Editors' view

1974–2014: Reflections on the evolution of clinical pharmacology in the past 40 years and a message to our readers

James M. Ritter^{1,2}

¹Department of Clinical Pharmacology, St Thomas's Hospital, London and ²Quintiles (London), Guy's Hospital, London, UK

"Who can find a virtuous Journal? . . . for its price is above rubies" (misquoted from Proverbs 31:10).

In youth, each birthday is eagerly anticipated. By 30 some of the enthusiasm at another milestone may have worn a bit thin – though the British Journal of Clinical Pharmacology (BJCP) was in buoyant spirits [1]. Staid 40-year-olds are still less likely to be dropping not-so-subtle hints to their loved ones of the impending anniversary. However, BJCP eschews all such modesty and takes this opportunity to reflect briefly on our subject while glancing into the mirror. The first number of the Journal back in 1974 contained (among others) research articles on pharmacodynamics (PD), pharmacokinetics (PK), drug metabolism, therapeutics and analytical methodology. Now, as then, we consider papers on all aspects of drug action in man. How has this approach stood up to the challenges posed by the profound changes in biomedicine that have ensued over the intervening 40 years? These changes include revolutions in intellectual approach and theory as much as dizzying practical advances that have occurred in some areas of therapeutics.

Evidence-based medicine

The seemingly bland assertion that health interventions should be validated against clinical endpoints [2] has changed medical practice profoundly and forever. Clinical trials (e.g. [3, 4]) in which drugs with seemingly well-understood pharmacology, and with demonstrable seemingly beneficial PD effects and credible scientific rationales [5], nonetheless worsened survival have chastened clinicians and shaken regulators. This has not, however, marginalized PD studies which have assumed an even greater importance in current translational experimental medicine.

Translational experimental medicine

The new emphasis on clinical endpoints has actually increased the need for PD studies focused on intermediate endpoints ('biomarkers'). Dose–response (and model-based) studies using such biomarkers remain the rubric of classical clinical pharmacology and are crucial for the proof of concept studies which add so much more value to early phase drug development than the rather pallid exploratory 'safety and tolerability' first in human studies that BJCP tends to reject on grounds of their limited priority and interest [6]. The ethics, methods and analysis of good early clinical pharmacology studies are quite specialized and distinct from those of basic pharmacology and BJCP editors and peer reviewers are steeped in the various aspects of work of this kind. Unsurprisingly, many of the original papers we enthusiastically publish, sometimes incorporating PK data and measures of *in vivo* receptor occupancy, fall into the PD proof of concept category.

Positive 'negative' studies

When well-planned and well-conducted early phase studies are scientifically valid but 'negative' (perhaps more correctly 'neutral', since a negative result implies a change in the wrong direction) in the sense that they disprove a seemingly attractive hypothesis, they may be both of considerable scientific interest (as they are telling us something important) and of commercial value in redirecting resources before committing to disproportionately expensive phase II or III trials. Negative findings in clinical pharmacology studies can be as important as positive ones to funding bodies and researchers, provided the study is

sufficiently powered to exclude a biologically meaningful difference between active and comparator. We therefore favour presenting the absolute mean difference together with its 95% confidence interval for important negative findings. BJCP champions publication of such work after proper peer review [7]. Recently (and not so recently [8]) a somewhat different reason for making 'negative' data available has been emphasized, namely the malign effect of publication bias on the evidence base available to authors of systematic reviews and meta-analyses. Editorial decisions can be a source of publication bias if editors favour manuscripts with positive, striking or significant results. Peer-reviewed journals are (in our view appropriately) unwilling to accept incomplete work. Investigators without support to respond adequately to the critique of the reviewers thus have a legitimate need for a suitably curated repository where such data can be publicly accessed. A new BPS publication ('Pharmacology Research and Perspectives' – PRP) set up in collaboration with the American Society for Pharmacology and Experimental Therapeutics (ASPET) will hopefully help to meet this need.

Potential of pharmacogenomics to refine individualized therapy

For some treatments, one size really does fit all (think childhood immunizations, and perhaps muse on the 'poly-pill' concept of later life vascular disease prevention [9]). Often, however, a tailored approach is needed – which drug class or classes to prescribe, which member(s) of each class and in what dose(s), are all *a priori* indeterminate in the individual. Therapeutics in such circumstances is approached empirically, for want of anything better, sometimes with disastrous consequences in terms of lack of efficacy or of drug-induced harms. Improving this is a holy grail of clinical pharmacologists long pre-dating the current focus on pharmacogenetics. Indeed the first number of the BJCP contains a paper, cited over 100 times and co-authored by Sylvia Dobbs who is now tirelessly investigating connections between infection and Parkinson's disease – on dose individualization of gentamicin by means of a creatinine-based nomogram [10]. This is a topic of massive and still current practical importance (how many lives saved? how many patients spared dialysis?). The subsequent emergence of pharmacogenomics adds a whole new dimension and has already led to practical applications, for example tests for polymorphisms in human leukocyte antigen (HLA) genes (adverse drug reaction susceptibility to *abacavir*, anticonvulsants *clozapine* and *dapsone*), in genes influencing drug metabolism – thiopurine-S-methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPYD) and CYP isoenzymes (CYP2D6 and CYP2C9/2C19) and for drug targets such as the epidermal growth factor receptor HER2, tyrosine kinase inhibitors and the main target for *warfarin*, vitamin K epoxide reductase complex, subunit 1 (VKORC1)

[11]. Psychologically more important than this scratch on the surface of current medical practice, we have glimpsed a simple chip-based technology that could routinely better predict individualized safety and efficacy. Unsurprisingly, pharmacogenomics and stratified medicine has also been an area that the Journal has promoted tirelessly and in which we have again benefitted hugely from world-class expertise in the membership of our editorial boards.

Macromolecular drugs

Monoclonal antibodies have provided us with superb tools for proof of concept studies in many cases in which a key target (often identified from the human genome project data) is physically accessible from the extracellular milieu (i.e. favourable PK). Their specificity and the availability of technology for bulk synthesis of antibody proteins of consistent quality (gifted to us all by Cesar Milstein), together with their benign secondary pharmacology in contrast to the toxicity of low molecular weight organic chemicals, have also transformed much of clinical practice. Unlike other proteins (which are typically rapidly degraded *in vivo*), immunoglobulins have evolved to survive for prolonged periods in extracellular fluid, so their PK is favourable for therapeutic applications. Immunological harm has been at least partly overcome by techniques to humanize therapeutic antibodies. Monoclonals have transformed rheumatology (anti-TNF drugs such as adalimumab, etanercept and infliximab [12]), and notched up real successes in oncology (trastuzumab for HER2-positive breast cancer and antiVEGF antibodies for age-related macular degeneration), rarities such as paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome (the anti-complement antibody, eculizumab), the severest end of dermatology (ustekinumab, which antagonizes IL-12 and IL-23, for severe plaque psoriasis), inflammatory bowel disease including Crohn's disease (adalimumab) and highly active relapsing-remitting multiple sclerosis (natalizumab, an anti-integrin which attenuates leukocyte migration into the CNS). Their limitations are mainly down to PK, including the need for parenteral administration and the inaccessibility of intracellular or trans-cellular targets, as well as residual problems of immunogenicity which, despite the advances in humanizing antibodies, are not trivial especially when it comes to biosimilar substitution at the end of patent protection and even to batch to batch variation. BJCP has senior editors expert in these fields [13] and does everything possible, within our remit, to promote them.

Antisense DNA offers the opportunity to influence *intracellular* targets with exquisite selectivity, provided the molecular entity can be protected from degradation in the extracellular fluid and can be safely delivered into the nuclei of the relevant cell type – a tall order! Nevertheless an antisense drug (mipomersen) has been developed and

licensed in the USA for homozygous familial hypercholesterolaemia [14] – exciting times, and more such molecules will surely follow.

Small interfering RNA (siRNA). An alternative approach is to target RNA signalling via siRNA, potentially an extraordinarily versatile and selective method of silencing gene output with a small(ish) (approximately 19 base) RNA drug capable of intracellular drug delivery, more than one of which has achieved proof-of-concept in translational studies [15, 16].

The future

Predictions are always a bit wobbly, but in the spirit of birthday bonhomie we shall not baulk our fancy. This is for a continued mixed economy of small molecule drugs plus macromolecular biologicals (sometimes separately, sometimes in combination, as in the case of ado-trastuzumab-emtansine, which is an antibody drug conjugate (ADC) of trastuzumab with T-DM1 (a microtubule inhibitor) which most closely resembles the concept of the 'magic bullet' and is approved in the US for the treatment of metastatic HER2 +ve breast cancer [17]). In the longer run the disadvantages of proteinaceous drugs that need to be injected and carry subtle but profound risks of immunogenicity will favour a second wave of low (or, in the case of siRNA, intermediate) molecular weight drugs that combine with validated targets. Validation will often have been achieved by studies with humanized monoclonal antibodies, especially where the targets are on the surface membrane of immune cells or on extracellular proteins. Intracellular targets will more likely be identified by manipulation of gene transcription or transduction in experimental animals.

The message

So what is our blushing ruby 40th birthday message to you, our much appreciated family of readers, authors and potential authors? One of unashamed mutual self-interest: the tiresome types who monitor your performance are wising up. They no longer care so much about a trophy publication in a first tier high impact factor journal, but rather care more about *your* individual impact as a researcher, something they may try to get at via metrics such as your h-index. This is much more dependent on your total citations and highly cited papers (over time, not a short window and indeed the longer the half-life the better) than on the citations garnered by papers by other authors in your journal of choice within a short and arbitrary time window. Of course you will submit your most stunning findings to the *New England Journal* (don't we all!) but when you have other great work that fits the BJCP remit and our editorial expertise, do point it at us – and

bear in mind that the most highly cited paper of the 20th century was published in a journal of modest impact factor (the *Journal of Poultry Science*. The paper was by Rous on the sarcoma virus, proving a viral origin of some malignancies). We do not promise to publish it, but we do promise you that it will be assessed swiftly and professionally and if we deem it to be a potential flier it will be peer reviewed by investigators who are truly your peers, and could have had a shot at doing what you aspired to if they had had the idea first. From personal experience, your h-index will benefit, and so will the BJCP impact factor – currently 3.6 for 2012 (the latest available), up from 2.9 in 2011. Good luck!

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