Appreciation

Sir David Jack: an extraordinary drug discoverer and developer

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The authors of this piece have also drawn together a virtual issue of Sir David's key papers from his career, which can be found at [http://onlinelibrary.wiley.com/journal/10.1111/\(ISSN\)1365-2125/homepage/sir_david_jack.htm](http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1365-2125/homepage/sir_david_jack.htm)

Sir David Jack, FRS, was a remarkable man, driven by altruistic intent, a passionate and exceptional scientist, who was able to apply the full power of his impressive intellect to the discovery of new and important medicines for the benefit of patients in need. This involved not only a critical focus on basic discovery, but also the proper application of drug development sciences (pharmacology, drug metabolism, toxicology, analytical chemistry, chemical manufacturing, pharmaceuticals and clinical medicine) to ensure that a sound scientific idea at the bench could be turned into the reality of a useful medicine for patients.

His broad, applied and integrated approach to drug discovery is what makes David Jack stand out, even among others highly regarded and acknowledged for their contributions to medical research and drug discovery. In addition he was a great leader and commanded the respect of all who worked for him, no matter where they worked in the organization. All he asked was that each and every employee focused on the task in hand, namely to find 'better medicines for the treatment of poorly-treated common diseases'. He repeatedly espoused the idea that if you did not know 'how in general terms' what you were doing might eventually lead to this end then you should not be doing it. If such focused efforts proved to be successful, patients would benefit and so would the company and the resulting revenue generated would provide yet more opportunity to find different or further improved medicines. With David's vision and leadership an amazingly impressive number of important new medicines materialized from the Allen and Hanburys site at Ware, including inhaled beclomethasone dipropionate (Becotide®), fluticasone propionate (Flixotide®), salbutamol/albuterol (Ventolin®) and salmeterol (Serevent®) for asthma therapy, labetalol (Trandate®) for hypertension, ranitidine (Zantac®) for gastric acid diseases, ondansetron (Zofran®) for the treatment of emesis associated with cancer chemotherapy and sumatriptan (Imigran®/Imitrex®) for the treatment of

migraine and cluster headache. Soon after David Jack's death in November 2011, GlaxoSmithKline fittingly renamed the old Allen and Hanburys R&D site at Ware as the 'David Jack Centre' in his memory, a great tribute to the man who started work in the pharmaceutical industry at Glaxo laboratories in 1951. He then went on to Smith Kline and French, followed by Allen and Hanburys at Ware and finally became overall Head of Research and Development at Glaxo until 1987.

David will undoubtedly be most remembered for his enormous contribution to the field of respiratory medicine. On arriving at Allen and Hanburys in 1961 as Research Director, David set himself the task of finding a more selective bronchodilator than isoprenaline, the non-selective β -adrenoceptor agonist, which was widely in use at the time but caused unwanted effects on the heart at doses that caused bronchodilation, even when inhaled. This led to the discovery of salbutamol, as the first selective β_2 -adrenoceptor agonist for the treatment of bronchospasm associated with airway diseases such as asthma [1]. Salbutamol was quickly marketed as Ventolin (the blue inhaler much loved and trusted by patients with asthma) and still remains the most widely prescribed bronchodilator for the acute treatment of asthma today.

Around the same time David had also correctly appreciated that asthma involved more than just bronchospasm and he was very aware of the work showing the effectiveness of cortisone as an anti-inflammatory drug. However, cortisone had to be administered systemically causing a lot of unwanted side effects, thus restricting its clinical use to more severe patients. Following the logic that glucocorticosteroids were very effective for inflammatory skin conditions when administered topically, David set about finding a glucocorticosteroid that could be inhaled and thus exert topical anti-inflammatory effects on the surface of the respiratory tract. This led to the discovery of beclomethasone dipropionate for both oral and nasal inhalation, although according to one of the early clinical

investigators involved in studying beclomethasone dipropionate for the treatment of asthma, Dr Morrow Brown, this invention almost did not get developed [2]. The judicious use of the McKenzie test on animal and human skin helped in the selection of the dipropionate form of beclomethasone; and you were for the high jump if you ever left the 'dipropionate' out of your description of this glucocorticosteroid, as this would cause David to become very agitated and let everyone know very clearly that 'without the 'dipropionate', you have a different drug. In fact so good was the McKenzie test at predicting topical potencies of glucocorticosteroids that it was later used to help with the development of other more potent, topically active glucocorticosteroids for the treatment of asthma and rhinitis such as fluticasone propionate [3]. The much improved safety profile of inhaled glucocorticosteroids in the clinic led ultimately to this class of drug being recommended by most clinical authorities as first line treatment of asthma, even for children, and today there are even over the counter formulations of these drugs marketed for the treatment of rhinitis. This is a profound testament to David's breadth of scientific understanding and his pioneering vision in this therapeutic area that these drugs remain the most effective anti-inflammatory drugs available even today for the treatment of inflammatory diseases of the respiratory tract.

However, David was not satisfied with just discovering the two major classes of drugs for the treatment of diseases of the respiratory tract. He realized that whilst salbutamol was a very effective bronchodilator, it had a limitation in having a relatively short duration of action, such that it had to be used up to four to six times a day to maintain patients as symptom free. He therefore had the idea of extending the duration of action of salbutamol by modifying its chemical structure by adding a lipophilic 'tail' moiety to the 'head' group and using this approach the medicinal chemists at Ware came up with the long acting β_2 -adrenoceptor agonist (LABA), salmeterol [4]. The concept of the 'lipid tail' modification converted the structure of salbutamol into a larger, more lipophilic molecule with a much longer duration of action, making it a drug that only required twice daily dosing. Salmeterol was quickly shown to be of benefit in the maintenance treatment of asthma, particularly in the control of nocturnal symptoms [5]. One of us (CP) had their first encounter with David around the clinical launch of salmeterol in 1991, having just published a hypothesis in the *Lancet* [6] as to why β_2 -adrenoceptor agonists should not be used as monotherapy in the treatment of asthma and which questioned the basis of the launch of salmeterol in the UK. This led to some very heated exchanges with David, who never believed that there was a problem with the regular use of inhaled β_2 -adrenoceptor agonists, despite the growing disquiet in some quarters that finally led to the FDA insisting on 'black box' warnings on medicines containing LABAs in 2005 [7]. Furthermore the FDA recently mandated several

large pharmaceutical companies to investigate 64 000 asthma patients using LABA therapy as a post-marketing surveillance study [8]. We await the results of such unprecedented studies to see what, if any, consequences they might have. Regardless, millions of asthma sufferers worldwide continue to enjoy a good quality of life that could not have even been dreamt of 50 years ago. The discovery of salmeterol inevitably led to other LABAs being found and developed into clinically successful drugs, particularly formoterol [9]. More recently there has been the introduction of the so called ultra LABAs, such as indacaterol recently launched [9] and vilanterol currently in phase 3 development [9]. All of these drugs ultimately stem from the pioneering work of David and the Ware teams that discovered salbutamol and salmeterol.

With the discoveries of the first β_2 -adrenoceptor selective agonist and the first topically active inhaled glucocorticosteroid to his name, David readily appreciated that the most effective treatment for most patients with asthma should be the inhaled combination of a good bronchodilator and a good topical anti-inflammatory drug. Patients clearly liked the rapid relief of symptoms enjoyed when they inhaled a β_2 -adrenoceptor agonist, whereas physicians treating them were increasingly aware that asthma was a chronic inflammatory condition and wanted their patients to be taking a topically active glucocorticosteroid. This led to the development of a combination of salbutamol and beclomethasone dipropionate in a single inhaler which was launched by Glaxo as Ventide® in 1984. Whilst conceptually this was the correct thing to do, combining a 'twice daily' drug with one that needed to be given four to six times daily meant physicians were never sure how best to use this fixed combination and so it was never widely used. However, with the discovery of a twice daily β_2 -adrenoceptor agonist (salmeterol) and a twice daily glucocorticosteroid (fluticasone propionate), their obvious combination into a single inhaler led to the development of Seretide® or Advair® which has become one of the world's top selling medicines, dominating the treatment of asthma and also chronic obstructive pulmonary disease (COPD). Parenthetically the pharmaceutical and technical demands of designing an efficient and effective inhaler for such drugs cannot be underestimated and were always under David Jack's close scrutiny. Once again his concept of a novel combination inhaler led ultimately to others following suit, e.g. the combination of budesonide and formoterol. Indeed so successful have these combination inhalers been for the treatment of respiratory disease that different variations on this approach now dominate the field of new medicines under development (see [9], where some 30 different combinations or formulations of a LABA and a topically active glucocorticosteroid are described as under development). This clinical sea change in the approach to the treatment of asthma and COPD since the 1960s is a testament to the enormous importance of David's early vision in this area, stemming from the

development of salbutamol and beclomethasone dipropionate, which led to the enormous improvement in the lives of millions of patients and to a new clinical understanding of respiratory diseases themselves (see [10]).

While David focused much of his thinking and energy on respiratory diseases throughout his career, he was also committed to pursuing his approach to drug discovery in other therapeutic areas. Not forgetting his own mantra (better medicines for poorly-treated common diseases), he began building an organization that could look for new drugs to treat conditions such as gastric ulceration, hypertension, migraine and various central nervous system diseases, as well as improved neuromuscular blocking drugs for better clinical control of surgical anaesthesia.

Early work outside the respiratory area focused on areas of existing expertise within the relatively small Department of Pharmacology, in Allen and Hanburys, overseen by Roy Brittain. The areas covered included mainly investigations of potential new approaches to finding better drugs for hypertension and gastric acid diseases, as well as trying to develop a better neuromuscular blocking drug. In all three of these areas new medicines were discovered and developed, namely the combined α - and β -adrenoceptor blocking drug, labetalol [11, 12], the histamine H_2 -receptor blocking drug, ranitidine [13–15] and the non-depolarizing neuromuscular blocking drug, fazadinium [16, 17]. All proved to have unique profiles and were effective clinically, but for various reasons only ranitidine became a major drug commercially.

Indeed the revenues resulting from the marketing of ranitidine, at one stage the biggest selling drug in the world, transformed Glaxo into the company it is today and provided the resources for the research and development organization to expand into new and more speculative areas. This pleased David and his senior research leaders who were convinced that his approach was the right way to find yet more new medicines. The only modification was to allow, in some agreed areas of research, more speculation and risk in the targets pursued, in expectation of greater gains in the form of new and better medicines for needy patients. This calculated change of strategy was underpinned by David's comment 'if you are going to make a mistake you had better make a big one'. This pioneering approach took Glaxo into big research programmes in a number of areas, but in particular prostaglandins and 5-hydroxytryptamine.

Work on prostaglandins began at Ware on the basis that these endogenous lipid mediators could cause both constriction and relaxation of bronchial smooth muscle as well as being involved in inflammatory processes. The possibility of a new type of drug for respiratory disease seemed possible, although the multitude of other actions of the various prostaglandins suggested that one might also find drugs for other conditions such as cardiovascular and gastrointestinal diseases. However, David would never have allowed such work to begin on such a scale had it not

been that some of the chemists at Greenford had shown it possible to make synthetic prostanoids with the potential to become drugs. The other essential requirement was to understand the nature of the receptor types involved in the actions of prostaglandins. This might have been considered a daunting task in the absence of information in an era preceding the advent of molecular biology. However, some pioneering, receptor characterization work in the Pharmacology Department at Ware, first instigated by Ian Kennedy and Bob Coleman [18], led to a unique understanding of prostaglandin receptor functions. The initial classification of prostaglandin receptor types and their function by the Ware group has stood the test of time [19, 20]. Indeed as the various receptor types were gradually identified at the molecular level, scientists had to refer to the work on functional receptor characterization to rationalize the nomenclature [21, 22]. However despite this tremendous achievement, no new medicines emanated from this work. The closest, potential candidate was a thromboxane receptor blocking drug as an anti-platelet agent to improve on aspirin, whose full clinical value was not appreciated at the time [23, 24].

The work on 5-hydroxytryptamine proved to be much more profitable. One of us (PPAH) was hired early on by David Jack, as part of his team building plan, and asked to initiate and lead a project on migraine. This led to an exploratory period where the possible involvement of prostaglandins and/or 5-hydroxytryptamine (5-HT) was considered. In keeping with David's rational and consistent approach to his staff, he handed over full authority for decision making, but one was always aware of being fully accountable and woe betide you if you were not able to respond accordingly when challenged. The decision to work on 5-HT receptors was accepted and excitingly evidence for a previously unidentified receptor in the vasculature emerged and was presented to the British Pharmacological Society at a meeting in Manchester in 1977 [25, 26]. Although the importance of this observation was not appreciated by most at the time, a team of chemists was assigned to the project at Ware and under the leadership of one of us (PPAH) finally produced a drug (the 5-HT_{1B/D} receptor agonist, sumatriptan) that was marketed in 1991 and has provided profound benefit to millions of migraine sufferers right up to the present day [27–30]. Although there were many difficulties and hurdles presented throughout the project life, David was always supportive providing that one could identify likely ways of circumvention that could be readily tested. During this period too, new information about 5-HT receptor types and their potential importance in other disease areas was discovered. As the number of new 5-HT receptor types identified grew, Ware scientists became internationally recognized for their work in the field of 5-HT receptor characterization and classification [31–34], never forgetting, or being allowed to forget, the applied importance of the work.

Efforts to capitalize on this knowledge proceeded rapidly with a big focus on the central nervous system and gastrointestinal tract. This led to the development of 5-HT₃ receptor antagonists that were explored for a variety of uses. Initial excitement for their potential utility in a variety of CNS disorders including anxiety, schizophrenia, drug addiction and cognition proved to be unfounded in man [35, 36]. However ondansetron proved to be a remarkably effective anti-emetic when emesis was induced by agents such as cisplatin, cyclophosphamide or radiation [37, 38] and was launched in 1990 for the treatment of patients undergoing cancer chemotherapy or radiotherapy. As is the case for sumatriptan, ondansetron has provided enormous relief to patients and prevented many from giving up their treatment and their hope of survival because of the severe nausea and vomiting caused by their anti-cancer treatments.

In parallel, work was proceeding on the role of 5-HT₃ receptors in the gastrointestinal tract that led to the concept that a 5-HT₃ receptor antagonist might be useful clinically in the treatment of irritable bowel syndrome, particularly in those patients with diarrhoea [39–41]. This approach led to the development and marketing of the long acting 5-HT₃ receptor antagonist, alosetron (Lotronex®) in 2000. Although it has proved to be very effective in patients with severe symptoms, the unexpected side effect of ischaemic colitis in some individuals has markedly restricted its use to specific patients [42]. The mechanism of this unwanted effect of alosetron remains to be determined but is worthy of more investigation. It would be interesting to know what David Jack would have made of it all, but he had retired from Glaxo by then.

On leaving Glaxo, David helped establish Vanguard, a company that was seeking to take drugs that sat on the shelves of large pharmaceutical companies and develop them further. David was never convinced of this strategy and persuaded the company that they needed to invest some resource into finding drugs of their own. David had proposed that it should be possible to find a single molecule having both bronchodilator and anti-inflammatory activity based on inhibition of phosphodiesterases (PDE). However, to his annoyance he found his idea turned down by a number of companies. Not put off by a few 'no thank you' responses, he managed to secure a limited amount of funding from Vanguard and approached one of us (CP) to help with the biology and his ex Glaxo colleague, Dr Alec Oxford, to help with the chemistry. The trio set off to find what David described as 'his last good idea for a drug before he died'. This collaboration led to the preclinical discovery of a series of compounds having bronchodilator and anti-inflammatory activity in a single molecule [43]. One of these, RPL554, a topically active PDE3/4 inhibitor is now in clinical development and has been shown to be an excellent bronchodilator in patients with asthma or mild to moderate COPD and is currently being evaluated as an anti-inflammatory agent in man. David was delighted that

the funding had been found to take his final drug forward into the clinic. If his thinking is correct, this drug could be the first true new class of bronchodilator and anti-inflammatory agent for respiratory diseases since his discovery of β_2 -adrenoceptor agonists and inhaled glucocorticosteroids several decades earlier.

Regardless, David Jack's achievement in developing so many important new medicines was unprecedented. He will always be known for his extraordinary contribution to applied medical science and remembered by all who knew him as a man with great clarity of purpose who provided firm leadership that allowed others to flourish and collectively contribute to his mission of finding ever better medicines. David Jack's inspirational passion extended far beyond the company that he led into various industrial, professional and academic arenas. No more so was this felt among clinical pharmacologists of whom David used to say were 'the real drug discoverers' because one does not really know what one's drug does until it has been examined in people.

Competing Interests

CP and PPAH are both Directors of Verona Pharma plc who are developing RPL554.

REFERENCES

- 1 Cullum VA, Farmer JB, Jack D, Levy GP. Salbutamol: a new, selective beta-adrenoceptive receptor stimulant. *Br J Pharmacol* 1969; 35: 141–51.
- 2 Morrow Brown H. How Derby research revolutionised the treatment of asthma. *Allergy Update*. Spring 2012 Newsletter of the British Society of Allergy and Clinical Immunology. 8 (2012).
- 3 Phillipps GH. Structure-activity relationships of topically active steroids: the selection of fluticasone propionate. *Respir Med* 1990; 84: (Suppl A): 19–23.
- 4 Ball DI, Brittain RT, Coleman RA, Denyer LH, Jack D, Johnson M, Lunts LH, Nials AT, Sheldrick KE, Skidmore IF. Salmeterol, a novel, long-acting beta 2-adrenoceptor agonist: characterization of pharmacological activity in vitro and in vivo. *Br J Pharmacol* 1991; 104: 665–71.
- 5 Ullman A, Svedmyer N. Salmeterol, a new long acting inhaled beta-2 adrenoceptor agonist: comparison with salbutamol in adult asthmatic patients. *Thorax* 1988; 43: 674–8.
- 6 Page CP. One explanation of the asthma paradox: inhibition of natural anti-inflammatory mechanism by B₂ agonists. *Lancet* 1991; 337: 717–20.
- 7 Lemanske RF, Busse WW. The US Food and Drug Administration and long acting beta-2 agonists: the

- importance of striking the right balance between risks and benefits and therapy. *J Allergy Clin Immunol* 2010; 126: 449–52.
- 8 Chowdhury BA, Seymouu SM, Levenson MS. Assessing the safety of LABAs to inhaled corticosteroids for treating asthma. *New Engl J Med* 2011; 364: 2473–5.
- 9 Cazzola MC, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. *Pharmacol Rev* 2012; 64: 450–504.
- 10 Barnes PJ, Breckenridge A. Obituary: David Jack (1924–2011) who revolutionised the treatment of asthma. *Thorax* 2012; 67: 266–267.
- 11 Brittain RT, Levy GP. A review of the animal pharmacology of labetalol, a combined alpha- and beta-adrenoceptor-blocking drug. *Br J Pharmacol* 1976; 3: (4 Suppl. 3): 681–4.
- 12 Brittain RT, Drew GM, Levy GP. The alpha- and beta-adrenoceptor blocking potencies of labetalol and its individual stereoisomers in anaesthetized dogs and in isolated tissues. *Br J Pharmacol* 1982; 77: 105–14.
- 13 Bradshaw J, Brittain RT, Clitherow JW, Daly MJ, Jack D, Price BJ, Stables R. Ranitidine (AH 19065): a new potent, selective histamine H₂-receptor antagonist. *Br J Pharmacol* 1979; 66: 464P.
- 14 Daly MJ, Humphray JM, Stables R. Inhibition of gastric acid secretion in the dog by the H₂-receptor antagonists, ranitidine, cimetidine and metiamide. *Gut* 1980; 21: 408–12.
- 15 Woodings EP, Dixon GT, Harrison C, Carey P, Richards DA. Ranitidine – a new H₂-receptor antagonist. *Gut* 1980; 21: 187–91.
- 16 Bolger L, Brittain RT, Jack D, Jackson MR, Martin LE, Mills J, Poynter D, Tyers MB. Short-lasting, competitive neuromuscular blocking activity in a series of azobis-arylimidazo-(1,2-a)-pyridiniumdihalides. *Nature* 1972; 238: 354–5.
- 17 Brittain RT, Tyers MB. The pharmacology of AH8165: a rapid-acting, short-lasting, competitive neuromuscular blocking drug. *Br J Anaesth* 1973; 45: 837–43.
- 18 Coleman RA, Kennedy I. Contractile and relaxant actions of prostaglandins on guinea-pig isolated trachea. *Br J Pharmacol* 1980; 68: 533–9.
- 19 Coleman RA, Humphrey PP, Kennedy I, Levy GP, Lumley P. Comparison of the actions of U-46619, a prostaglandin H₂-analogue, with those of prostaglandin H₂ and thromboxane A₂ on some isolated smooth muscle preparations. *Br J Pharmacol* 1981; 73: 773–8.
- 20 Kennedy I, Coleman RA, Humphrey PP, Levy GP, Lumley P. Studies of the characterisation of prostanoid receptors: a proposed classification. *Prostaglandins* 1982; 24: 667–89.
- 21 Kennedy I, Coleman RA, Humphrey PP, Lumley P. Studies on the characterization of prostanoid receptors. *Adv Prostaglandin Thromboxane Leukot Res* 1983; 11: 327–32.
- 22 Coleman RA, Smith WL, Narumiya S. International Union of Pharmacology Classification of prostanoid receptors: properties, distribution and structure of the receptors and their subtypes. *Pharmacol Rev* 1994; 46: 205–29.
- 23 Lumley P, White BP, Humphrey PP. GR32191, a highly potent and specific thromboxane A₂ receptor blocking drug on platelets and vascular and airways smooth muscle *in vitro*. *Br J Pharmacol* 1989; 97: 783–94.
- 24 Humphrey PP, Hallet P, Hornby EJ, Wallis CJ, Collington EW, Lumley P. Pathophysiological actions of thromboxane A₂ and their pharmacological antagonism by thromboxane receptor blockade with GR32191. *Circulation* 1990; 81: 142–52. discussion 159–60.
- 25 Apperley E, Humphrey PP, Levy GP. Two types of excitatory receptor for 5-hydroxytryptamine in dog vasculature. *Br J Pharmacol* 1977; 61: 465P.
- 26 Fenink W, Humphrey PP, Levy GP. Further evidence for two types of excitatory receptor for 5-hydroxytryptamine in dog vasculature. *Br J Pharmacol* 1977; 61: 466P.
- 27 Humphrey PP, Feniuk W, Perren MJ, Connor HE, Oxford AW, Coates LH, Butina D. GR43175, a selective agonist for the 5-HT₁-like receptor in dog isolated saphenous vein. *Br J Pharmacol* 1988; 94: 1123–32.
- 28 Humphrey PP, Feniuk W, Perren MJ, Connor HE, Oxford AW. The pharmacology of the novel 5-HT₁-like receptor agonist, GR43175. *Cephalagia* 1989; 9: 23–33.
- 29 Humphrey PP. How it started. *Cephalagia* 2001; 21: 2–5.
- 30 Humphrey PP. Headache 2008; The discovery and development of the triptans, a major therapeutic breakthrough. 48: 685–7.
- 31 Bradley PB, Engel G, Feniuk W, Fozard JF, Humphrey PP, Middlemiss DN, Mylecharane EJ, Richardson BP, Saxena PR. Proposals for the classification and nomenclature of functional receptors for 5-hydroxytryptamine. *Neuropharmacology* 1986; 25: 563–76.
- 32 Humphrey PP, Hartig P, Hoyer D. A proposed new nomenclature for 5-HT receptors. *Trends Pharmacol Sci* 1993; 14: 233–6.
- 33 Hoyer D, Clarke DE, Fozard JR, Harting PR, Martin GR, Mylecharane EJ, Saxena PR, Humphrey PP. International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol Rev* 1994; 46: 157–203.
- 34 Martin GR, Humphrey PP. Receptors for 5-hydroxytryptamine: current perspectives on classification and nomenclature. *Neuropharmacology* 1994; 33: 261–73.
- 35 Barnes JM, Barnes NM, Costall B, Naylor RJ, Tyers MB. 5-HT₃ receptors mediate inhibition of acetylcholine release in cortical tissue. *Nature* 1989; 338: 762–3.
- 36 Costall B, Naylor RJ, Tyers MB. The psychopharmacology of 5-HT₃ receptors. *Pharmacol Ther* 1990; 47: 181–202.
- 37 Butler A, Hill JM, Ireland SJ, Jordan CC, Tyers MB. Pharmacological properties of GR38032F, a novel antagonist at 5-HT₃ receptors. *Br J Pharmacol* 1988; 94: 397–412.
- 38 Tyers MB, Bunce KT, Humphrey PP. Pharmacological and anti-emetic properties of ondansetron. *Eur J Cancer Clin Oncol* 1989; 1: S15–9.

- 39** Humphrey PP, Bountra C, Clayton N, Kozlowski K. Review article: the therapeutic potential of 5-HT₃ receptor antagonists in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 1999; 2: 31–8.
- 40** Jiang W, Kreis ME, Eastwood C, Kirkup AJ, Humphrey PP, Grundy D. 5-HT(3) and histamine H(1) receptors mediate afferent nerve sensitivity to intestinal anaphylaxis in rats. *Gastroenterology* 2000; 119: 1267–75.
- 41** Hicks GA, Coldwell JR, Schindler M, Ward PA, Jenkins D, Lynn PA, Humphrey PP, Blackshaw LA. Excitation of rat colonic afferent fibres by 5-HT(3) receptors. *J Physiol* 2002; 544: 861–9.
- 42** Nicandro JP, Shin P, Chuang E. Evaluation of treatment continuation with alosetron by IBS-D severity criteria. *Curr Med Res Opin* 2012; 28: 449–56.
- 43** Boswell-Smith V, Spina D, Oxford A, Comer MB, Seeds EAM, Page CP. The pharmacology of novel long acting phosphodiesterase inhibitors RPL554 and RPL565. *J Pharmacol Exp Ther* 2006; 318: 840–8.