Commentary

Pharmacology 2.0

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Introduction

Pharmacology occupies an unusual position within the life sciences. Unlike physiology, biochemistry or anatomy, for example, it would not have a function at all if we did not take medicines or drugs. Of course, clinical practice today without such resources is inconceivable. Drugs constitute one of the principal ways of combating and mitigating disease; according to the ABPI (2011), over a thousand million prescriptions are written each year in the UK, averaging some 20 per head of the population [1].

Biological organisms are intricate chemical machines. As the cosmologist Martin Rees has noted [2], we know more about what goes on in the centre of a star than we do in the brain of an insect. In attempting to fathom the complexity of the cell or the physiology of a multicellular organism, we are faced with huge challenges, but we are even more at a disadvantage when it comes to understanding drug action. One reason why pharmacology is so fascinating is because each drug interacts with living systems in a unique manner.

A good example of this is aspirin, which irreversibly inhibits the cyclo-oxygenase enzyme, reducing the synthesis of prostaglandins and diminishing fever, pain and inflammation. It would be tempting to conclude that its principal metabolite, salicylic acid, which has a substantially similar pharmacology, acts in the same way, but in fact it employs a distinct molecular mechanism. There is also the 'law of unintended pharmacological effects'; sildenafil, for example, was designed to improve the action of the failing heart and was observed, almost inadvertently, to be an excellent treatment for erectile dysfunction.

Pharmacology 1.0

Before reflecting on the status of pharmacology today, it is worth recalling how the science originally arose. Most ancient cultures had some knowledge of the medicinal effects of plants based upon empirical observations. Leake

[3] calls this period 'proto-pharmacology'. Collections of these traditional remedies, compiled into 'herbals' or pharmacopoeias, constituted the primary source of therapeutic information well into the late 19th century. The rise of pharmacological science may be traced to this era and to the contributions of researchers such as Buchheim, Schmeideberg, Fraser and others [4].

One of the key figures in the development of pharmacology in the UK was John Gaddum. He played a vital part in establishing the science, which he described as 'a mingling of *materia medica* with physiology', as a separate entity with its own viewpoint and agenda.

In the 1950s, Gaddum delivered an address to the American Society for Pharmacology and Experimental Therapeutics that was later published in *Nature* under the title of 'The Science of Pharmacology' [5]. It was a manifesto for the emergent discipline of what I term 'Pharmacology 1.0'. Amongst Gaddum's top priorities were finding out how drugs work and removing remedies of dubious provenance and efficacy from the bloated pharmacopoeias of the time. Other tasks included the study of drug toxicity and pharmacokinetics, collaboration with clinicians to design clinical trials, the teaching of pharmacology to medical students and, of course, the discovery of new drugs.

Virtually all the (few really effective) drugs in use in Gaddum's time were small (<1.0 kDa), non-immunogenic molecules that were metabolized in the body as xenobiotics, often utilizing cytochrome P450-dependent mechanisms. The pioneering work of Clarke, Ehrlich, Langley and others had established a mathematical analysis of the dose-response curve and the principles of agonism and antagonism. There was a general view that drugs acted at 'receptors', but pharmacologists were almost completely ignorant of their nature or molecular mechanism. But despite this, the receptor notion was to provide a conceptual toolkit that had spawned many outstanding pharmaceutical innovations. One thinks, for example, of the development of β -blockers and of selective H_2 antagonists by James Black.

Pharmacology 2.0

In the closing decades of the last century and especially since the millennium year, a profound change occurred within the discipline as Pharmacology 1.0 gradually gave way to what I term 'Pharmacology 2.0'. During this period, pharmacologists made huge progress with some of Gaddum's tasks, such as drug discovery and elucidating mechanisms of action. Aspirin and morphine, for example, yielded up many, if not all, of their secrets. But as the choice of laureates for the 1998 Nobel Prize for Physiology or Medicine shows, there is still much to learn about even such apparently simple drugs as the nitrates. However, there have also been major changes in the intellectual landscape.

New drugs

Firstly, we have seen the introduction of entirely new classes of drugs. One example is the introduction into clinical practice of increasing numbers of 'biologics'. In contrast to 'traditional' drugs, biologics are generally large molecules of 20–50 kDa. They are often antibodies, chimeric proteins or proteins that have been modified by attachment to other prosthetic groupings, such as polyethylene glycol. Biologics are not synthesized by medicinal chemists but by bacteria or other cells *in vitro*. Most are therefore not homogeneous chemical substances but proteinaceous mixtures. They may be immunogenic and, because of the way that they are made, purification and removal of substances such as endotoxin is crucial.

Biologics may have multiple or even unknown modes of action and, partly because of their complex drug–receptor or drug–ligand interactions, many have nonlinear dose–response curves. In the case of many monoclonal antibodies, there is a single optimal biological dose instead of the proportional effects that we are more accustomed to when dealing with small molecule drugs of 'classical' pharmacology. Their pharmacokinetics are different too [6]. The half-life is often long (days as opposed to hours), and we can no longer rely on the concepts such as 'phase 1' and 'phase 2' metabolism to predict how they will be eliminated.

Other macromolecules are also being trialled as drugs. There is a burgeoning interest in the therapeutic potential of small interfering RNA and micro-RNA. Recently, gene delivery has been used successfully in several cases. This raises questions about the nature of drugs as pharmacologists are used to thinking of them. Are genes drugs? And what about other macromolecules? Is a vaccine a drug, for example? According to conventional definitions, it would be difficult to argue that it was not, even if it shares virtually no characteristics with small molecule drugs, either in the way it is produced or in the way that it acts or is eliminated. There are, however, many who believe that vaccines can be used instead of conventional pharmaceuticals for many

indications, including the treatment of smoking and other addictions as well as provision of long-lasting contraceptive protection [7].

New receptors

Originally, the term 'receptor' was applied generically to all drug targets because there was no clear sense of how binding gave rise to a biological effect. Some of these targets subsequently turned out to be enzymes or other molecules, and the term was generally reserved for molecules that acted as biological signal transducers. However, these concepts have been constantly challenged. What are we to make, for example, of protease-activated receptors, which seem to have their ligands already attached? Or of 'decoy receptors' that lack signalling properties altogether? 'Inverse agonists' exert paradoxical effects on cells and other drugs can behave as antagonists or agonists depending on how they are administered. Embarrassingly, even the fundamental pharmacological notion of drug efficacy at receptors has proved difficult to explain mechanistically.

Even stranger was the finding, reported by Jones *et al.* in 2005 [8], that interleukin-6 can signal by binding simultaneously to a soluble receptor and a coreceptor, GP-130. Such exotic interactions between ligands and their receptors are obviously of great biological importance, although we have not yet been able to exploit these subtle interactions. This will be one of the tasks facing future pharmacologists.

Safety

The advent of new types of pharmaceuticals also has important implications for safety pharmacology. Ever since Ehrlich coined the phrase, the concept of the 'magic bullet' has been a sort of Holy Grail for pharmacologists. Some new biologics are approaching this type of selectivity, but sometimes with frightening consequences.

On 15 March 2006 we awoke to news of a clinical trial tragedy. *The Sun* newspaper, with characteristic journalistic restraint, ran the headline 'We saw human guinea pigs explode' [9]. The reference was, of course to the phase I trial of TGN-1412, a humanized anti-CD28 monoclonal antibody being tested as a potential treatment for a variety of diseases, including leukaemia, arthritis and multiple sclerosis. Within hours of receiving the active drug, all six subjects experienced a severe 'cytokine storm', which left several with lasting tissue damage.

The final results of the MHRA's investigation were released the following May. Whilst the tragedy was attributed to an unpredictable biological reaction, the report made 22 recommendations for improving the conduct of such trials and caused many to think very hard about how the safety of these types of drugs could be assessed in the future [10]. Conventionally, safety testing is conducted in rodents, other species and sometimes nonhuman primates, but clearly this strategy depends

upon the fact that drug candidates are less than completely specific for their intended human target. In the case of biological reagents such as the monoclonal antibodies, however, we are confronted, for the first time, with the possibility of a drug candidate so specific for its human target that it does not significantly cross-react with the homologous target in other animals. How then is it to be tested?

This is a good example of the type of challenge posed to future generations of pharmacologists by the advent of such exquisitely specific drugs.

New tasks for pharmacologists

'Alternative' medicines

There are several outstanding tasks that pharmacologists today must address, or at least tackle with fresh enthusiasm.

In Gaddum's day, one of the main tasks of the pharmacologist was the removal of ineffective medicines from the pharmacopoeias. In fact, Gaddum once joked that *materia medica* was the only discipline that grew smaller as it advanced [11]. The modern-day pharmacologist has his or her own challenges in this respect.

We have, for example, the issue of homeopathic drugs. It is generally held that these medicines are at worst harmless and that they have no adverse effects, but there are occasions when a choice of a homeopathic remedy can jeopardize health. In January 2011, the General Pharmaceutical Council severely censured pharmacies that had advised people to take homeopathic remedies claiming to provide malaria prophylaxis, rather than conventional anti-malarial drugs. The Government's chief scientist, John Beddington, called the underpinning of homeopathy 'scientific nonsense', and even the head of the Royal London Homeopathic Hospital, Peter Fischer, told the BBC that there was no reason to think homeopathy works to prevent malaria [12].

In a similar vein, no less a high-street institution than *Boots* was investigated by the Advertising Standards Authority in 2011 for promoting dozens of vitamin supplements, homeopathic and other products for which there was no supporting evidence of efficacy [13]. Other 'alternative medicines' are dangerous for different reasons. Some imported ayurvedic medicines are contaminated with heavy metals [14]. Chinese herbal medicines for skin disorders, available over the counter, have been found spiked with mercury or steroids or, in the case of the *Shubao* slimming capsules reported in *The Times* a few years ago, a cocktail of amphetamines, antipsychotics and sibutramine. It is no wonder that some consumers suffered from irreversible liver failure [15].

Another difficult area can be 'nutraceuticals', i.e. food-stuffs with claimed medicinal properties. Such substances can be sold as foods or food additives and, as such, are not

regulated in the same way as medicines. In fact, regulatory authorities cannot hope to test all the many different 'traditional' and other substances with claimed medicinal properties that make their way into our retail stores, posing the question of how this should be managed. As pharmacologists, it is up to us to provide input and insight into these problems.

Public engagement

Medicines are a bit like sausages. The general public consume them eagerly but do not care to know the details of how they are made. Clarifying how the pharmaceutical industry works and the necessity for animal experimentation and explaining why the costs of drug discovery are so high and the lead time so long are obviously important, but it does not end there.

When, some 150 years ago, Charles Darwin published his book *On The Origin of Species*, the first edition was sold out almost overnight. It has often been remarked that this was probably the last time when a piece of original science was so enthusiastically endorsed by the general public. Today the communication of science is much more difficult. Our fields of research have become so specialized that sometimes we cannot completely comprehend even what our colleagues are doing. This makes it even more important that we should be prepared to explain the nature of our research to the general public. Nevertheless, there are problems. For example, the Eurobarometer Poll of 1999 reported that 35% of the public thought that normal tomatoes did not contain genes unless genetic engineers put them there, and only 42% knew that eating such fruit would not influence one's own genes [16].

It is the responsibility of all practising scientists to rectify this type of ignorance through our writings and public lectures.

Pharmacological education

The decline in the amount of practical science teaching in our schools and universities is a major concern. Robert Winston, in a recent interview in the *Sunday Times* [17], commented that he had been asked to give a biology lesson to 20 secondary school teachers only to find that none of them had ever dissected a rat. In many schools and institutions, experimental work is being abandoned and instead, students are being instructed in what Peter Atkins calls 'science's sociological shadow, the scientific method' [18].

Nothing can replace the experience of actually performing a scientific experiment oneself. It is important not only for heuristic reasons, but also for the thrill that it produces when you find something new and the skills that you acquire during its execution. We must fight to maintain this important training.

Pharmacology in the UK

In the UK, we have a very strong pharmacological tradition that is reflected in the enormous contribution that the British pharmaceutical industry has made to both health and wealth.

According to the ABPI's latest (2011) figures, the UK pharmaceutical industry produced about 20% of the top 100 medicines in use around the world today and was responsible for net exports of £7 billion in 2009. It is also the industry which invests by far the most in research and development – some £4.4 billion last year – and it employs some 72 000 people, about a third of whom are highly trained scientists and doctors [19].

Since its inception as a separate discipline, pharmacology has always had a strongly interdisciplinary flavour. Gaddum himself described pharmacologists as a 'jack of all trades' [11]. Many institutions have sought to encourage interdisciplinary research by abolishing the traditional departmental structures, but Gaddum's idea of organized 'team' science was a bit different. His concept of collaboration was that of a synergistic interaction between specialists, and I suspect he might have argued that this could not be achieved simply by changing the names on laboratory doors, but rather by building upon the unique contributions that each separate discipline can make to the business of drug discovery and to an understanding of drug action.

The future

Our planet faces many challenges, including overheating, shortage of food, overpopulation and overcrowding [20]. Pharmacologists can help solve some of these problems.

The global population is increasing at a rate of 75 million per year and is set to hit 9 billion by 2050. The planet cannot sustain this number of people using existing agricultural techniques. Food 'inflation' is already with us, and grocery bills have skyrocketed in the UK although, as always, the poorest countries feel the effect even more acutely.

More food will be required; this means more staples, such as rice and wheat, but also more meat and dairy products. One way to increase the supply of these is by reducing wastage, and that means preventing illness in cattle and food animals. According to Defra [21], for example, almost 35 000 cattle were slaughtered in 2010 because of bovine tuberculosis alone here in the UK. Even this substantial economic loss pales into insignificance when compared with the £9 billion loss of livestock caused by the foot and mouth epidemic in 2001. It is unfortunately the case that too many veterinary medicines are simply second-hand human medicines and are not always ideal for the purpose.

The whole area of veterinary pharmacology needs to be adequately resourced and reinvigorated if we are to get on top of this situation.

Overpopulation of the planet is also a problem. Globally, the mean human birth rate is falling to subreplacement levels, but we have to deal with a huge increase in the ageing population. According to figures from the United Nations, the median age of the population in the most developed countries rose from 29 years in 1950 to 37.3 years in 2000 and is estimated to rise to 45.5 years by 2050.

This ageing population does not pose problems only for the pension industry, but also for healthcare providers and pharmacologists. Medicines that are very effective in younger people are not always suitable for the elderly. Such patients are more susceptible to anticholinergics and some analgesic drugs, for example. The chance of an adverse drug reaction increases with age, and so does reduced renal and hepatic function, with obvious consequences for altered drug elimination.

All these examples should make us sensible of the fact that there is enormous scope for research for the pharmacological community.

Conclusion

In this article, I have tried to highlight some of the ways in which pharmacology has changed since the 1940s and 1950s, to indicate ways in which Pharmacology 2.0 might develop and some of the new areas in which pharmacologists might become profitably involved. It is, of course, a personal view, but it has been informed by contacts with many friends and colleagues throughout the biosciences whom I have been lucky enough to know throughout my career.

Competing Interests

The author has completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the author) and declares that he has received no support from any organization for the submitted work and that there are no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. There are also no other relationships or activities that could appear to have influenced the submitted work.

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