THE CHANGING PROFILE OF EXPERIMENTAL PHARMACOLOGY. ARE WE DEVELOPING THE RIGHT PROFICIENCIES FOR FUTURE PHARMACOLOGISTS?

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Abstract

This paper reviews the research themes and techniques that were published in the British Journal of Pharmacology from 1979 to 2009. From its earliest beginnings pharmacology has relied on empirical data collected through experimentation. This review illustrates the changes during the last 30 years that has taken place in the methods employed in pharmacological research and how this impacts on current teaching practice. The review examined papers published in the September edition of the British Journal of Pharmacology from 1979 to 2009. For the ease of data collection a review took place for every fifth year to determine the various type of pharmacological research, as well as the experimental design used. Furthermore, to establish current student perceptions, students from an undergraduate pharmacology course were surveyed to determine their attitudes towards experimental classes with respect to learning pharmacology and the development of their laboratory skills.

Isolated tissue/organ bath methods and associated data analysis are the mainstay of pharmacological studies published in the British Journal of Pharmacology over the past 30 years. More recently there has been a significant rise in the use of techniques in molecular biology and protein chemistry. Surveyed pharmacology students in undergraduate medical science degree programs indicated that they found practical classes effective in helping them understand key concepts in each of the subject areas and also in the development of their laboratory skills. The basic concepts of measuring drug action and potency have not changed over time; however some of the techniques to achieve these outcomes continue to evolve. The teaching of experimental pharmacological techniques should be dependent on the need to develop student understanding as well as keeping up to date in the technological changes that are occurring in society.

Keywords: pharmacology, laboratory, education, learning.

1 INTRODUCTION

Pharmacology is the study of drugs and their actions on target sites in biological systems [1]. In Australia, pharmacology is taught to undergraduate students in the medical sciences or in clinical programs such as medicine, pharmacy, nursing, dentistry and veterinary science.

Teaching within the discipline of pharmacology commonly relies on experiments conducted on biological cells or tissues primarily derived from laboratory animals, although limited experiments are done on human subjects (for example the collection of blood products to enable the used of platelets and peripheral mononuclear cells).

Experimental pharmacology uses animals in several ways; to detect acute, subacute and chronic toxicity, carcinogenicity or teratogenicity of new compounds [2] or to identify receptor targets and their signalling pathways. Current trends in teaching and learning are for the reduction in use of laboratory animals and as such there are even greater pressures on Universities to redesign courses [3]. Research in pharmacology usually requires excised isolated organs or tissues that are surgically prepared to allow for the study of drugs and their interactions with targets within tissues (e.g. smooth muscle preparations such as isolated uterus and ileum or skeletal muscle preparations such phrenic nerve diaphragm and frog rectus abdominus muscle), see Kitchen, [4]. Mammals are the most frequently used animals: mice are often chosen because of their size, ease of breeding and short life span [2] however rats, guinea-pigs, rabbits and dogs are used depending on the tissue type and drug target systems that are located in these tissues. The aim of most pharmacological investigations is to

determine how drugs work in biological systems (e.g. binding receptors, ion channels, carrier systems or enzymes). The analysis of drug action is to transform molecular and cellular discoveries into clinical practice [5]. Isolated organ bath experiments provide evidence for the determination of drug potency in biological tissues which can be directly translated to human studies [6].

The teaching of practical skills in pharmacology involves a range of possible activities including in-vitro, in-vivo, and computer assisted simulations such as Ileum® [7]. Concerns raised as to the use of simulation software in the teaching of laboratory classes is that they do not develop the physical skills or implicit understanding for working experiments in the laboratory even though they may improve student understanding of the fundamental concepts underpinning pharmacological theory. Computer/web-based simulations are reported to complement the practical training of undergraduates [8], but the pivotal question relates to what are the learning objectives of the laboratory class. Hughes [7] wrote that it is not just the development of laboratory skills but what is learnt with regard to scientific protocol, the application of theory and communication proficiencies. Therefore we ask as to the importance of skills learnt in laboratory classes? Skills that students are expected to learn in pharmacology practical classes are as follows; To understand the ethical implications of using animals for research purposes. To attain and implement theoretical knowledge with respect to the biological systems being investigated. To develop practical laboratory skills such as the use of isolated organ bath equipment, including the associated drug calculations, the operation of data acquiring systems, the use of pipettes and performing serial drug dilutions. To acquire problem solving skills and an appreciation of experimental design. To manage data with the appropriate analytical applications, to develop verbal and written communication skills and to be able to work in groups.

The educator needs to implement activities with an explicit expectation as to what the benefits of practical classes or simulation protocols will provide a student.

In the School of Medical Sciences at Griffith University, pharmacology students are enrolled in Biomedical, Health and Medical Science programs. Given the very limited options in Australia for students to enter into the pharmaceutical industry, students completing their undergraduate degrees enter the workforce, enrol into research programs or enrol in professional programs such as medicine, pharmacy or nursing. Over time, as the numbers of students entering tertiary education are forecasted to rise [9] there will be increased pressure to provide additional staff and facilities to ensure a comprehensive range of laboratory classes are made available to students, with consideration that the curriculum will need to develop in order to cover both old and new technologies in practical classes [10]. The introduction of molecular biology techniques have already been implemented with a loss of more-specialist practical teaching such as whole animal pharmacology and physiology [10].

The purpose of this study was to (a) review techniques used in the study of pharmacology during the last 30 years with the aim of observing changes in practical methods used to study drugs and predicting the directions in the education of pharmacology students and (b) Seek student feedback as to determine the relevance of practical classes to student learning, hence a survey of undergraduate biomedical science students was undertaken to ascertain whether practical classes aided in expanding their understanding of pharmacology and their laboratory skills.

2 METHODS

2.1 Review of the pharmacology approach

To investigate changes in pharmacological methods over the past 30 years the periodical British Journal of Pharmacology was evaluated. The British Journal of Pharmacology is the highest ranked general pharmacology research journal, currently ranked 19th in the ISI Pharmacology and Pharmacy category. It is a broad-based journal presenting leading international coverage of all aspects of experimental pharmacology. It is a journal of the British Pharmacology Society which covers the whole spectrum of pharmacology, including laboratory, clinical, and toxicological aspects and the support of members in academia, industry and the health services. Published papers in the journal in the month of September from 1979 every 5 years until 2009 were assessed.

Papers were reviewed with respect to four major areas;

1. Categories of pharmacological research,
2. Types of techniques used for research,
3. Sources of tissues for experimentation, and
4. Statistical analysis.

Pharmacological research was subdivided in to the following categories:

1. Drug action, that is the effect of a drug in a biological system
2. Receptor pharmacology - the mechanism of drug action via specific receptors
3. Second messenger signalling studies,
4. Pharmacokinetics, the process by which a drug is absorbed, distributed, metabolized, and eliminated by the body.
5. Other which includes behavioural pharmacology, immunology and physiology.

Techniques used in pharmacological research were separated into groups below:

1. Isolated tissues or primary cell culture,
2. Receptor binding techniques using tissue homogenates
3. In vivo studies for integrated pharmacology,
4. Biological assays which could include high pressure liquid chromatography, enzyme linked immunoassays, radioimmunoassay etc
5. Electrophysiology which incorporated patch clamp techniques in the study of ion channels,
6. Cell culture and cloning,
7. Molecular biology techniques such as transfection techniques and polymerase chain reaction
8. Protein biology and Western blot methods.

Multiple methods and statistical tests were commonly used within each published study. Statistical tests were identified as generic tests such as Student's t-test and analysis of variance (ANOVA) whereas the pharmacology specific data analysis was categorised according to whether it involved drug quantification with nonlinear regression curves with the derived agonist and antagonist potency and efficacy outcomes or receptor quantification (which can also provide drug potency) and receptor numbers via the Scatchard plots.

2.2 Survey of 3rd year undergraduate pharmacology students

Students surveyed were completing a pharmacology course (Pharmacology 3002MSC) from Health, Biomedical and Medical Science programs within the School of Medical Sciences at Griffith University at the end of 2009. Students were typical of most undergraduates being of an average age of 20-22 years. Students in the above mentioned course participated in three practical classes which were; (i) The determination of the effect of muscarinic agonists and antagonists and quantification of drug action in the Guinea-pig isolated ileum; (ii) Examining the effect of antagonists of acetylcholinesterases in plasma using Michaelis-Menton enzyme kinetics and (iii) Measuring the effect of alkaline or acidic urine on urinary aspirin excretion in humans.

The objectives of the laboratory course were for students to understand the general principles of how drugs act in biological systems and be able to investigate methods by which drug action is measured. At the end of each semester, course evaluation surveys were obtained. A 7 point Likert scale was implemented as follows. 1 = unacceptable; 2 = Very Poor; 3 = Poor; 4 = Average; 5 = Good; 6 = Very Good; E = Excellent.

3 RESULTS

3.1 Review of published pharmacology journal papers over 30 years

The number of articles printed in the British Journal of Pharmacology during the month of September over the years 1979 to 2009 rose by some 300% over the 30 years from 20 in 1979 to 61 in 2009 with the numbers of reviews rising steeply over the past 10 years to 30% of articles in the September, 2009 issue.

Fig 1 illustrates the various types of pharmacological research reported over the period of review. Drug action, where the effect of a drug in a biological system is studied comprises the bulk of the literature. Research reports featuring drug receptors (outcomes of stimulation of drug receptors) also had a considerable representation in the published reports since 1984. The pharmacological evaluation of signalling pathways in cells and tissues became more prevalent from 1999 to 2004. Most issues contained small numbers of papers focussing on pharmacokinetics and ion channel

pharmacology. An examination of research techniques utilised in the surveyed literature published in the British Journal of Pharmacology as previously described, has shown that most work reported featured isolated organ bath, isolated tissues or cells as the basis of the study (see Fig 2). Receptor binding techniques that allow the measurement of receptor numbers in tissues and potency of drugs and in-vivo studies comprised a small proportion of studies in each issue. The use of assays to measure tissue or cell products have risen steeply since the year 1994 and may reflect the large number of commercial kits currently available to measure signalling biomolecules.

During the last decade there has been a rise in reported techniques in molecular biology and protein measurement where Western blot analysis now provides a viable semi-quantitative estimation of drug targets in cells and tissues.

Sources of tissues for pharmacological studies reported in the journal are shown in Fig 3. Rats are the species that provide the bulk of tissues used for experimentation in the published articles. Small numbers of human studies have been published over the past 30 years, whereas the use of Guinea-pig and rabbit derived tissues appear to be in decline over the past ten years. During the last 15 years there has been a rise in mice as the source of tissues probably due to the development of the genetically modified mouse. Subsequently, the utilisation of isolated cells has risen since 1994 with the application of cells in signalling assays and the employment of molecular biology techniques that permit the cloning of drug targets.

With regards to analysis of data, almost 100% papers over the past 30 years contained data that was expressed as mean and SEM, see Fig 4. The Student's t-test and ANOVA were also highly represented in publications. Pharmacology specific analysis of data was primarily completed for drug quantification where nonlinear regression of concentration-response curves allowed for measurement of drug potency (eg. EC_{50}, pD_2) and efficacy (α) for agonists and (eg. K_B, Schild plots) for antagonists.

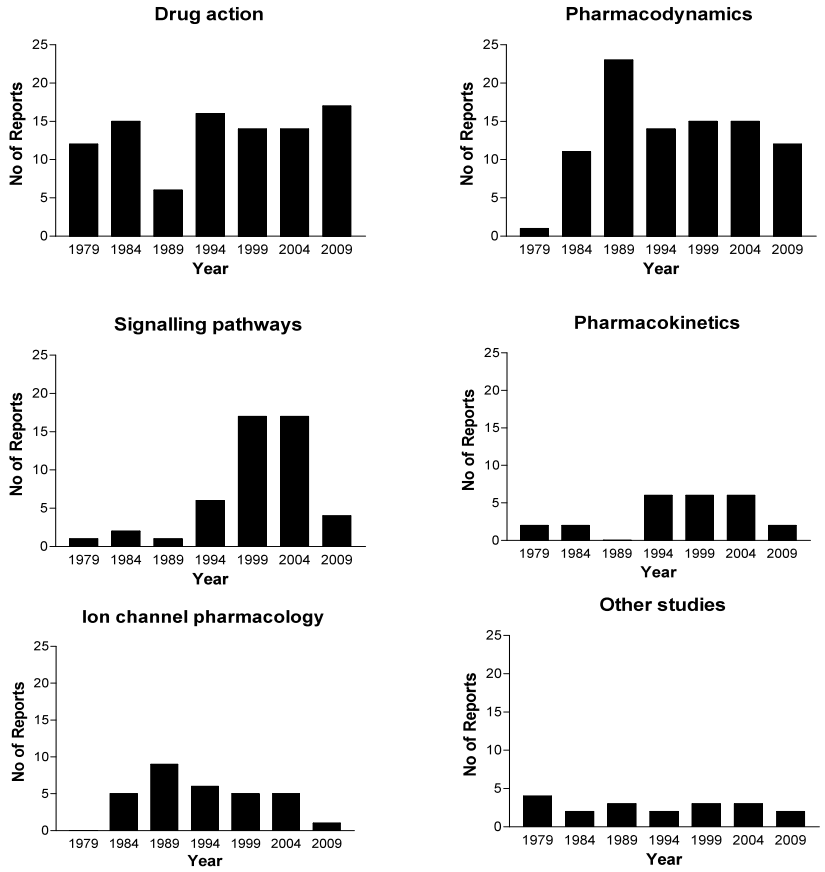

Fig 1. Types of research reported in the British Journal of Pharmacology during the month of September 1979 to 2009.

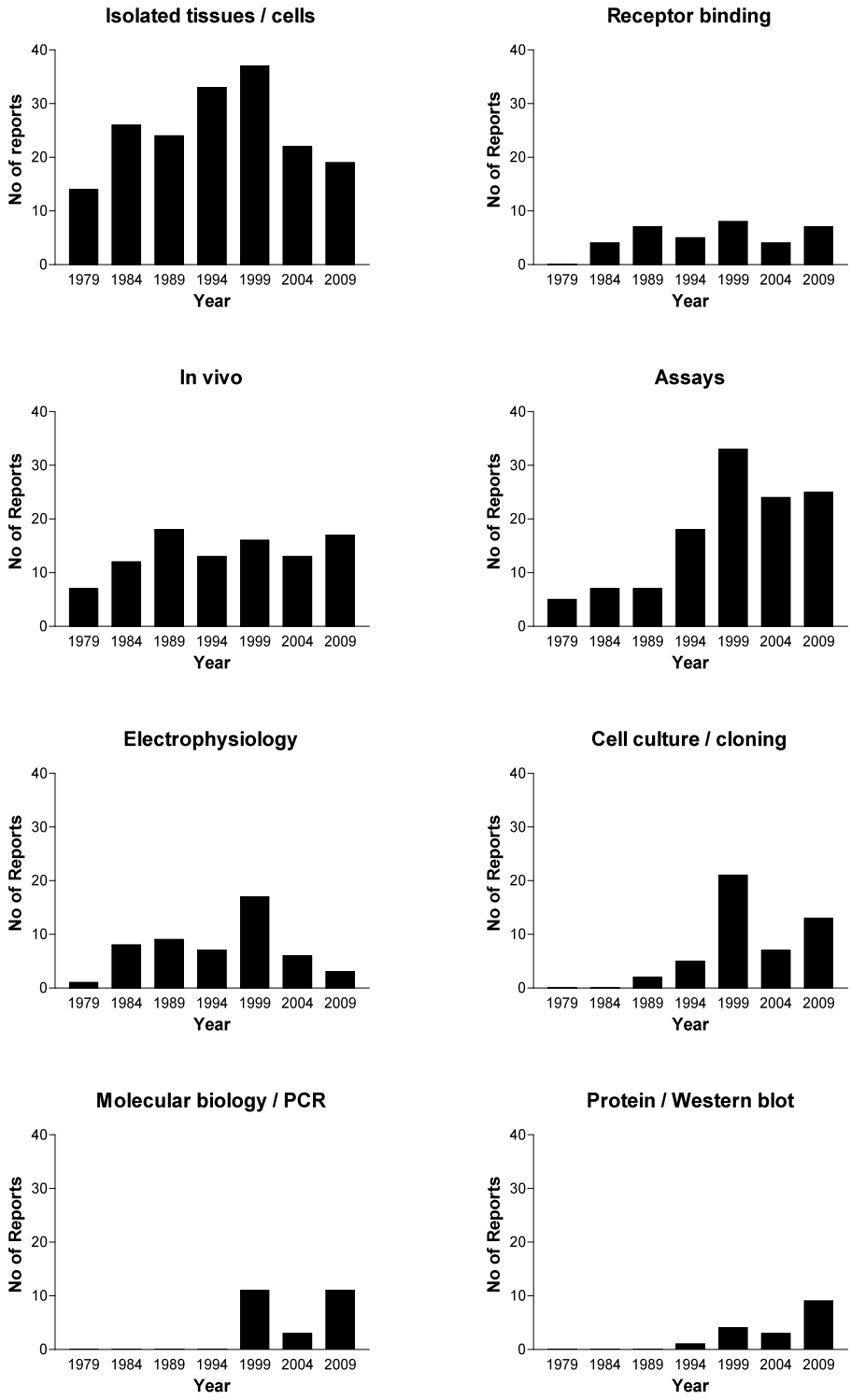

Fig 2. Types of research activities reported in the British Journal of Pharmacology during the month of September 1979 to 2009.

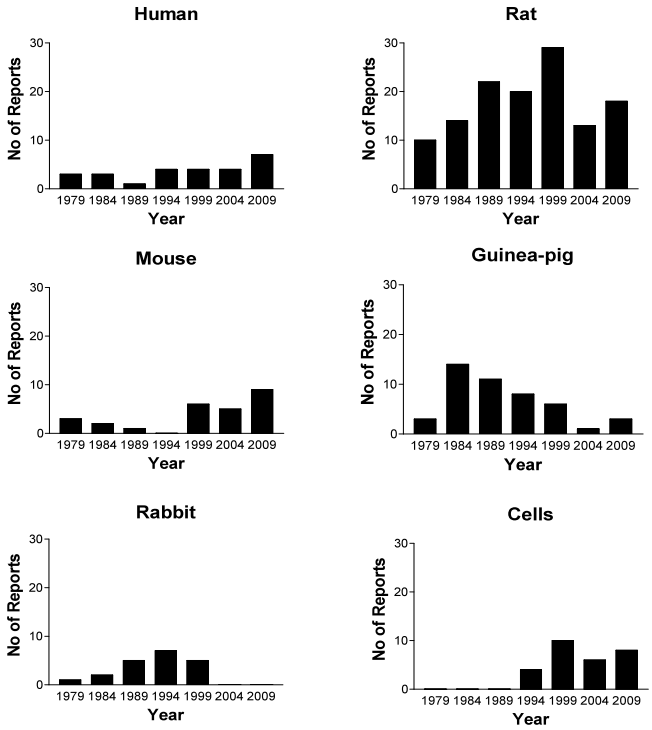

Fig 3. Sources of tissues used in studies reported in the British Journal of Pharmacology during the month of September 1979 to 2009.

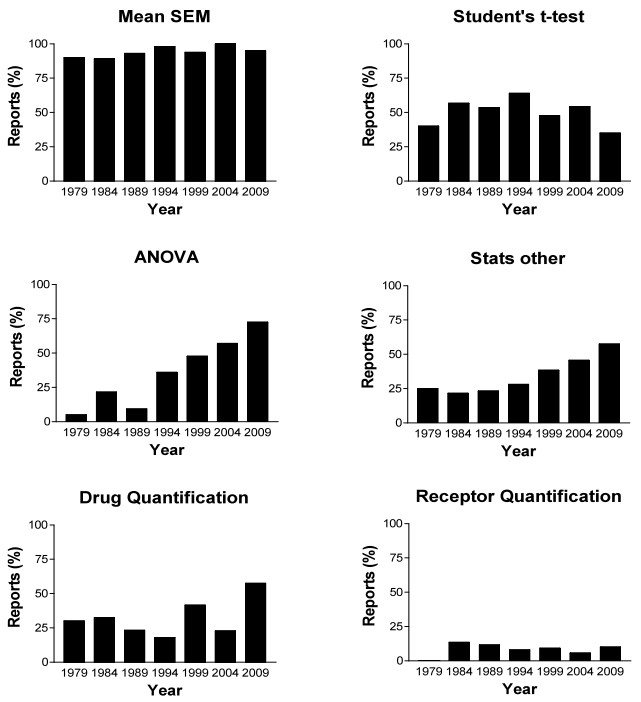

Fig 4. Statistics used in analysis of studies reported in the British Journal of Pharmacology during the month of September 1979 to 2009.

3.2 Survey of pharmacology students

Forty five students responded to the survey as to their attitudes towards practical classes taught during semester (see Fig 5). Students reported that the practical classes maintained their interest and enhanced learning and understanding of pharmacological concepts. They also indicated that the laboratory classes improved their practical skills (understanding the ethical implications of using animals for research purposes, implementing theoretical knowledge, developing practical laboratory skills, using data acquisition systems, acquiring problem solving skills, understanding experimental design, managing data using appropriate analytical applications and communication skills).

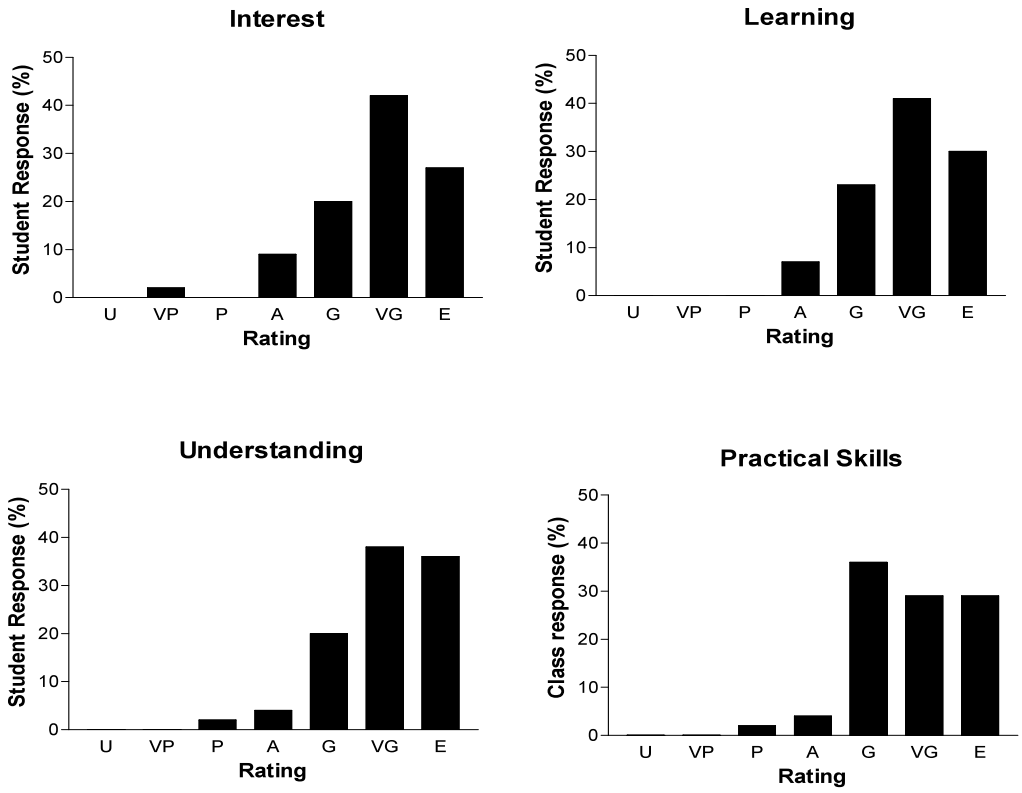

Fig 5. Student evaluation of laboratory classes in the third year School of Medical Science pharmacology course.
Interest: How effective were the laboratory classes in maintaining your interest?
Learning: How effective were the laboratory classes in helping you learn?
Understanding: How effective were the laboratory classes in helping you understand pharmacological principles
Practical Skills: How effective were the laboratory classes in providing you with practical skills.
Ratings: U; Unacceptable, VP; very poor, P; Poor, A; Average, G; Good, VG; Very good, E; Excellent. N= 45 students which represented 55.56% of the total cohort

4 DISCUSSION

This project had a twofold purpose. Firstly review the changes in the teaching of pharmacological techniques for undergraduate students based on experimentation reported in the literature for the development of laboratory skills and secondly to determine the usefulness of these classes in teaching underlying concepts in pharmacology and skills in researching drug action. As the review of the British Journal of Pharmacology involved the evaluation of publications that occurred in one month (September) only every 5 years there are limitations in the data, this was just a series of snapshots,

furthermore it is understood that organ or disease specific research may be published in other journals (e.g. cardiovascular research, cancer research).

There are some difficulties in the implementation of practical components in pharmacology courses, these include shortage of space, increased student numbers, lack of staff time and skills, and the need to ensure cost efficiencies [7] as well as the desire to reduce animal experimentation. Furthermore, the rise of molecular biology has had a significant impact on drug discovery in its offering of over 30000 genes and protein products as potential drug targets [5]. This research observed the rise in the use of tissues or cells from mice in pharmacological studies over recent years. The development of the genetically modified mouse, where genes can be inserted or deleted to alter the expression of gene products has also impacted on the research field remembering that the first gene knockout mouse was created by Mario R. Capecchi, Martin Evans and Oliver Smithies in 1989 and the area of research has evolved such that many genes have been altered in this model.

Do all students need to be taught lab skills? Pharmacology knowledge is a vital part of clinical practice [11] however, only a handful of pharmacy and medical students will ever need pharmacology laboratory skills [7]. Hence, for cohorts of students entering clinical professions, simulations (or computer assisted learning) can provide the data required for experimental analysis and interpretation [7]. There is much opportunity to develop educational initiatives to expand student learning in pharmacology and medication management [11] through problem based-learning [12] or Web based exercises [13, 14].

Given that research in pharmacology involves the use of animal tissues or cells it has been juxtaposed by the continued effort of agencies to reduce numbers of animals used in biomedical research [10]. The British Pharmacological Society has reported that 2% of biomedical science students receive skills training in in-vivo experimentation, that the number is likely to reduce in the future and will lead to a shortage of personnel with the technical skills for conducting tests using animals [5, 10]. In Australia there has been considerable effort to reduce the use of animals for teaching purposes. There are still some research areas in which alternatives can not be used and animal experimentation is essential [3]. Studies using experimental animals must be carried out by highly trained personnel to minimise pain to the animals and ensure experimental success. Animal models are commonly used to progress understanding of the physiological mechanisms of normal function and disease in the development of effective therapies [15]. Although not the scope of this paper the use of experimental animals and efforts to reduce the use through implementing other methods such as cell culture [16] should be discussed with students.

The rise in molecular biology techniques cannot be ignored, however, the older pharmacological techniques are still relevant in the study of new drugs even if they have been derived from proteomics or biotechnology [17]. It would be expected that students enrolled in an undergraduate biomedical/medical science degree program would be exposed to the concepts and experimental techniques associated with molecular and protein biology in other courses. Consequently, the application of these techniques to pharmacology should be discussed with students.

The laboratory experience is essential for students in the biomedical or health sciences who are learning research methods. The problem of using the experimental experience for verification and illustration of scientific concepts is that it is compounded by the deficiencies of the students and their apparati. Students are still developing their skills and their apparatus may be a limited version of real research equipment [18]. A comparison of computer simulation to wet lab studies has showed a poorer performance in practical class write up assessment outcomes which was explained by the quality of data acquired by students [7], however when asked questions relating to the experimental details of the practical class, students taught the wet lab performed better.

The goal of tertiary education is the preparation of students for either independent scientific work or the application of scientific insights and methods [18]. The use of practical classes should be for the development of skills in conducting tests, learning the academic approach to working through an experimental protocol and to gain knowledge of different scientific phenomena and their settings [18].

Reflection is an essential element of experiential learning [19], hence following laboratory classes, students need to discuss their results, reconcile the outcomes to their knowledge in the field and consider why experiments succeed or fail. Learning requires social interaction, including feedback and collaboration on shared activities in an authentic context. Examples of such methods include action learning in which peers engage in reflection as they work together on real problems in real contexts [19].

Regardless of the origins of drugs, students should be trained in the principles of pharmacology to understand how they work and advance the knowledge generated by them [17]. Students in the undergraduate pharmacology course who are enrolled in biomedical science programs at Griffith University, School of Medical Sciences comprises a diverse group of students, some of whom have direct entry into the Griffith Graduate School of Medicine, and others who may enter into postgraduate allied health programs, research degrees or enter the workforce. An evaluation of student attitudes to pharmacology laboratories demonstrated that students recognise the value laboratory classes in learning the fundamental way in which drugs are tested and analysed and developing skills in this discipline.

In conclusion, practical classes contribute to student learning in the discipline of pharmacology. A review of trends in pharmacological research over the past 30 years has shown that animal isolated organ or tissue experiments are still the most commonly used methods to measure drug action. However, a mix of simulation classes to generate viable data for analysis and practical classes to develop laboratory skills and an understanding of research protocols would probably provide the most valuable learning outcomes for students. The practical classes taught should reflect the learning objectives of the course (which should vary according to the program within which it is taught) and if able to implement within reasonable costs, newer techniques should be included or at a minimum discussed.

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