stimulate NO and ROS production (Figure 1), leading to the upregulation of antioxidant gene expression via the Nrf2/ARE/EpRE defence pathway.

Figure 1



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References:

1) Mueller CF, Laude K, McNally JS, Harrison DG: ATVB in focus: redox mechanisms in blood vessels. Arterioscler Thromb Vasc Biol 2005; 25:274-278.

2) Van Gaal LF, Mertens IL, De Block CE: Mechanisms linking obesity with cardiovascular disease. Nature 2006; 444:875-880.

3) Levonen AL, Vahakangas E, Koponen JK, Yla-Herttuala S: Antioxidant gene therapy for cardiovascular disease: current status and future perspectives. Circulation 2008; 117:2142-2150.

4) Siow RC, Li FY, Rowlands DJ, Winter P, Mann GE: Cardiovascular targets for estrogens and phytoestrogens: transcriptional regulation of nitric oxide synthase and antioxidant defense genes. Free Radic Biol Med 2007; 42:909-925.

5) Mann GE, Rowlands DJ, Li FY, Winter P, Siow RC: Activation of endothelial nitric oxide synthase by dietary isoflavones: role of NO in Nrf2-mediated antioxidant gene expression. Cardiovasc Res 2007; 75:261-274.

6) Lissin LW, Cooke JP: Phytoestrogens and cardiovascular health. J Am Coll Cardiol 2000; 35:1403-1410.

7) Mendelsohn ME, Karas RH: Molecular and cellular basis of cardiovascular gender differences. Science 2005; 308:1583-1587.

8) Vina J, Borras C, Gambini J, Sastre J, Pallardo FV: Why females live longer than males? Importance of the upregulation of longevity-associated genes by oestrogenic compounds. FEBS Lett 2005; 579:2541-2545.

9) Kuiper GG, Carlsson B, Grandien K, Enmark E, Haggblad J, Nilsson S, Gustafsson JA: Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology 1997; 138:863-870.

10) McCarty MF: Isoflavones made simple - genistein's agonist activity for the beta-type estrogen receptor mediates their health benefits. Med Hypotheses 2006; 66:1093-1114.

11) Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van HL, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S: Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004; 291:1701-1712.

12) Hulley SB, Grady D: The WHI estrogen-alone trial--do things look any better? JAMA 2004; 291:1769-1771.

13) Williams RJ, Spencer JP, Rice-Evans C: Flavonoids: antioxidants or signalling molecules? Free Radic Biol Med 2004; 36:838-849.

14) Xu JW, Ikeda K, Yamori Y: Genistein inhibits expressions of NADPH oxidase p22phox and angiotensin II type 1 receptor in aortic endothelial cells from stroke-prone spontaneously hypertensive rats. Hypertens Res 2004; 27:675-683.

15) Miller AA, Drummond GR, Mast AE, Schmidt HH, Sobey CG: Effect of gender on NADPH-oxidase activity, expression, and function in the cerebral circulation: role of estrogen. Stroke 2007; 38:2142-2149.

16) Adlercreutz H, Mazur W: Phyto-oestrogens and Western diseases. Ann Med 1997; 29:95-120.

17) Setchell KD, Cassidy A: Dietary isoflavones: biological effects and relevance to human health. J Nutr 1999; 129:758S-767S.

18) Cassidy A, Brown JE, Hawdon A, Faughnan MS, King LJ, Millward J, Zimmer-Nechemias L, Wolfe B, Setchell KD: Factors affecting the bioavailability of soy isoflavones in humans after ingestion of physiologically relevant levels from different soy foods. J Nutr 2006, 136:45-51.

19) de Kleijn MJ, van der Schouw YT, Wilson PW, Grobbee DE, Jacques PF: Dietary intake of phytoestrogens is associated with a favorable metabolic cardiovascular risk profile in

postmenopausal U.S.women: the Framingham study. J Nutr 2002; 132:276-282.

20) Sacks FM, Lichtenstein A, Van HL, Harris W, Kris-Etherton P, Winston M: Soy protein, isoflavones, and cardiovascular health: an American Heart Association Science Advisory for professionals from the Nutrition Committee. Circulation 2006; 113:1034-1044.

21) Setchell KD, Clerici C, Lephart ED, Cole SJ, Heenan C, Castellani D, Wolfe BE, Nechemias-Zimmer L, Brown NM, Lund TD, Handa RJ, Heubi JE: S-equol, a potent ligand for estrogen receptor beta, is the exclusive enantiomeric form of the soy isoflavone metabolite produced by human intestinal bacterial flora. Am J Clin Nutr 2005; 81:1072-1079.

22) Tormala R, Appt S, Clarkson TB, Groop PH, Ronnback M, Ylikorkala O, Mikkola TS: Equol production capability is associated with favorable vascular function in postmenopausal women using tibolone; no effect with soy supplementation. Atherosclerosis 2008; 198:174-178.

23) Walker HA, Dean TS, Sanders TA, Jackson G, Ritter JM, Chowienczyk PJ: The phytoestrogen genistein produces acute nitric oxide-dependent dilation of human forearm vasculature with similar potency to 17beta-estradiol. Circulation 2001; 103:258-262.

24) Chin-Dusting JP, Boak L, Husband A, Nestel PJ: The isoflavone metabolite dehydroequol produces vasodilatation in human resistance arteries via a nitric oxide-dependent mechanism. Atherosclerosis 2004; 176:45-48.

25) Nestel P, Fujii A, Zhang L: An isoflavone metabolite reduces arterial stiffness and blood pressure in overweight men and postmenopausal women. Atherosclerosis 2007; 192:184-189.

26) Altavilla D, Crisafulli A, Marini H, Esposito M, D'Anna R, Corrado F, Bitto A, Squadrito F: Cardiovascular effects of the phytoestrogen genistein. Curr Med Chem Cardiovasc Hematol Agents 2004; 2:179-186.

27) Kreijkamp-Kaspers S, Kok L, Bots ML, Grobbee DE, Lampe JW, van der Schouw YT: Randomized controlled trial of the effects of soy protein containing isoflavones on vascular function in postmenopausal women. Am J Clin Nutr 2005; 81:189-195.

28) Joy S, Siow RC, Rowlands DJ, Becker M, Wyatt AW, Aaronson PI, Coen CW, Kallo I, Jacob R, Mann GE: The isoflavone Equol mediates rapid vascular relaxation: Ca2+-independent activation of endothelial nitric-oxide synthase/Hsp90 involving ERK1/2 and Akt phosphorylation in human endothelial cells. J Biol Chem 2006; 281:27335-27345.

29) Hall WL, Formanuik NL, Harnpanich D, Cheung M, Talbot D, Chowienczyk PJ, Sanders TA: A meal enriched with soy isoflavones increases nitric oxide-mediated vasodilation in healthy postmenopausal women. J Nutr 2008; 138: 1288-1292.

30) Mahn K, Borras C, Knock GA, Taylor P, Khan IY, Sugden D, Poston L, Ward JP, Sharpe RM, Vina J, Aaronson PI, Mann GE: Dietary soy isoflavone induced increases in antioxidant and eNOS gene expression lead to improved endothelial function and reduced blood pressure in vivo. FASEB J 2005; 19: 1755-1757.

31) Knock GA, Mahn K, Mann GE, Ward JP, Aaronson PI: Dietary soy modulates endothelium-dependent relaxation in aged male rats: Increased agonist-induced endothelium-derived hyperpolarising factor and basal nitric oxide activity. Free Radic Biol Med 2006; 41:731-739.

32) Douglas G, Armitage JA, Taylor PD, Lawson JR, Mann GE, Poston L: Cardiovascular consequences of life-long exposure to dietary isoflavones in the rat. J Physiol 2006; 571: 477-487.

33) Ruehlmann DO, Steinert JR, Valverde MA, Jacob R, Mann GE: Environmental estrogenic pollutants induce acute vascular relaxation by inhibiting L-type Ca2+ channels in smooth muscle cells. Faseb Journal 1998; 12:613-619.

34) Valverde MA, Rojas P, Amigo J, Cosmelli D, Orio P, Bahamonde MI, Mann GE, Vergara C, Latorre R: Acute activation of Maxi-K channels (hSlo) by estradiol binding to the beta subunit. Science 1999; 285:1929-1931.

35) Dick GM, Rossow CF, Smirnov S, Horowitz B, Sanders KM: Tamoxifen activates smooth muscle BK channels through the regulatory beta 1 subunit. J Biol Chem 2001; 276: 34594-34599.

36) Wyatt AW, Steinert JR, Wheeler-Jones CP, Morgan AJ, Sugden D, Pearson JD, Sobrevia L, Mann GE: Early activation of the p42/p44MAPK pathway mediates adenosine-induced nitric oxide production in human endothelial cells: a novel calcium-insensitive mechanism. FASEB J 2002; 16: 1584-1594.

37) Liu D, Homan LL, Dillon JS: Genistein acutely stimulates nitric oxide synthesis in vascular endothelial cells by a cyclic adenosine 5'-monophosphate-dependent mechanism. Endocrinology 2004; 145:5532-5539.

38) Stocker R, Keaney JF, Jr.: Role of oxidative modifications in atherosclerosis. Physiol Rev 2004; 84:1381-1478.

39) Halliwell B: The wanderings of a free radical. Free Radic Biol Med 2009; 46:531-542.

40) Ishii T, Itoh K, Takahashi S, Sato H, Yanagawa T, Katoh Y, Bannai S, Yamamoto M: Transcription factor Nrf2 coordinately regulates a group of oxidative stress-inducible genes in macrophages. J Biol Chem 2000; 275:16023-16029.

41) Ishii T, Itoh K, Ruiz E, Leake DS, Unoki H, Yamamoto M, Mann GE: Role of Nrf2 in the regulation of CD36 and stress protein expression in murine macrophages: activation by oxidatively modified LDL and 4-hydroxynonenal. Circ Res 2004; 94:609-616.

42) McMahon M, Thomas N, Itoh K, Yamamoto M, Hayes JD: Redox-regulated turnover of Nrf2 is determined by at least two separate protein domains, the redox-sensitive Neh2 degron and the redox-insensitive Neh6 degron. J Biol Chem 2004; 279:31556-31567.

43) Jaiswal AK: Nrf2 signaling in coordinated activation of antioxidant gene expression. Free Radic Biol Med 2004; 36:1199-1207.

44) Kong AN, Owuor E, Yu R, Hebbar V, Chen C, Hu R, Mandlekar S: Induction of xenobiotic enzymes by the MAP kinase pathway and the antioxidant or electrophile response element (ARE/EpRE). Drug Metab Rev 2001; 33:255-271.

45) Itoh K, Tong KI, Yamamoto M: Molecular mechanism activating Nrf2-Keap1 pathway in regulation of adaptive response to electrophiles. Free Radic Biol Med 2004; 36:1208-1213.

46) Tong KI, Padmanabhan B, Kobayashi A, Shang C, Hirotsu Y, Yokoyama S, Yamamoto M: Different electrostatic potentials define ETGE and DLG motifs as hinge and latch in oxidative stress response. Mol Cell Biol 2007; 27:7511-7521.

47) Mann GE, Bonacasa B, Ishii T, Siow RC: Targeting the redox sensitive Nrf2-Keap1 defense pathway in cardiovascular disease: protection afforded by dietary isoflavones. Curr Opin Pharmacol 2009. Jan 19 [EPAH]

48) Siow RC, Sato H, Mann GE: Heme oxygenase-carbon monoxide signalling pathway in atherosclerosis: anti-atherogenic actions of bilirubin and carbon monoxide? Cardiovasc Res 1999; 41:385-394.

49) Calabrese V, Butterfield DA, Scapagnini G, Stella AM, Maines MD: Redox regulation of heat shock protein expression by signaling involving nitric oxide and carbon monoxide: relevance to brain aging, neurodegenerative disorders, and longevity. Antioxid Redox Signal 2006; 8:444-477.

50) Kobayashi M, Yamamoto M: Nrf2-Keap1 regulation of cellular defense mechanisms against electrophiles and reactive oxygen species. Adv Enzyme Regul 2006; 46:113-140.

51) Gao L, Mann GE: Vascular NAD(P)H Oxidase Activation in Diabetes: A Double-Edged Sword in Redox Signaling. Cardiovasc Res 2009. doi:10.1093/cur/cup031

52) Chen XL, Varner SE, Rao AS, Grey JY, Thomas S, Cook CK, Wasserman MA, Medford RM, Jaiswal AK, Kunsch C: Laminar flow induction of antioxidant response element-mediated genes in endothelial cells. A novel anti-inflammatory mechanism. J Biol Chem 2003; 278:703-711.

53) Dai G, Vaughn S, Zhang Y, Wang ET, Garcia-Cardena G, Gimbrone MA, Jr.: Biomechanical forces in atherosclerosis-resistant vascular regions regulate endothelial redox balance via phosphoinositol 3-kinase/Akt-dependent activation of Nrf2. Circ Res 2007, 101:723-733.

54) Warabi E, Takabe W, Minami T, Inoue K, Itoh K, Yamamoto M, Ishii T, Kodama T, Noguchi N: Shear stress stabilizes NF-E2-related factor 2 and induces antioxidant genes in endothelial cells: Role of reactive oxygen/nitrogen species. Free Radic Biol Med 2007, 42:260-269.

55) Hosoya T, Maruyama A, Kang MI, Kawatani Y, Shibata T, Uchida K, Warabi E, Noguchi N, Itoh K, Yamamoto M: Differential responses of the Nrf2-Keap1 system to laminar and oscillatory shear stresses in endothelial cells. J Biol Chem 2005; 280:27244-27250.

56) Dai G, Vaughn S, Zhang Y, Wang ET, Garcia-Cardena G, Gimbrone MA, Jr.: Biomechanical forces in atherosclerosis-resistant vascular regions regulate endothelial redox balance via phosphoinositol 3-kinase/Akt-dependent activation of Nrf2. Circ Res 2007; 101:723-733.

57) Borras C, Gambini J, Gomez-Cabrera MC, Sastre J, Pallardo FV, Mann GE, Vina J: Genistein, a soy isoflavone, up-regulates expression of antioxidant genes: involvement of estrogen receptors, ERK1/2, and NFkappaB. FASEB J 2006;20:2136-2138.

58) Villa P, Costantini B, Suriano R, Perri C, Macri F, Ricciardi L, Panunzi S, Lanzone A: The differential effect of the phytoestrogen genistein on cardiovascular risk factors in postmenopausal women: relationship with the metabolic status. J Clin Endocrinol Metab 2009; 94:552-558.

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The mission of the External Affairs committee is to foster on behalf of the Council all matters of external relations with international federations of pharmacology, national learned societies and committees as well as industry. Specific aims are to encourage publicity and press coverage of pharmacology in order to advance the discipline and promote understanding of pharmacology across society.

In 2009 the Society proposes to support speakers at forthcoming science festivals which have large audiences and also receive substantial press coverage - the Cheltenham Science Festival, one of the largest in UK with an audience of 20,000 and with other members of the Bioscience Federation, the British Association for the Advancement of Science, which concentrates on the public discussion of developments across the many different fields of science. The Society is working with a PR company (see report below) to identify at forthcoming meetings, speakers and areas of research suitable for press releases to the media.

Anthony Davenport,
President External Affairs Committee

Media Relations Report, BPS Winter Meeting (16-18 Dec 2008)

The media coverage achieved from the 2008 BPS Winter Meeting in Brighton was extremely pleasing, with stories appearing in both trade and specialist publications and on major international news websites.

The brief was to produce a pre-conference press announcement followed by three press releases, one for each day of the conference. Dr Mick Bakhle again proved invaluable in helping to advise which subject areas might prove most newsworthy.
Two presentations were selected for consideration for day one of the conference – Dr Stephen Poole and Prof Luke O'Neill. Both academics were interviewed and it was decided to issue a release about Dr Poole's research into the Northwick Park drug trial, while Prof O'Neill's work on Toll-like receptors was included in the advanced press notice.

The presentation selected for the second day of the conference was Dr Nick Finer's research on anti-obesity drugs and his call for their wider use by GPs in order to reduce the need for surgery in later life. The final day's press release highlighted Prof Christine Mummery's research on embryonic stem cells and how they might be used in drug testing.

Dr Stephen Poole's, (National Institute for Biological Standards and Control), press release received initial interest from Kate Devlin, Medical Correspondent at the Daily Telegraph, The British Medical Journal, which ran a page lead in the news section of the January 3 edition. The release was also carried by the Pharmaceutical Journal, as well as several medical / science websites.

Dr Nick Finer, Consultant in Obesity Medicine at Addenbrooke's Hospital, received extensive online coverage, the press release was picked up by the Daily Telegraph and was published online on 16 December. It is worth noting that the Daily Telegraph website is visited by about 20 million people a month. The press release was also carried by USA Today online, resulting in widespread, positive exposure for the BPS and the Winter Meeting.

Prof Christine Mummery, a UK researcher formerly at The University of Nottingham but now at Leiden University in the Netherlands, proved excellent at describing her research in lay terms. Once a release was agreed, a copy was sent to Prof Mummery's host institution and, at her request, to Stem cells for Safer Medicines (SC4SM), as it referenced them, and they were grateful for the notification.

The release was picked up by the major US news outlet CNN, which was running a special programme on stem cells close to Christmas and requested an interview with Prof Mummery. A very positive piece on Prof Mummery's work subsequently appeared on the CNN website a few days after the conference ended, which mentions the BPS Winter Meeting. The website receives an average 35 million page views a day.

The conference also received additional media attention after the Press Association singled out the research of Dr James Dear, from Edinburgh University, who was presenting at the conference. The story was carried by several Scottish newspapers.

Press coverage can be viewed in the Media section of the BPS website.

As always, a huge thank you must go to Dr Mick Bakhle for his help and guidance in identifying possible stories from the conference and teasing out the strongest and most appropriate angles.

Anna Muir and STEHM Media

Meetings Report

Robin Hiley
Vice President
(Meetings)

After the earliest start to cold weather for a long time, a winter's week in Brighton was probably not one that many BPS members looked forward to, despite the promise of a rich programme. On arrival, spirits were rapidly raised by the aerobatic display put on by the huge starling colony on the wrecked West Pier, and the warm welcome in the Hilton courtesy of the huge infra-red heaters in the meeting rooms.

The Clinical Section perhaps reflected the nation's gloom by following the Specialist Registrars' Session with a debate about the death of the discipline. David Back's Lilly Lecture showed that defeatism was not appropriate by his brilliant exposition of the way in which clinical pharmacology can markedly enhance the effectiveness of therapy as shown by his work on drug interactions in HIV. Sadly, in view of the quality of the talks, the symposia on Tuesday morning were thinly attended, especially in the first session, which did not reflect well on the Society, especially to those speakers who were non-members - the question of start time is clearly something we will have to think about.

Pic 1:
Shahmime Guul & Mike Curtis

Wednesday was Young Persons' Day, and was enhanced by the presence of 21 posters presented by undergraduates nominated to present results by their institutions [pic 1]. Members were very supportive of these fledging pharmacologists, and the feedback that has reached me has been very positive. Other young pharmacologists were recognised by the awards of prizes, all of which were hard fought [pg 17, pic 3]. Symposia on Obesity (appropriate on the day of the Official Dinner) and using Receptor Structure/Function Studies in Drug Design, were followed by Andrew Kicman's Tocris Lecture on Anabolic Drugs in the Gym. He led us through the bizarre Pharmacological abuses people subject themselves to in order to reach a single end and the efforts by his and other labs to catch them out. The Official Dinner was noteworthy for the inpressive range of the talent rewarded by the Society's prizes more than by the food, and the Society's Photographer obtained evidence of Arthur Weston's intentions towards the referees who kept asking him to get out his K^+-selective electrode. Arthur's Gaddum Lecture [pg 17, pic 2] the next day was entertaining, informative and revealed a deep love for his subject. He showed how K^+ channels, long championed by him while overshadowed in many other's minds by those flashier cellular citizens, the Na^+ and Ca^{2+}channel, are central to vascular regulation.

Pic 2: Peter Hicks, Mandy MacLean & Grame Henderson

On Thursday lunchtime, Anne Stephenson gave the lecture in memory of Gary Price. She thoughtfully presented views on the possibility of regulating receptor trafficking to therapeutic ends. Thursday morning's symposia were of the same outstanding quality as those on the previous days, covering the major topics of Cys-loop receptors, Cytokines and Depression, and Stem Cell Therapy in the Heart and the Society was fortunate to gather together so many excellent speakers.

Jeff Aronson, our President had to miss the meeting through ill-health. His recovery was no doubt hastened by the good wishes sent by many members from the meeting, but possibly also by the absence of so many clinical pharmacologists from the wards. Mandy MacLean was also unable to say a final goodbye, beyond those said at the Dinner [pic 2] as she also was struck down on Thursday morning and had to head back early to Scotland. This left your new Meetings Vice President having to call the last survivors away from the wine bar to review the final posters, while contending with an amplifier that had clearly been used to generate voices on children's cartoons. The meeting survived all these glitches, thanks to the unstinting efforts of the BPS staff.

The success of this meeting is largely due to Mandy MacLean, who put together the first-rate programme and will be a hard act to follow. She has presided (or is it vice-presided?) over a series of wonderful meetings and this last is likely to remain one to beat for many years to come. We all owe her a great debt for safeguarding the vibrancy of our scientific meetings.

Next year, to try to make it easier for members to attend, and to gain a bit of shelter from sea breezes, the Winter Meeting returns to London, to the Queen Elizabeth II Conference Centre in Westminster, using what used to be a ministerial suite. Can the pigeons of the City of Westminster put on a display to beat that of Brighton's starlings?

Come and see.

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

DAP BPS Diploma in Advanced Pharmacology

Jill Darton from GlaxoSmithKline completes the BPS Diploma in Advanced Pharmacology

The BPS developed the BPS Diploma in Advanced Pharmacology in 2006, following a request by members to provide training opportunities for research scientists who lacked a formal education in Pharmacology. There was much discussion whilst we designed a course that was feasible in terms of time for students, from both industry, and academia. In addition, we wanted the workshops to provide interactive teaching, enabling students to build upon their experience through a course of topics learnt in the workshops. After much discussion, we agreed to a course that involved attendance at six cutting edge workshops, two communications to the Society, and a dissertation. We now have 40 registrants in various stages of the Diploma.

Jill Darton from GSK is our first candidate to complete the Diploma. She followed a pathway that took her just under 2 years and consisted of attendance at the following workshops: General and Advanced Receptor Theory; Drug Discovery and Safety Pharmacology; Statistics; Ischaemia-reperfusion Injury; Molecular Biology Techniques in Pharmacology and Pharmacokinetics. She gave an oral communication entitled, '*Inhibition of gastric acid secretion by different mechanisms of action in the conscious gastric fistula rat*', and a poster communication entitled, '*Potency and selectivity of GSK1325831A, a small molecule ghrelin receptor agonist.*' Her dissertation on '*Evaluation of the clinical and cost-effectiveness of Herceptin in the treatment of early and late stage breast cancer*', was supervised by Dr Martin Lennard from the University of Sheffield.

Sue Brain and Jill Darton

The BPS formally presented Jill with her Diploma on the occasion of the dinner at the Winter Meeting in Brighton. I am sure everyone will join me in congratulating Jill on being the first student to obtain the Diploma and wish her all the best for her career in a new post at GSK.

SD Brain, Vice-president Academic Development

Biotechnology YES: A Contestant's Perspective

Two members of the British Pharmacological Society's Younger Members Committee recently celebrated their success at the 2008 Biotechnology YES (Young Entrepreneurs' Scheme) competition. Biotechnology YES is an entrepreneurial competition aimed at enhancing understanding of the importance of scientific research to the commercial sector among life scientists. Scientific innovation is a valuable contributor to the economy, especially in turbulent times such as a recession. Scientists, however, rarely think beyond the confines of the laboratory and about the potential commercialisation of their research. Biotechnology YES aims to change this.

Throughout the UK, heats are held at which postgraduate and postdoctoral life scientists are given three days of expert tuition from leading figures, on the various aspects of business that are required to establish a viable and profitable company. The topics include business planning, finance, intellectual property, marketing strategies and operational aspects. The three days culminate in a Dragons' Den-style competition, in which contestants are required to present a realistic business plan for a hypothetical bioscience product to a panel of potential investors. The top 3 teams from each heat are then sent to the illustrious London final to compete for a £1000 prize.

This year 73 teams from all around the UK entered the competition. Follix, the brainchild of a team of University of Manchester PhD students (consisting of BPS committee members Annie Geraghty and Tom Longden, along with their colleagues Leon Adams, Alexandra Hughes, and Laura Roberts) won the Central Regional heat with their microsphere platform technology. According to their business plan, Follix would use this technology as a vehicle to deliver and retain a hair-removal cream at the hair follicle. Following investment, this initial product would be sold throughout Europe to raise capital for further research and development of the company's pipeline products. The Central Regional heats were held at the renowned Old Trafford football stadium, home of Manchester United, after which the winners were invited to the London finals.

Annie Geraghty and Tom Longden (3rd from left), along with their colleagues Leon Adams, Alexandra Hughes, and Laura Roberts

This year's final was held at the Marriott Hotel County Hall on the banks of the Thames, overlooking the Houses of Parliament. After a day of intense competition, the winners were announced and Ovega, from Reading University, took the top prize with their plan for healthier Omega 3-enriched cooking oils. Follix were proud to take the Syngenta prize for 'Best plant science-based business plan', especially as they were a team of physiologists and pharmacologists!
The competition was an exciting and very memorable experience for all the Follix team. Not only did we make friends and have great fun, but the competition also raised awareness of the importance of thinking about scientific research from a business perspective and highlighted some previously-unconsidered career options for the entire team. If we could enter again next year we certainly wouldn't hesitate!

The competition is open for entry all year round and more information is available at www.biotechnologyyes.co.uk.

Thomas Longden, University of Manchester

Pharmacologists in the *Oxford Dictionary of National Biography*

Jeff Aronson,
President, BPS

The original *Dictionary of National Biography* was a typical Victorian enterprise. It was first edited by Sir Leslie Stephen, Virginia Woolf's father, and later by Sidney Lee, and was published in 63 volumes between 1885 and 1900 (www.oup.com/oxforddnb/info/prelims/intro/intro1/#history). Several supplements were subsequently published under the general editorship of Christine Nicholls, in collaboration with, on different occasions, Sir Edgar ('Bill') Williams, Lord Blake, and Sir Keith Thomas. In 1992 it was decided to overhaul the dictionary completely, and Colin Matthew, Professor of Modern History in Oxford, was given the task of editing the new edition. Colin, a much respected scholar, whom a colleague described as 'one of the few wholly irreplaceable people in [Oxford] University', died suddenly and unexpectedly in 1999 and was replaced by Brian (now Sir Brian) Harrison of Corpus Christi College. After the second edition had been published in 2004, Lawrence Goldman, another Oxford historian, took over as editor. Entries in the Dictionary are constantly being added, as eminent people die and become eligible for inclusion.

A search of the current on-line edition of the dictionary (*The Oxford Dictionary of National Biography*; http://ezproxy.ouls.ox.ac.uk:2117/index.jsp) reveals 26 individuals to whom the main description 'pharmacologist' is given. They are listed in Table 1. Although only one is described as a clinical pharmacologist, five others are described as physicians and pharmacologists. Two were born in the 18th century (the *Oxford English Dictionary* records the first use of the word "pharmacologist" in 1728), 12 in the 19th century, and 12 in the 20th century (if one includes 1900 in that century). The list includes three women, Edith Bülbring, Marthe Vogt, and Eleanor Zaimis, and two Nobel prizewinners, Henry Dale and John Vane.

Table 1. Pharmacologists in the Oxford Dictionary of National Biography

Name	Dates	Description
Blaschko, Hugh [formerly Karl Felix Hermann]	1900-1993	biochemist and pharmacologist
Brunton, Sir Thomas Lauder, first baronet	1844-1916	physician and pharmacologist
Bülbring, Edith	1903-1990	pharmacologist and physiologist
Buttle, Gladwin Albert Hurst	1899-1983	physician and pharmacologist
Cash, John Theodore	1854-1936	physician and pharmacologist
Clark, Alfred Joseph	1885-1941	pharmacologist
Cushny, Arthur Robertson	1866-1926	pharmacologist
Dale, Sir Henry Hallett	1875-1968	physiologist and pharmacologist
Dixon, Walter Ernest	1870-1931	pharmacologist
Feldberg, Wilhelm Siegmund	1900-1993	pharmacologist and physiologist
Fraser, Sir Thomas Richard	1841-1920	pharmacologist
Frazer, Alastair Campbell	1909-1969	pharmacologist and food scientist
Gaddum, Sir John Henry	1900-1965	pharmacologist
Gray, Samuel Frederick	1766-1828,	naturalist and pharmacologist
Hanbury, Daniel	1825-1875	pharmacologist
Ing, (Harry) Raymond	1899-1974	chemical pharmacologist
Kosterlitz, Hans Walter	1903-1996	pharmacologist
Paton, Sir William Drummond MacDonald	1917-1993	pharmacologist
Pereira, Jonathan	1804-1853	pharmacologist and physician
Perry, Walter Laing Macdonald, Baron Perry of Walton	1921-2003	pharmacologist and university administrator
Vane, Sir John Robert	1927-2004	pharmacologist
Verney, (Ernest) Basi	1894-1967	physiologist and pharmacologist
Vogt, Marthe Louise	1903-2003	pharmacologist and neurochemist
Williams, (Richard) Tecwyn	1909-1979	clinical pharmacologist
Williams, Robert	c.1787-1845	physician and pharmacologist
Zaimis [née Christides; other married name Chrysafis], Eleanor	1915-1982	pharmacologist

There is another (longer) list of others who had some contact with pharmacology at some time during their careers (Table 2). They are not described as pharmacologists in the *Oxford Dictionary of National Biography*,

although some of them should be. For example, Sir Edward Johnson Wayne (1902–1990) is billed as a physician, but he was appointed to the chair of pharmacology and therapeutics in the University of Sheffield in 1934 and was also at one time chairman of the joint formulary committee of the British Medical Association and the Pharmaceutical Society and chairman of the British Pharmacopoeia Commission. And Sir Derrick Melville Dunlop (1902–1980), also described as a physician, is well known to clinical pharmacologists as the chairman of the Committee on Safety of Drugs (the Dunlop Committee) in the 1960s, whose work led to the Medicines Act of 1968 and the establishment of the Committee on Safety of Medicines; he was also at one time chairman of the British Pharmacopoeia Commission and a director of Winthrop Laboratories. In other cases the connection with pharmacology is tenuous; for example, Lydia Pasternak Slater gained her degree in biochemistry from the Institute of Pharmacology in Berlin.

Table 2. Others with pharmacological connections listed in the Oxford Dictionary of National Biography

Name	Dates	Description
Bashford, Ernest Francis	1873-1923	oncologist
Battley, Richard	bap. 1772, d. 1856	apothecary and manufacturing chemist
Bennett, John Joseph	1801-1876	botanist
Brown, Sir (George) Lindor	1903-1971	physiologist
Campbell, Sir David	1889-1978	physician
Carling, Sir Ernest Rock	1877-1960	surgeon and developer of radiotherapy
Cook, Robert Percival	1906-1989	biochemist
Danielli, James Frederic	1911-1984	biologist
Davson, Hugh	1909-1996	physiologist
Dawes, Geoffrey Sharman	1918-1996	physiologist
Doyle, Sir Arthur Ignatius Conan	1859-1930	writer
Dunlop, Sir Derrick Melville	1902-1980	physician
Etheridge [Etherege], George	1519-1588?	physician and classical scholar
Gamgee, Arthur	1841-1909	physiologist
Hale-White, Sir William	1857-1949	physician
Hamilton [formerly Himmelschein], Max	1912-1988	psychiatrist
Harington, Sir Charles Robert	1897-1972	biochemist and medical administrator
Hart, Francis Dudley [Frank]	1909-2004	rheumatologist
Hay, Matthew	1855-1932	physician and expert in forensic medicine and public health
Laidlaw, Sir Patrick Playfair	1881-1940	medical scientist
McElwain, Timothy John	1937-1990	cancer physician
McKendrick, John Gray	1841-1926	physiologist
Marsden, (Charles) David	1938-1998	neurologist and neuroscientist
Maund, John	1823-1858	physician and analytical chemist
Mellanby, Sir Edward	1884-1955	medical scientist and administrator
Pearson, Richard	bap. 1764, d. 1836	physician
Pickford, (Lillian) Mary	1902-2002	neuroendocrinologist
Pitt-Rivers, Rosalind Venetia Lane Fox [née Rosalind Venetia Henley]	1907-1990	biochemist
Ray [formerly Wray], John	1627-1705	naturalist and theologian
Ringer, Sydney	1835-1910	physician and physiologist
Roberts, Sir William	1830-1899	physician and physiologist
Rosenheim, (Sigmund) Otto	1871-1955	organic chemist and biochemist
Sanderson, Sir John Scott Burdon, baronet	1828-1905	pathologist and physiologist
Sheehan, Harold Leeming	1900-1988	pathologist
Slater, Lydia Elisabeth Leonidovna Pasternak	1902-1989	biochemist, poet, and translator
Wall, Patrick David [Pat]	1925-2001	neuroscientist
Walshe, Sir Francis Martin Rouse	1885-1973	neurologist
Wayne, Sir Edward Johnson	1902-1990	physician
Whitteridge, David	1912-1994	physiologist
Willcox, Sir William Henry	1870-1941	physician and toxicologist
Young, Sir Frank George	1908-1988	biochemist and educationist

If you think that any of those listed in Table 2 deserve to be described as pharmacologists, please let me know and I shall speak to the Editor. Similarly, let me know if there are any late UK pharmacologists, not currently in the *Oxford Dictionary of National Biography*, who would, in your view, justify inclusion. I already have a few in mind.

BPS Diploma Workshop Report: General and Advanced Receptor Theory

Old theory for new technologies: BPS General and Advanced Receptor Theory Workshop applying classical receptor theory to modern drug development.

BPS Diploma Workshop on "General and Advanced Receptor Theory", In association with the BPS Christmas meeting 15-17th December, 2008.

Organizers: D. Armstrong (Astrazeneca), A.J. Gibb (UCL), J. Koenig (Cambridge), E. Lilley (Novartis), M. Trevethick (Pfizer).

INTRODUCTION: what might the Roman philosopher Lucretius, Paul Ehrlich and Sir James Black have in common? Participants who attended the second BPS Diploma Workshop on General and Advanced Receptor Theory (GART) discovered a common interest in the actions of hormones and drugs and in understanding these according to physical principles. The technology available to study ligand-receptor interactions in the modern pharmaceutical industry would have seemed like science fiction to pharmacologists of 50 years ago. The use of robotic technologies to conduct scintillation proximity radioligand binding assays, PET and SPECT to measure ligand binding in the awake human brain, or patch-clamp single-channel recording to study receptor activation kinetics seem a long way from the classical work of A J Clark on the dose-response curve of the isolated frog rectus abdominus muscle. The participants of this workshop though, enjoyed seeing how many of the principles for the analysis and interpretation of drug action data that were developed so carefully by the early work of Hill, Clark, Gaddum, Schild and Katz can be directly applied to data from modern assay systems.

BACKGROUND: the BPS Diploma in Advanced Pharmacology developed out of a recognised need within the Society to provide a mechanism for developing pharmacological knowledge among postgraduate students and professional scientists now working in the discipline but lacking formal training in it, or desire further professional development in this area. A wider aim is to promote networking and sharing of knowledge in pharmacology, and recently the workshops have been opened up to a larger audience, non-diploma candidates are now welcome to attend. To these ends each workshop is designed to include opportunities for discussion and socialising among the participants and most workshops are held in association with Society meetings. The first GART Workshop ran in Glasgow in 2007 in association with the Life Sciences meeting, and was the first workshop to run that was specifically designed for the Diploma. In their feedback many of the participants expressed the view that receptor pharmacology was an ideal topic to launch this exciting new venture.
Further workshops have followed in Drug Development and Safety Pharmacology, and Ischaemia-Reperfusion Injury (in association with the Winter BPS meeting in Brighton, 2007) followed by Applying Receptor Theory to Drug Discovery (March 2008), Statistics (March 2008), Pharmacokinetics (June 2008), and Molecular Biology Techniques in Pharmacology (September 2008).

LOCAL ORGANIZATION: The GART course was ably managed by the BPS Education and Meetings teams who handled the organization of the course web site, provision of course materials to the participants, coordinated registration of participants, collated the course feedback and Workshop Reflective Accounts, and provided professional support to all the Workshop organizers.

WORKSHOP OVERVIEW: the 18 course participants were mainly from the UK pharmaceutical industry and university research with a few participants from abroad, including two from the pharmaceutical industry in Costa Rica. The workshop was structured over 1.5 days with 2 lectures on the afternoon of the first day ('Classical approaches to the study of drug-receptor interactions' - Elliot Lilley, 'Introduction to the principles of radioligand binding' - Mike Trevethick) and on the second day ('Partial agonists, agonist efficacy, receptor constitutive activity and inverse agonism' – Duncan Armstrong, 'Competitive and non-competitive antagonism' – Jenny Koenig), Lectures were interspersed with quantitative exercises on analysis of the actions of agonists and antagonists and Excel spreadsheet tutorial exercises provided practical experience of modelling drug action at receptors and analysis of agonist dose-response data using non-linear least-squares curve fitting (Jenny Koenig and Alasdair Gibb). The workshop was rounded off with a discussion and tutorial exercise highlighting the role of quantitative receptor theory in drug discovery during the development of ß2 agonists for the treatment of asthma (Mike Trevethick and Duncan Armstrong). The Workshop represents a heavy workload, but was undertaken with enthusiasm and good humour from the participants.

The lectures concerned classical and modern principles of selected areas of receptor pharmacology. Most participants were familiar with at least some of the material covered, the majority having experience of GPCR systems, either *in vitro*, or *in vivo*. The academic content of the workshop centred around the principles of quantifying drug action at receptors. The work of Ehrlich, Langley, Hill and others established what can now be recognised as Pharmacology's 'Big Idea' (Rang, 2006) the concept of the receptor. This opened the route to understanding hormone and neurotransmitter action while providing a rational basis for understanding drug effects and developing new drug therapies, propelling the pharmaceutical industry to astonishing success in the 2nd half of the 20th century, transforming medical practice and enhancing the quality of life for millions of people. Many of the workshop participants particularly appreciated the opportunities created by the workshop for discussion with experts directly involved in drug development in the pharmaceutical industry.

The GART workshop is focused on agonists, antagonists and receptor activation. Basic theory relating to the interpretation of dose-response and radioligand binding data, and measures of agonist and antagonist receptor affinity was developed and used to lead into more advanced material on measures of agonist efficacy, partial and inverse agonism. One of the subsidiary aims of the workshop was to dispel some of the myths that the algebra underlying quantitative receptor pharmacology may be too difficult for those without mathematical training (and the Workshop encouraged participants to be bold in this and make use of some excellent material available in text books on this topic: e.g. Jenkinson, 2002). The mathematical aspects were clearly challenging for most of the participants who may not have used algebraic manipulations in their work for a number of years. It was satisfying to note that after some initial dismay, by lunchtime the paper napkins were being put to good use in discussion of the relationship between the dose-response curve and the Hill-Langmuir equation.

Quantitative exercises and discussion material were used to consolidate the lecture material on agonists, antagonists and receptor activation, beginning with the use of the Law of Mass Action to derive the Hill-Langmuir equation, and the extension of this provided by the del-Castillo and Katz (1957) mechanism

$$A + R \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} AR \underset{\alpha}{\overset{\beta}{\rightleftharpoons}} AR^* \qquad (1)$$

that allows the concepts of agonist affinity (dissociation equilibrium constant, K_A = k-1/k+1) and efficacy (constant, E = β/α) to be quantified and the dependence of the shape of the dose-response relation on these two parameters to be quantitatively modelled and described. The approach of the Workshop is to first present the topic in a formal lecture and then explore the underlying ideas using quantitative exercises and modelling. Comparison of the relationship between ligand concentration, [A], and proportion of receptors in the active conformation (pAR*)

$$p_{AR^*} = \frac{E[\mathrm{A}]}{K_\mathrm{A} + (1+E)[\mathrm{A}]}, \text{ maximum } p_{AR^*_{Max}} = \frac{E}{1+E} \qquad (2)$$

with the relationship between ligand concentration and proportion of receptors occupied (pocc=pAR+pAR*)

$$p_{occ} = \frac{[\mathrm{A}]}{\frac{K_\mathrm{A}}{1+E} + [\mathrm{A}]}, \text{ maximum} = 1 \qquad (3)$$

provides a useful starting point to discuss firstly, the meaning of the half-maximum concentration, [A]50, in the relationship between [A] and the proportion of active receptors, and secondly, the meaning of the half maximum point (KL) on a radioligand binding curve:

$$[A]_{50} = K_L = \frac{K_\mathrm{A}}{1+E} \qquad (4)$$

noting that the constant derived from fitting the binding curve (K_L) depends on both the affinity (K_A) and efficacy (E). Thus, in general, it is not possible to determine whether a change in the chemical structure of the agonist, or receptor structure has altered affinity or efficacy using measures of equilibrium binding affinity or dose-response curve half-maxima (Colquhoun, 1998). These concepts were explored in an Excel-based curve fitting and modelling exercise, where the workshop participants could spend some time observing the effect of varying [A]50 and Hill coefficient, nH, on the shape of a simulated dose-response relation, and then use the same approach to investigate the effect of varying KA and E on the shape of the relation for the del-Castillo & Katz mechanism described by equation (2). The Excel add-in 'Solver' function was employed to demonstrate the use of non-linear least-squares curve fitting in Excel to estimate [A]50 and nH for the Hill equation.

A second general discussion point arises from recognising that each of the receptor conformations depicted conceptually in the del-Castillo & Katz mechanism in fact represents multiple states (for example, receptors most likely have more than one active conformation, more than one resting, inactive conformation etc). It is clear that the equilibrium constants describing the del-Castillo & Katz mechanism are, in reality, composite constants representing multiple underlying equilibria. These considerations illustrate one of the ideas discussed in the Workshop that the [A]50 from a dose-response curve, or the constant from a radioligand binding assay will, in principle, depend on all the conformational states of the receptor. Further complications appear when attempts are made to understand the molecular basis of partial agonism, inverse agonism or the consequences of GPCR dimerization in the analysis of affinity and efficacy at G protein-coupled receptors.

Receptor antagonism and the quantitative treatment of two competing ligands formed a second theme of the Workshop. Beginning with the situation where two ligands bind to the receptor in a mutually exclusive manner

$$\begin{array}{ccc} B+A & R & \overset{K_A}{\rightleftharpoons} AR \\ & K_B \Big\Updownarrow & \\ & BR & \end{array} \qquad (5)$$

the Gaddum and Schild equations were derived

$$p_{AR} = \frac{[\mathrm{A}]}{K_\mathrm{A}\left(1 + \frac{[\mathrm{B}]}{K_\mathrm{B}}\right) + [\mathrm{A}]} \qquad r - 1 = \frac{[\mathrm{B}]}{K_\mathrm{B}} \qquad (6)$$

and discussion of the inhibition curve obtained from a binding experiment and how the IC50 for the inhibitor, I, depends on the equilibrium constants for both I and the radioligand, L, (K_I and K_L).

$$Bound = B_{([I]=0)} \frac{[L]}{K_L\left(1+\frac{[I]}{K_I}\right)+[L]}$$

$$IC_{50} = K_I\left(1+\frac{[L]}{K_L}\right) \quad (7)$$

These principles were then applied in a tutorial exercise examining the blocking action of a series of anti-malarial drugs at α9α10 neuronal nicotinic receptors.

The final discussion session of the Workshop focused on the impact of some of the principles of receptor pharmacology on one area of drug development and design: beta agonists in asthma. Here questions of drug selectivity, and whether agonist potency is dominated by affinity or efficacy were combined with consideration of factors affecting the duration of action of agonist drugs in vivo and the unusual behaviour of drugs like salmeterol.

Obviously no single workshop can cover everything and it is important to view each Workshop of the BPS Diploma as a starting point for further discussion of material which the participants are familiar with from their own work and so part of the participants reflective account of the Workshop includes an analysis of some appropriate data that illustrates some of the Workshop principles. For most participants, the Workshop was challenging, but satisfying, judging from feedback comments provided after the workshop. The excellence of the material included in the post-Workshop Reflective Accounts is a good measure of the commitment and enthusiasm of the participants following the Diploma.

The following workshops will be held in 2009: Statistics (May 13th, London), Applying Receptor Theory to Drug Discovery (July 6th, Edinburgh) Pharmacokinetics (July 7th, Edinburgh), Early Phase Trials of New Drugs (September 1st, London) and Drug Discovery (December, London). If you would like to register for any of these BPS workshops please contact sm@bps.ac.uk. For further details about applying for the BPS Diploma in Advanced Pharmacology, see the BPS website (www.bps.ac.uk) or contact meetings@bps.ac.uk.

References:

del Castillo, J. & Katz, B. - Interaction at endplate receptors between different choline derivatives. Proc Roy Soc Lond. 1957; B 146, 369-381.

Colquhoun, D. - Binding, gating, affinity and efficacy. The interpretation of structure-activity relationships and of the effects of mutating receptors. Br J Pharmacol 1998; 125, 924-947.

Jenkinson, D.H. - Classical approaches to the study of drug-receptor interactions. pp 3-78. In Textbook of Receptor Pharmacology. 2nd Ed. Foreman, J.C. & Johansen, T. CRC Press Inc 2002; Florida, USA.

Rang, H.P. - The receptor concept: pharmacology's big idea. Br J Pharmacol 2006; 147, S9-S16.

Those wishing to learn more about the BPS Diploma in Advanced Pharmacology and related Workshops, should visit the BPS website (www.bps.ac.uk) or contact Judith Hall (jmh@bps.ac.uk).

Alasdair Gibb, University College London
Gart Workshop Organizer

Profile: Emily Davies, participant on the BPS/ Physiological Society *in vivo* short course

Eight years ago, BPS and The Physiological Society set up Short Courses on Integrative *in vivo* Pharmacology/Physiology for undergraduate and postgraduate students in response to the decrease in the number of universities in the UK that offer *in vivo* training within their institutions. Funding for the courses, additional to that provided by BPS and the Physiological Society, comes from the Wellcome Trust, the BBSRC, and the Pharmaceutical Industry, covers the cost of running the courses, student travel, accommodation expenses, attendance at a Home Office training course (modules 1-4), and the *in vivo* training course itself. Three courses are run each year, currently at Kings College London, the University of Bristol, and the University of Glasgow.

Emily Davies obtained a first class degree in Pharmacology from the University of Bristol and stayed on to study for her PhD in Physiology. The title of her PhD is: "Developing somatosensory evoked potentials in vivo - a translational model for pain". She attended the in vivo short course during her undergraduate degree.

How did you find out about the BPS/Physoc *in vivo* short courses?
I was informed about the course in a lecture during the 2nd year of my undergraduate degree at the University of Bristol. I was keen to participate as I was considering a career in research at the time and knew the course would provide me with invaluable skills. The course is organized and funded by BPS and Physiological Society, and sponsored by a consortium of pharmaceutical companies, BBSRC and Wellcome Trust, and is therefore nationally recognised. A large proportion of biomedical undergraduate students do not get the chance to gain such skills and so it was a great opportunity.

When and where did you carry out your short course?
The week long course took place in June 2007 at the University of Bristol, within the Department of Physiology and Pharmacology. Many different research laboratories within the University were involved. Prior to the summer course, I attended a 2 day Home Office Personal Licence training course and examination in order to hold a Personal Licence to carry out experiments under the Animals (Scientific Procedures) Act 1986.

Can you describe what the short course entails.
This intensive, specialised course involves a mixture of lectures, observation and hands-on experimentation, in order to gain an understanding of the physiological and pharmacological principles underlying *in vivo* experimentation. I was able to learn techniques such as small animal surgery, data acquisition and experimental design. Lectures were given by academic and industry representatives on the use of animals in biomedical research. During the course we were able to carry out and have input in our own experiments. Participants also had the opportunity to observe *in vivo* electrophysiological experiments in various labs within the University and get a taster of research life. Due to the large number of staff associated with the course, and the small student numbers, there was a great deal of expert guidance and instruction. Towards the end of the week there was a dinner which allowed us to socialise with PIs, post-docs and PhD students within the University.

Did the course reinforce your desire to do *in vivo* research as a career?
The course certainly provided me with many opportunities and confirmed my intention to pursue a career in research. I decided to use my training and skills gained on the course to best advantage and I selected an *in vivo* final year undergraduate research project. This *in vivo* electrophysiological project gave me the opportunity to present work at international conferences including the triennial meeting of the International Association for the Study of Pain and the main meeting of the Physiological Society. I am now undertaking a PhD which also expands on the techniques I learnt. I believe my interest and enthusiasm in pursuing an *in vivo* research career in neuroscience has largely stemmed from the BPS/Physoc *in vivo* short course and the opportunities arising from it.

Why do you think that *in vivo* work is important in advancing biological science?
In vivo experiments are necessary in order to investigate whole system physiology and pharmacology and understand interactions between different body systems and their modification by drugs. This is not always possible using alternative methods in novel research.

How much of the course focused on ethics of animal experimentation and how important do you feel this is to someone planning a career in *in vivo* pharmacology?
Both the Home Office licence training course and the *in vivo* short course gave serious consideration of the ethics of animal experimentation. They emphasised the ethical requirements under 'ASPA' and the requirements of the University of Bristol. We were also taught about seeking and using alternative approaches and the importance of experimental design for *in vivo* research. I believe it is crucial for anyone embarking on an *in vivo* research career to have a comprehensive understanding of the legal framework relating to the use of animals in research and the ethical considerations.

How did the *in vivo* training course help you in choosing your PhD?
Gaining *in vivo* training at an early stage in my research career gave me the chance to continue *in vivo* research during my undergraduate degree and during this time I developed a keen interest in neuroscience, in particular pain research. This is the area of research I have now decided to pursue in my PhD.

How would you compare the value of the hands on course with using computer simulations instead?
Computer simulations are particularly useful in reinforcing theory for undergraduate students but the hands on course allowed me to put that theory into context. Although my undergraduate degree programme widely used alternative *in vitro* and computer aided education methods, for individuals intending to undertake an *in vivo* research career it is important to learn the relevant skills in order to carry out productive research later in their careers.

Who do you think would benefit most from attending a short course?

I would definitely recommend the course to undergraduate students who are interested in a research career as I think it would benefit them the most, but also to postgraduate students wishing to gain new skills. There is a shortage of graduates with an education involving *in vivo* research, and in my case I found that potential supervisors when applying for my PhD really valued this training.

Where do you see yourself in 5 years time and what are your long-term career aims?
I would like to stay in academia and at the moment my career aim, following my PhD, is to take on a post-doc position and contribute original research to the field of neuroscience.

The courses are aimed at both undergraduates and postgraduates, with calls for nominations going out via Heads of Departments in the 4th quarter of the year preceding the course. For further details, please contact jmh@bps.ac.uk or ebell@physoc.org.

Interview by Jude Hall
Education and Training Manager

Biology in the Real World Brought the Curriculum to Life!

Report of the annual conference of the ASE: University of Reading, 2009

As part of our schools outreach programme, BPS joined forces with the Physiological Society (PS) and the Biochemical Society (BS) to share an exhibition stand, and to contribute to the one-day symposium *Biology in the Real World: Bringing the Curriculum to Life*, at the annual conference of the Association for Science Education (ASE) at the University of Reading. The annual conference is aimed at all science educators including teachers; technicians; advisors; consultants and school inspectors with the aim of improving science education in Britain.

Biology in the Real World
The *Biology in the Real World* symposium was organized by members of the Nucleus Group; an informal group of not for profit organizations who work together, pooling resources and expertise, to provide curriculum enrichment and enhancement and careers advice for schools and colleges. Nucleus Group members in addition to BPS, PS and BS who contributed to the symposium this year included: the Wellcome Trust; the Association of the British Pharmaceutical Industry; Microbiology in Schools Advisory Committee; the Society for General Microbiology; the Association for the Study of Animal Behaviour; Royal Botanic Gardens, Kew; Institute of Biology; the Society for Endocrinology and the British Ecological Society.

The Nucleus Group has organised symposia at the annual ASE conference for several years, and uses the conference as an opportunity to help teachers develop and expand on biological concepts and scientific method they teach in schools, and to inform them of current research in those areas. In view of recent significant changes to key stages 4 and 5 National Curricula, and curriculum emphasis on *How Science Works*, the 2009 symposium was designed specifically to provide curriculum support and enrichment on new areas of study that may be less familiar to teachers, and to provide ideas of how this knowledge can be used in the classroom, in order to inspire pupils and inform them of the opportunities a career in science can bring. Topics this year were therefore chosen to complement subject areas of the 2009 GCSE and A level specifications.

The symposium was one of the most popular and highly attended events of the conference. The following symposium sessions were expertly chaired by Dr Gail Bromley (Royal Botanic Gardens, Kew): *What is diabetes*, Dr Aileen King (King's College London); *Why do we need a new vaccine for tuberculosis?*, Dr Helen Fletcher (University of Oxford); *Drugs of Abuse: psychoactive and performance enhancing drugs*, Dr Emma Robinson (University of Bristol); *What would a monkey do?*, Dr Lynda Boothroyd (University of Durham); *Health impacts of climate change*, Dr Hugh Montgomery (UCL Institute for Human Health and Performance) and *Flowers, Forensics and Pharmaceuticals*, Prof Monique Simmonds (Royal Botanic Gardens, Kew). The ideas and information provided in the various presentations were skillfully drawn together at the end of the day in an interactive session focusing on *How Science Works* led by Dr Jeremy Airey (National Science Learning Centres) and Ms Karen Devine (British Ecological Society) in a session entitled *Bringing the Real World into the Classroom*.

To complement the *Biology in the Real World* session this year, a resource booklet was produced to accompany the symposium. The booklet

was designed and prepared in-house by BPS, and provides teachers with a professionally prepared hard copy resource which can be used to provide curriculum enrichment in the classroom. The booklet includes a synopsis of each presentation, relevant links to GSCE and A level specification sections, web and other teaching resource links and web addresses for careers advice. Feedback from the symposium and conference in general suggests that subject specific resources of this type are very valuable to teachers, and we received many requests for access to similar specialist literature to complement standard teaching resources in the classroom.

Speakers at the symposium were sponsored by members of the Nucleus Group. BPS is particularly grateful to members Emma Robinson (sponsored by BPS and the Society for Endocrinology) and Aileen King (sponsored by BS and PS). Both speakers are RCUK Fellows funded by the BPS's Integrative Pharmacology Fund who provided excellent presentations on drugs of abuse and diabetes respectively at the symposium.

Looking ahead

BPS, PS and BS benefit greatly from sharing exhibition stands and pooling resources at conferences such as the ASE conference and the Life Sciences Careers Conference (see report page 14). At the school level there is little distinction between the scientific disciplines of our individual organizations, and there is much overlap in the content of resource information. This collaboration adds to improving the working relationships between the Education Managers involved, identifying any crossovers or forming ideas for further joint work and is useful in terms of promoting the aims of the three societies. The three societies plan to further develop and extend collaborative working in 2009.

If you are interested in contributing to BPS's schools outreach programme, please contact jmh@bps.ac.uk. The resource booklet can be downloaded from the BPS and PS websites (www.bps.ac.uk) and www.physoc.org/schools).

Jude Hall, Education and Training Manager, BPS
Chrissy Stokes, Head of Education and Membership, PS
Hannah Baker, Science Education Manager, BS

The BSF Education Colloquium: Supporting Outreach and Enrichment in Schools

Organized by the Biosciences Federation (BSF) and hosted by The National Science Learning Centre, this interactive discussion focused on outreach and enrichment provision by the Biology community. Engaging the next generation of scientists through outreach is high on the agenda at both The Physiological Society and BPS, and for this reason both societies were well represented at the colloquium.

With the invitation open to teachers (the 'customers') and outreach providers ('the practitioners') alike, the programme held high promise for us to learn what constitutes effective outreach in biology 'from the horse's mouth'. However, enthusiasm was dampened when it became apparent that the number of teachers attending the event was very low; no doubt this reflects the obstacles faced by teachers to secure teaching cover for continuing professional development (CPD) and similar activities.

As Director at the National Science Learning Centre, John Holman opened proceedings. Professor Holman highlighted factors that he considers to be the key influences to the number of individuals studying STEM and the numbers gaining strong STEM qualifications. It was clear that there are specific areas where our societies could have an impact: professional development for teachers, careers advice, and enhancing and enriching the curriculum and particularly targeting the first three years of secondary school (key stage 3). Indeed, both societies are already very active in the latter two of these areas.

The two talks that followed Professor Holman's came from individuals actively involved in science outreach. Karen Bultitude (University of the West of England) talked in detail about the STEM directories, which provide a coherent resource signposting the 'customers' to UK-wide outreach activities in all STEM subjects. Jeremy Pritchard's (University of Birmingham) talk addressed science outreach from the perspective of an academic; sharing anecdotes from his own experience and highlighting the benefits of science outreach, he was perhaps preaching to an already converted audience. However, it was interesting to share his experiences of how best to approach outreach aimed at different levels of education.

The remainder of the day had been designed to encourage active communication between the delegates, each having the opportunity to sign up to two of five possible workshops: *Teacher-Scientist Networks, Junior Café Scientifique, Working with STEMNET, Science Learning Centres or Good practice in university outreach*. Each session focussed on a different aspect of science outreach with a discussion facilitated to enhance interaction on the topic in question. Without many teachers in each of the groups, feedback from the customers was limited.

Dr Phil Smith and Claire Willis led an interactive, role-play workshop on '*Teacher-Scientist Networks*'. Founded in 1994, there are now over 240 teachers and 80 scientists on the scheme which links single teachers with individual scientists with the aim of establishing long term partnerships in order to encourage students to engage with contemporary science. The TSN scheme was set up and runs in Norwich and is funded by the Gatsby Charitable Foundation and other organisations. Claire Willis described her work as a TSN coordinator with responsibility for a scientists at work scheme in the North East of England.

Phil Waywell stood in at short notice to describe his work with *Junior Café Scientifique*. The junior version, founded by Pablo Jensen, builds on the success of the popular and established Cafe Sci to promote a mechanism by which young people can discuss scientific issues in an informal environment. The discussions are student-led and individual Cafes are arranged, publicised and run by the young people themselves, giving them ownership of what they learn. In an informal situation, the focus is on discussion, not debate or learning, consistent with the underlying feeling that classrooms are for lessons and cafes are for conversation. Students choose their own topics and then invite an expert (who could be a scientist or, for example, a science journalist) to the discussion. Examples of topics discussed so far include: eating disorders; designer babies; aliens; Dr Who; time travel; heroes; drugs; stem cells; could men have babies?; and perhaps the most intriguing, how do you get holes in crumpets?

Delegates attending the *Working with STEMNET* workshop had the opportunity to learn more about how STEMNET has evolved and is now outsourcing much of the work to outreach 'partners'. The workshop was facilitated by Harriet Dow and Steve Hutcheon, both working with the North Yorkshire Business and Education Partnership Ltd (NYBEP), which holds the STEMNET contract for North Yorkshire. NYBEP, like other contract holders, has excellent links with local businesses

and schools. Through this network, NYBEP coordinates outreach to all secondary schools in the local area; it provides strategic advice and individually tailored services to help schools and colleges enrich the curriculum, businesses engage actively in the development of their future workforce, and learners better understand their personal skills and future choices. As a contract holder, NYBEP coordinates over 100 Science and Engineering Ambassadors (SEAs) working in the North Yorkshire area. Steve Hutcheon works as a SEA for NYBEP, and shared with the group some of his experiences; he also facilitated the group discussion on what makes outreach effective, the challenges we face and the importance of evaluating success and how best to gather this information. One of the strongest messages delivered in this workshop was for outreach to be considered effective, the impact within the classroom must be long lasting.

Jeremy Airey, a Senior Professional Development Leader at the National Science Learning Centre, facilitated a discussion on how Science Learning Centres operate to provide teachers with CPD. Whilst it is undeniable that the courses offered by the SLCs offer invaluable training and 'thinking' space away from the classroom, getting the time away is both difficult and expensive. The message from this workshop was that CPD must help *develop* the teachers, not simply train them; it is important to ensure that the training is taken back to both students and colleagues for capacity building and long-term effect. Again, evaluation was considered to be central to ensuring future CPD success. Jeremy was keen to stress that CPD courses run at the nine regional learning centres and in the national learning centre, and the over-arching aim is to share teaching methods and skills and knowledge.

The importance of *Good Practice in University outreach* was covered in a final workshop, and the day's proceedings were expertly wrapped up by Sue Assinder (Chair, BSF Education Committee) who brought together the various topics covered during the day in an audience led survey from the perspective of the various stakeholders represented in the audience

Learned societies are, of course, only a small part of the network working to support science education and, whilst it is important we continue to develop our own strategies and activities to support enrichment and enhancement, we must be careful not to re-invent the wheel but to contribute to and complement external programmes where appropriate.

Chrissy Stokes (Head of Education and Membership, Physiological Society) and Jude Hall (BPS).

National Science Learning Centres: www.sciencelearningcentres.org.uk
Bioscience Federation: ww.bsf.ac.uk
Teacher scientist network:www.tsn.org.uk
STEMNET: www.stemnet.org.uk
Researchers in residence: www.researchersinresidence.ac.uk
Scientists at work: www.slcne.org.uk

Life Science Careers Conference 2008

The 2008 Life Science Careers Conference was organized by member organisations of the Biosciences Federation (BSF) and was led this year by the Physiological Society. The purpose of these conferences is to provide careers advice – primarily to undergraduate students studying for a life science degree.

The conference was hosted by King's College London on 26 November, where around 200 delegates registered to learn more about the broad career opportunities that would open up to them after graduation.

The organizing committee was careful to focus on opportunities for Life Science graduates – a topic that is considered to be poorly covered by other careers events.

The format for the day included 7 talks, 1 workshop and an exhibition. The talks covered careers from academic research to science communication; the workshop was lead by Irrum Magre - The Physiological Society's Education and Membership co-ordinator – who gave an energetic insight into preparing the perfect CV; finally, the exhibition provided delegates with the opportunity to talk to employers, recruitment consultants and professional bodies.

The event would not have been possible without the generous sponsorship provided by AstraZeneca; with further support from the BSF, The Physiological Society, the Biochemical Society, the Society for Endocrinology and the Society for Experimental Biology. This year, BPS were involved in hosting the event, and particular thanks to BPS member Andy Grant (King's College London), for his support at the BSF exhibition stand on the day.

We have received excellent feedback from delegates, exhibitors and speakers alike.

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

Preserving Clinical Pharmacology in the NHS?

Tanweer Hussain

Tanweer Hussain graduated in medicine from the University of Liverpool in 1994 where inspirational pharmacology lectures by Professor Breckenridge would influence his decision to purse a career in Clinical Pharmacology. Following a period of general medical training in the east midlands, he spent 2 years as a physician in a one of the largest independent clinical pharmacology units in the UK, undertaking phase I clinical trials in healthy volunteers on behalf of the international pharmaceutical industry; from first-into-man administrations of new chemical entities to complex pharmacokinetic-pharmacodynamic studies. Returning to the NHS he was appointed Specialist registrar in Clinical Pharmacology & Therapeutics in March 2003. Dr Hussain is also an Honorary Lecturer at Liverpool University where he is currently completing MD in pharmacogenetics. He completed higher medical training in Clinical Pharmacology & Therapeutics and General (Internal) Medicine in December 2008.

I recently attended meetings at the MHRA and a clinical pharmacology colloquium with a large number of specialist registrars in clinical pharmacology and therapeutics. Inspired by the large turnout the chair at both meetings remarked perhaps that the predictions about the imminent demise of clinical pharmacologist were premature. However the optimistic sentiments conflict with reality: a Royal College of Physicians survey published in 2007 revealed that the NHS did not employ any clinical pharmacologists between 2005 and 2007. In fact numbers are in decline and there are concerns about the viability of clinical pharmacology as a speciality. Many training vacancies within clinical pharmacology remain unfilled despite junior doctors' fears about unemployment.

Clinical pharmacologists have a well-defined role in the teaching centres, with the most academic candidates going on to be heads of department and take leading roles in national organisations. I think the current crisis is a result of failures to develop a unique role in the district general setting and to attract candidates who would otherwise be competent clinicians. A policy statement in the British Journal of Clinical Pharmacology over thirty years ago defined the role of the clinical pharmacologist in the district general hospital. The authors believed there was an urgent need to increase the number of general physicians with a special interest in clinical pharmacology in non- teaching centres. At that time the authors defined the following special roles for clinical pharmacologist in the district general setting:

- Management of complex toxicology
- Therapeutic drug monitoring
- Drug information service offering pharmacoeconomic advice.

Such roles were subsequently generally and readily taken up by other professionals such as pharmacists, clinical chemists and emergency physicians. The battle to establish clinical pharmacology in the district general has been lost and this failure may have far-reaching effects. The important issue facing clinical pharmacologists at the moment is how to the speciality will survive in the NHS. Some clinical pharmacologists may argue that they should be lead local drugs and therapeutic committees promoting rational prescribing at a local level, although there are many others who perform equally well in this role.
Clinical pharmacologists are frequently excellent general physicians and perhaps the last of a dying breed. The obvious role for clinical pharmacologist is to take a lead role in developing the academic basis for acute medicine and in the age of PBL (Problem Based Learning) ensure undergraduates have the ability to prescribe rationally. While acute medicine may help preserve clinical pharmacology in the NHS it may only be a temporary respite. Changes to the acute medicine curriculum may exclude clinical pharmacologists from leading acute medicine teams in the future.

In 2005 Professor Ritter headed a think-tank debating the future of clinical pharmacology. His findings have been published in the Royal College bulletin. He contrasts the fortunes of clinical pharmacology and pharmaceutical medicine. He points out that while the importance of medical education in clinical pharmacology has been recognised, the speciality is not attracting new academic lecturers. In contrast pharmaceutical medicine which contains a substantial element of clinical pharmacology is flourishing.

Perhaps forging links with the faculty of pharmaceutical medicine would increase awareness of clinical pharmacology amongst trainees, while there may be no difficulty in recruiting doctors to the industry there are problems attracting them to clinical pharmacology.

The unfortunate events following TGN 1412 may present an opportunity to the speciality. Following adverse reactions experienced by participants in the clinical trial of the drug known as TGN1412 in 2006 the Expert Scientific Group (ESG) convened by the Secretary of State for Health to look at how to improve the safety of drug trials involving products such as monoclonal antibodies.

The recommendations included:

- The development of specialist centers to undertake phase one studies on higher risk agents.
- They also pointed out that organizations set up to conduct clinical trials are increasingly separate from a medical environment and from academic or other educational centers. This is affecting their ability to train the next generation of relevant staff, especially clinical pharmacologists. This should be addressed by better access to "hands on" experience in the planning and conduct of clinical trials for relevant staff.

The ABPI guidelines for phase 1 clinical trials suggest that those individuals who act as Principal Investigators have specific qualifications including a certificate of completion of clinical training training (CCT) in clinical pharmacology and a minimum of two years phase 1 experience. Except for of a handful of doctors in the country few individuals will have the necessary qualifications. So perhaps a rethink is in order with regards training clinical pharmacologist in this country to fulfill demands when the current crop of phase 1 clinical pharmacologists retire.

In my opinion what is required is active collaboration with parties with a vested interest in preserving the speciality, this involves a three-fold alliance between the industry, MHRA and academic departments of clinical pharmacology. Training programmes should be developed to give individuals the opportunity to pursue a portfolio career between acute medicine and industry (including phase 1 clinical pharmacology) and the MHRA. What form this eventually takes will require careful thought by the appropriate parties. However failure to take radical changes now will mean it is unlikely the speciality will survive.

Tanweer Hussain, Specialist Registrar in Clinical Pharmacology & Therapeutics

Forthcoming BPS Meeting Deadlines

2009 Summer Meeting, 8 - 10 July 2009, Edinburgh, UK

Abstract submission: 27 April

Early bird registration: 12 June

EACPT 2009 Congress of the European Association for Clinical Pharmacology and Therapeutics, Edinburgh, Scotland 12 - 15th July 2009

Registration open-www.eacpt2009.org

7th James Black Conference: Integrative Pharmacology and Physiology: translating "omics" into functional and clinical applications, 1-3 September, 2009, King's College London, UK

Abstract submission: 29 May

Early bird registration: 31 July

2009 Winter Meeting, Queen Elizabeth II Conference Centre, London, 15 - 17 December 2009

The Meetings Committee is pleased to announce the programme of symposia:

Tuesday 15 December

"Cannabinoid signalling in brain repair"
Organizer: Dr Francisco Molina-Holgado, Wolfson Centre, King's College London, UK

"Chemokine antagonists as therapeutic agents"
Organizers: Prof. John Westwick, Novartis, UK & Prof. Tim Williams, Imperial College London, UK

"Delivering safe prescribing in the NHS"
Organizer: Dr Simon Maxwell, University of Edinburgh, UK

Wednesday 16 December

"$GABA_B$ receptors - becoming part of the A team?"
Organizers: Prof. Nicholas Barnes, University of Birmingham & Dr Tom Blackburn, TP Bioventures, USA

"The kinetics of drug-receptor interactions: the benefit and detriment to drug discovery" **Organizer:** Dr Steven Charlton, Novartis, UK

"Translational pharmacology- optimizing Academic/Industry partnerships"
Organizers: Younger Members Committee

Thursday 17 December

"Antibody therapeutics"
Organizer: Dr Andrew Ramage, University College London, UK

"Targeting the cannabinoid system for GI diseases"
Organizers: Prof. Roger Pertwee, University of Aberdeen, UK, Prof. Keith Sharkey, University of Calgary, Canada and Dr Karen Wright, Lancaster University, UK

"The histamine H4 receptor: new multi-use therapeutic target"
Organizer: Dr Paul Chazot, University of Durham, UK

Abstract submission: 28 August-28 September

Online registration will open in September

Future Meetings

2009

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

7 - 9 May — Joint Focused Meeting with Deutsche Gesellschaft für experimentelle und klinische Pharmakologie und Toxikologie (DGPT) 'New Drugs in Cardiovascular Research'. Dresden, Germany

12 May — Statistics Workshop. **PhD students only.** King's College, London, UK.
E-mail: meetings@bps.ac.uk

13 May — Statistics Workshop. **Open to all members and non-members.** King's College, London, UK.
E-Mail: meetings@bps.ac.uk

14 May — Young Life Scientists' Symposium 'Neurological disorders: from molecules to medicine - Incorporating the Promega UK Young Life Scientist Awards'. The Council House, Bristol, UK. Email: yls-09-bristol@bristol.ac.uk

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

6 July — Applying Receptor Theory to Drug Discovery Workshop. **Open to all (including non-diploma attendees).** Edinburgh, UK. E-mail: meetings@bps.ac.uk

7 July — Pharmacokinetics Workshop. **Open to all (including non-diploma attendees).** Edinburgh, UK.
E-mail: meetings@bps.ac.uk

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

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

1 September — Early Phase Trials of New Drugs Workshop. **Open to all (including non-diploma attendees.)** King's College, London, UK. E-mail: meetings@bps.ac.uk

1-3 September—7th James Black Conference 'Integrative Pharmacology and Physiology: translating "OMICS" into functional and clinical applications'. King's College, London, UK
Abstract Submission: 29 May, Early Bird Registration: 31 July

6-8 September — Drug Discovery 2009: Joint Meeting with ELRIG (European Laboratory and Robotics Interest Group) & SBS (Society for Biomolecular Sciences), Liverpool, UK. E-mail: jackie.howard@lab-robotics.org

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

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

2010

17-23 July- WorldPharma 2010 (IUPHAR Congress). Copenhagen, Denmark. www.worldpharma2010.org/

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

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