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Antiarrhythmic drug research

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This article was written as part of the 75th anniversary celebration of the British Pharmacological Society (BPS). It discusses antiarrhythmic drug research conducted by members of BPS, and as published in the *British Journal of Pharmacology* (*BJP*). BPS members, past and present, as well as antiarrhythmic manuscripts published in the *BJP* have been identified. From these data, the article attempts to semiquantitatively summarize results published in the journal, but only quotes selected manuscripts and individuals. Apologies are offered for omissions and errors, but as in any history, a writer's biases and opinions are unavoidable.
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Abbreviations: 4AP, 4-aminopyridine; TEA, tetraethyl ammonium; SSRI, selective serotonin re-uptake inhibitor

General introduction

Antiarrhythmic drugs and related subjects have occupied a small but significant fraction of *BJP* publications. Such work has generally added incrementally to antiarrhythmic drug knowledge. However, sometimes the field has received a major boost from studies reported in the *BJP*. One example is the work of Vaughan Williams and Singh at Oxford in the 1960s and 1970s. The result was a classification system for antiarrhythmic drugs that has proven invaluable, and is still in use today. Other members have, over an extended period, provided a knowledge base that was significant in the discovery of new antiarrhythmic drugs. Useful work, first described in the *BJP*, has helped our understanding of the mechanisms that underlie the genesis of arrhythmias, particularly those due to myocardial ischaemia/infarction as well as other arrhythmic mechanisms.

Obviously, the antiarrhythmic studies reported in the *BJP* are only a fraction of the antiarrhythmic work published by BPS members. However, such work will only be alluded to in this review, when necessary, to provide an appropriate context. A complete description of all aspects of the antiarrhythmic work of members of the BPS would be too voluminous, and would not add qualitatively to a description based upon *BJP* publications. Similarly, the antiarrhythmic material in the *BJP* is only the tip of an iceberg of all antiarrhythmic drug studies. However, all of the major antiarrhythmic areas are represented in the *BJP*. In the following review, an attempt is made to provide a global context for each topic.

On an introductory note, antiarrhythmic drug therapy is currently under a cloud; few new antiarrhythmic drugs are being introduced and older drugs are falling into disuse. There is no antiarrhythmic drug discovery research taking place in much of the pharmaceutical industry. This is partly because of a past history of toxicity catastrophes with older antiarrhythmic drugs, and the lack of new seductive molecular targets. Of greater importance are the advances that have been made in arrhythmic therapy with the use of electrical devices. Thus, as the clinical use of antiarrhythmic drugs lessens, there is continuing introduction of new electrical and surgical techniques for controlling arrhythmias. Such changes are reflected in the content of the antiarrhythmic drug papers in the *BJP*.

From an editorial viewpoint, whatever the current fashions in antiarrhythmic therapy are, it remains a fact that arrhythmias are still a prominent cause of mortality and morbidity. Independent of the method of epidemiological analysis used to arrive at the figures, most causes of sudden death are cardiac in origin, and because of ventricular fibrillation. Sudden death is a major cause of death in richer countries. A drug that prevents ventricular fibrillation, and is sufficiently non-toxic to be used prophylactically, would be a blockbuster. However, current thinking is that such an ideal is not attainable. Thus, both scientific and pharmaceutical research interests are low. Interestingly, there is only a low level interest in new antiarrhythmic drugs for the treatment of atrial flutter and fibrillation, despite its presence in up to 10% of the elderly. Finally, it cannot be assumed that implanted electronic devices are either usable, or acceptable, to all arrhythmia patients.

Published material on antiarrhythmic drugs in the BJP

It was possible to identify most BPS members, and *BJP* papers, concerned with antiarrhythmic drugs using a combination of manual and electronic searches. The temporal and geographical distribution patterns of publications in the *BJP* papers are given in Figure 1 and Table 1. Such data are dependent on the criteria used in the search, but any paper indexed under arrhythmias and antiarrhythmic drugs, and which appeared to relate to arrhythmias, were collected, as was any paper containing the name of a researcher active in this field. Such a search strategy resulted in several irrelevant papers. Where possible, such data were not used.

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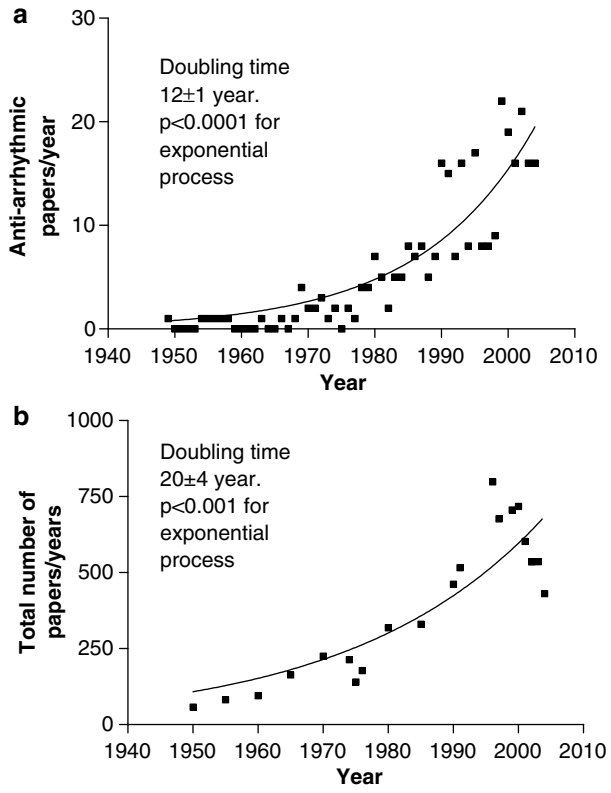

Figure 1 (a) and (b) show the growth curves for antiarrhythmic papers (a), and for all papers (b), in the *BJP*. In both cases an exponential correlation was found. The doubling times and statistical significance for the correlations are shown in the insert in each case.

Table 1 Geographic source of antiarrhythmic papers in the *BJP*

Country	*Years*		
	2001–2005	*2000–1991*	*1990–1981*
GB	10	25	17
GERMANY	10	5	3
U.S.A.	9	14	5
JAPAN	7	15	8
CANADA	8	6	6
HUNGARY	9	4	
SPAIN	3	10	1
AUSTRIA	3	5	1
ITALY	2	6	1
HONG KONG	2	4	1
FRANCE	2	5	2
MEXICO	2	0	
TAIWAN	2	5	
SAUDI ARABIA	0	2	
AUSTRALIA	2	5	1
CHINA	0	1	
SOUTH KOREA	0	2	
SWITZERLAND		1	1
BRAZIL	1		
INDIA	1	1	1
BELGIUM	1		
NETHERLANDS	1		1

Papers were categorized as originating from a particular country on the basis of the address(es) given by the majority of the authors. In the few cases where there appeared to be two equally important locations, these were scored as 0.5.

Overall, there has been a steady increase in papers published in the *BJP*. This was particularly so for antiarrhythmic papers (Figure 1a), especially when compared with the yearly total of *BJP* papers shown in Figure 1b. The growth curves for both 1a and 1b approximate to the exponential process although the statistical fit was better in Figure 1a. In Figure 1b, after the year 2000, the totals fell, leading to deviations from the exponential. Whether this change was a result of changes in the strategies of editor(s) or publisher is not known. The inflection point seen in Figure 1b is not observed in 1a. Exponential growth is not unexpected, and reflects similar growth in all scientific publishing. The doubling time for the two growth curves, however, were not the same. It was 12 years for antiarrhythmic papers *versus* 20 years for general growth despite a reduced interest in antiarrhythmic drugs.

The number of antiarrhythmic papers varied between years with a hint of periodicity. If periodicity was present, it is not known whether this reflected changes in the editorial policy, or other factors. Apparent periodic maxima were seen in 1970, 1980–1985, 1990 and 2000. Changes in *BJP* format did not seem to be responsible for this pattern. Unfortunately submission data for the same period were not obtained.

As a general pharmacology journal the *BJP* is not specifically interested in antiarrhythmic drugs. Despite this, the *BJP* continues to publish antiarrhythmic papers. Whether this reflects the fact that many of the senior authors are members of the BPS is not known. The last decade appears to have seen an increase in the number of papers whose authors are not members of the BPS. Perhaps the latter reflects the fact that the journal has a very respectable impact factor in pharmacology.

Laboratories publishing in the BJP

The type of antiarrhythmic drug papers in the *BJP* has changed as techniques have changed with time. The main emphasis has been electrophysiological (*in vitro*) and functional (*in vivo*). The former, which began as cardiac intracellular potentials studies, have to moved to patch clamp and molecular biological studies. *In vivo* work was performed with rats, rabbits and dogs, in that order, the former being by far the most popular. The techniques used were dependent upon the laboratory considered, but not exclusively so. Some laboratories used the *BJP* as their main reporting journal.

A notable example of this was the development of the classification system mentioned above. Other examples include studies into the mechanisms underlying arrhythmias, especially those caused by myocardial ischaemia, as well those concerning the functional actions of antiarrhythmic drugs. More recently, molecular biology has been brought into play with drugs acting on the delayed rectifier potassium channel.

The pattern that emerges is the recurring presence of certain authors, many of whom were U.K. trained and members of the BPS, for example, in alphabetical order: Terrence J. Campbell, Susan Coker, Michael J. Curtis, Eva Delpon, Kathleen A. Kane, R. Marshall, Basil J. Northover, Julius G. Papp, James R. Parratt, Robin G. Shanks, Bramah N. Singh, Lazlo Szekeres, E. M. Vaughan Williams, Cherry L. Wainwright, Michael J.A. Walker, Eileen Winslow, Harry J. Witchel and Brian Woodward, a few of whose likenesses are shown in Figure 2. This list is not meant to reflect national biases but the U.K. is the source of most *BJP* publications as shown Table 1.

Figure 2 Photos of some of those workers mentioned (Photos from author's collection or supplied by individuals).

However, this pattern seems to be changing. Strong U.K. affiliation reflects the fact that the BPS is the parent organization of the *BJP*, and that the BPS is a national rather than international society. In Table 1, the equal and high representation of papers from Japan and Canada is interesting, as is a comparison between Germany and the U.S.A.

Some of the patterns in Table 1 reflect training in particular laboratories. Therefore, such a factor weights any geographical analysis. Analysis of the location of laboratories, which publish repeatedly in the *BJP*, provides the data in Table 2. The antiarrhythmic activities of the laboratories identified in Table 2 are considered in detail in this review, together with a general review of the history of antiarrhythmic drugs, particularly as it relates to the BPS members, and the *BJP*.

History of arrhythmias and antiarrhythmic drugs

The early history of arrhythmic drugs pre-dates the BPS, and hence the *BJP*. In general terms, the history of antiarrhythmic drugs is fascinating in both in its complexity and the lessons it offers. Mistakes have been made and progress has been steady rather than dramatic. As indicated above, greater progress has been made with electrical devices rather than with drugs. Such devices are a consequence of increased understanding of cardiac electrophysiology, electronics and computing. Such a shift has occurred despite extensive arrhythmic drug research. The drug treatment of arrhythmias began over 100 years ago, long before what could be called 'electrotherapy'. The

beginning of antiarrhythmic drug therapy was hall-marked by Wenckebach's introduction of quinidine (see later).

The slow pace of discovery of new antiarrhythmic drugs has many causes and some of these are discussed below. The recent introduction of reductionist approaches to drug discovery has not yet had an impact. It may be that such an approach is based upon the erroneous assumption that single molecular events are responsible for the genesis of different arrhythmias.

Table 2 Contributions of various groups to the antiarrhythmic papers in the BJP

Person	*Laboratory*	*Number of papers*		
	UK	*>10*	*5–10*	*4*
Coker and others	Liverpool		+	
Curtis and others	London			+
Witchel/Hancox and others	Bristol		+	
Parratt and others	Glasgow		+	
Vaughan Williams and others	Oxford	+		
	Europe			
Valenzuela/Delpon/ Tomargo and others	Madrid	+		
Papp/Vegh and others	Szeged		+	
	North America			
Giles and others	Calgary			+
Lucchesi and others	Ann Arbor			+
Walker and others	Vancouver	+		
Campbell and others	Sydney		+	

For the sake of convenience, papers emanating from a particular laboratory, in the sense that it was the address for correspondence, or for most of the authors, have been identified and grouped for the purposes of the table. Obviously such quantitation is open to interpretation. Therefore, the data are presented in a qualitative manner using an arbitrary cut-off point of 4. The table is not an exact indication of who did what, but gives a sense of the origins, and of the flow of antiarrhythmic papers to the journal. In any one group members of the BPS are listed first.

This view neglects the fact that many arrhythmias depend critically upon dynamic interactions between the various electrophysiological properties of the heart. At the simplest mechanistic level, the heart's orderly beating (under sinoatrial node control) depends upon each and every type of cardiac tissue having its own appropriate four properties: automaticity (present or absent), excitability, conduction and refractoriness. Generally more than one of these properties has to be seriously perturbed before arrhythmias occur. Millions of years of evolution have ensured rhythmic heart beats that are not easily tripped into arrhythmias as a result of minor perturbations in any of the above four properties.

In the following, antiarrhythmic drugs are considered according to Vaughan Williams and Singh's antiarrhythmic drug classification (Table 3). This classification was revealed in part as *BJP* papers, in the 1960s and 1970s, and in Singh's D.Phil. thesis. The Classes (1 to 4) are, in order, primarily sodium current (1), beta adrenoceptor (2), potassium current (3) and calcium current (4) blockers, respectively. A later addition was used for specific bradycardics as in Class 5. In the author's opinion, it is entirely appropriate to use this classification, and not the Sicilian Gambit introduced in 1991 a complex antiarrhythmic drug classification system based on the molecular actions of a drug and the pathology of particular arrhythmias; named after the place where it was conceived and a gambit in chess. The latter is not so much a classification as a list of the actions of antiarrhythmic drugs, and is probably of less utility than the Vaughan Williams' classification.

The original antiarrhythmic drugs (quinidine and digitalis)

The effectiveness of quinine and related alkaloids (as used in antimalarial concoctions) in quelling atrial arrhythmias was noted in the 1800s (described by Levy & Azoulay, 1994). However, it remained for Wenckebach (1923) to first personally observe (in 1914) and then describe the use of the isomer of quinine, quinidine. Quinidine continues to be used (albeit under restricted circumstances) despite an intimidating

Table 3 A 21st century synoptic view of Vaughan Williams and Singh's classification of antiarrhythmic drugs

Classes	*Initial basis for classification*	*Current view*
Class 1	Effect on guinea pig atrial action potentials *in vitro* and ancillary electrophysiological effects *in vitro*	All primarily sodium channel blockers
Sub class 1a	As above but with marked effects on action potential duration	Moderate frequency dependence and action potential widening (potassium channel blockade). Expected consequences for the human ECG and cardiac electrophysiology
Sub class 1b	As above but with no effects on action potential duration	Marked frequency dependence of sodium channel blockade with few effects on the ECG at normal sinus rhythm
Sub class 1c		Very little frequency dependence of blockade of sodium channels
Class 2	Beta adrenoceptor blockers and other sympatholytic drugs	Beta blockers
Class 3	Selective action potential widening on guinea pig atrial action potentials *in vitro*	Generally, potassium channel blockers that prolong the Q-T interval of the ECG
Class 4	Calcium channel blockers	Calcium channel blockers typified by verapamil
Class 5	Selective bradycardic drugs	Selective bradycardic drugs blocking pacemaker currents

The Table is a simplistic overview of the classification system but reflects the various changes made with new discoveries. Much of the early work involved intracellular studies in guinea pig atria and some electrophysiological studies in whole hearts. An increased understanding of cardiac ion channels over time resulted in more mechanistic explanations for the original classification while studies in man provided a clinical reality that reflected and agreed with the original system. The use of Arabic rather than Roman numerals reflects their use in the early papers on classification.

toxicity profile that includes severe gastrointestinal symptoms, atropinic side effects and potentially lethal cardiac arrhythmias. The latter presaged future important discoveries in antiarrhythmic therapy. Quinidine syncope was a well known infrequent event, but no fruitful explanation of its cause were forthcoming until a particular form of ventricular tachycardia, torsades de pointes, was described by Dessertenne *et al*. (1966). Routine continuous ECG monitoring made it possible to causally relate quinidine syncope to the occurrence of torsades de pointes, and to the induction of this arrhythmia by other drugs.

Progress in antiarrhythmic research has not always followed progress in cardiac electrophysiology, or arrhythmia research. After the introduction of quinidine there was a very limited introduction of new antiarrhythmic drugs over the next decades despite steady progress in our understanding of cardiac electrophysiology. Over this period, the antiarrhythmic actions of the digitalis glycosides became better known and their appropriate and effective use in the treatment of atrial arrhythmias became both rationalized and institutionalized.

Procainamide

Procainamide's introduction was, in part, a consequence of World War II, and the loss of Indonesia as a source of quinine/quinidine. The loss of quinine stimulated research into new antimalarial drugs as well as antiarrhythmic alternatives for quinidine. The local anaesthetic procaine was recognized in 1936 to have antiarrhythmic actions that were limited by the drug's short half-life. Procainamide (the amide of procaine and resistant to esterases) quickly provided a useful alternative to quinidine. Unfortunately, the toxicity profile of procainamide proved to be similar to that of quinidine.

That progress was in fact slow is reflected in the 1970 edition (4th) of Goodman and Gilman, which listed only five available antiarrhythmics. These were the cardiac glycosides, quinidine, lidocaine, propranolol and diphenylhydantoin. However, 'advances' were on the horizon.

New sodium channel blocking antiarrhythmic drugs – Class 1

Following procainamide, there was a search for new antiarrhythmics and this included other local anaesthetics such as lignocaine which was quickly accepted although these days it is thought to have very limited utility. Out of cardiac electrophysiological studies, as exemplified by the work of Vaughan Williams (see later), an understanding of the electrophysiological actions of antiarrhythmic drugs, and the role of cardiac sodium channels developed. This focused the search for new antiarrhythmics, which were more potent and specific in their block of cardiac sodium channels. Some of these new antiarrhythmics (e.g. disopyramide) were similar in actions and toxicity to quinidine and procainamide, or to lignocaine. Potent cardiac sodium channel blockers were introduced, but trouble was brewing. As predicted by Hondeghem (1987), and shown clinically in the CAST (1989) trial, Class 1c antiarrhythmic drugs, and later other drugs, were shown to increase mortality in patients at risk of sudden cardiac death despite their being given specifically to prevent such arrhythmic deaths. Such results cast a deep gloom over antiarrhythmic drug research despite the fact that during that period, beta blockers were being shown to reduce mortality in post myocardial infarction patients.

Beta blockers – rational antiarrhythmics for sympathetic nervous system dependent arrhythmias – Class 2

When Sir James Black created clinically useful beta blockers for the treatment of angina he was not unaware of their other potential uses. The importance of cardiac beta adrenoceptor stimulation on cardiac rate, and rhythm, had been known for years. An obvious experimental example of this was when adrenaline was given to halothane (another ICI invention) anaesthetized dogs. The combination is particularly arrhythmogenic in dogs, although not in other species, including man.

Early investigations into the experimental and clinical antiarrhythmic actions of beta blockers were contemporary with other clinical studies into the uses of beta blockers. Early work in the mid 1960s suggested that beta blockers were beneficial in myocardial infarction, in addition to angina. However, enthusiasm waned, possibly because of the adverse effects associated with large doses of beta blockers given parenterally in acute myocardial infarction patients. For years thereafter, beta blockers were contraindicated in myocardial infarction and in congestive heart failure, but all that has now changed. On the other hand, the moderate antiarrhythmic effects of beta blockers have been consistently described. Vaughan Williams' group at Oxford soon realized (see later) that beta blockade constituted a second class of antiarrhythmic action (Class 2).

Beta blockers provide a vivid example of how the clinical use of drugs can change as new evidence emerges, and previous suppositions are invalidated. It took many clinical trials, and years, to establish that the routine use of beta blockers in post myocardial infarction patients reduces mortality by the order of 15%. Such protection may involve antiarrhythmic effects and/or prevention of reinfarction. It took even longer for beta blockers to become routine treatment in congestive heart failure; a condition where they also reduce mortality.

Apart from Vaughan Williams' group there were relatively few related publications on this subject in the *BJP*. Our studies with rats (1980–1990) appeared mainly in the *BJP* (e.g. Paletta *et al*., 1989). They suggested that the antiarrhythmic effects of beta blockers in acute myocardial infarction were indirect and because of blockade of beta2 adrenoceptors and a resulting elevation of serum potassium concentrations. Evidence included the fact that beta blockers were only antiarrhythmic in acutely prepared anaesthetized rats, and not in chronically prepared conscious rats. This was not an effect of anaesthetic, or alterations in CNS activity by CNS ablations (Curtis *et al*., 1985). Beta blockers only produced antiarrhythmic effects when they elevated serum potassium concentrations. There was an inverse relationship between serum potassium and arrhythmias, regardless of how potassium was elevated. As shown by Curtis, similar effects of elevated potassium concentrations occur in isolated rat hearts with acute myocardial infarction. Clinical literature suggests that moderate elevations of serum potassium confer antiarrhythmic activity in humans. Whether this relates directly to the mortality reducing effects of beta blockers and angiotensin converting enzyme inhibitors is not known.

Potassium channel blocking antiarrhythmic drugs – Class 3

The introduction of potassium channel blockers, now prototypical Class 3 antiarrhythmics, was because of Vaughan Williams and Singh's study of the cardiac intracellular potential widening (the Class 3 action) effects of reduced thyroid function, amiodarone, and later sotalol. Pharmaceutical research later focused upon sotalol as the pharmacophore for more potent and selective antiarrhythmics. This led to drugs such as dofetilide. It also eventually led to the recognition that the increase in action potential duration with Class 1 drugs such as quinidine and procainamide involved blockade of cardiac potassium channels, now known for *d*-sotalol and dofetilide to be the Kv4.5 (HERG) channel. Thus, work described in the *BJP* was instrumental in introducing potassium channel blocking antiarrhythmic drugs. The underlying concept was that increased refractoriness is antiarrhythmic by virtue of reducing the time window in the cardiac cycle when arrhythmias can occur. However, as appropriate intracardiac patterns of refractoriness are critical for orderly beating, it was not surprising to some workers that attractive as the hypothesis was, reality was different. The most effective way of prolonging action potential duration is to block the iKr current as occurs with *d*-sotalol, and its derivatives. However, once such drugs became readily available, a proarrhythmic Pandora's box was opened to reveal torsades de pointes (see above).

It is clear that blockade of iKr induces torsades, particularly when there are concomitant bradycardia and ionic disturbances. Two mechanisms have been suggested as being responsible for torsades: the first is mechanistically attractive and involves the action potential prolongation causing after-potentials, which initiate arrhythmias. The after-potentials are a result of increased intracellular calcium concentrations. The alternative explanation requires a dynamic view of interactions between conduction and refractoriness in which normal beating does not degenerate into chaos (fibrillation) because the normal intracardiac balance between conduction and refractoriness provides stable beating. Therefore, a major disturbance of one or both of these properties is necessary if arrhythmias are to occur. Thus, prolongation of the normal intracardiac pattern of refractoriness might be sufficient to cause torsades, a slowly twisting circulating wave of re-entry.

The fact that blockade of iKr induces torsades has led directly and indirectly to the publication of a number of papers in the *BJP*. There has also been a growth of interest in other potassium channel blockers. The classic nonspecific/selective blockers of potassium channels such as 4AP and TEA have long been used as probes for potassium currents, but both lack both potency and specificity. As a result, there is a continuing search for more potent drugs specific to particular potassium channels (see also Jenkinson, this issue). The iKATP channel has been of much interest in the *BJP*, but for their other pharmacological actions and not for antiarrhythmic reasons. Novel potassium channel blockers have been described in the *BJP*.

Calcium channel blocking antiarrhythmic drugs – Class 4

As is reflected by their rank as Class 4 antiarrhythmics, calcium channel blockers were the penultimate class to be identified. In part this reflects the fact that such drugs are more selective for vascular *versus* cardiac tissue, despite the presence of L-type calcium channels in both tissues. Only the less vascular-selective calcium blockers are clinically useful antiarrhythmics. Cardiac L-type channels are critical for conduction in nodal tissue as well as for excitation/contraction coupling. Thus, it is not surprising that Class 4 antiarrhythmics are used to reduce atrioventricular conduction, thereby terminating paroxysmal supraventricular tachycardias, or reducing the ventricular rate in atrial fibrillation. Neither is it surprising that hypotension and/or cardiac depression are the expected side effects.

Although the clinical antiarrhythmic actions of verapamil are confined to supraventricular arrhythmias, experimentally they have antiarrhythmic actions against ventricular arrhythmias because of myocardial ischaemia/infarction. Evidence for this comes from dog, pig and rat studies. Extensive rat studies were published in the *BJP* (1980s). Unfortunately, rats saved from an antiarrhythmic death by calcium blockers died of congestive heart failure.

Verapamil was used routinely as intravenous bolus doses to terminate some supraventricular nodal tachycardias but it has been replaced by the more efficacious adenosine.

Intravenous adenosine for paroxysmal supraventricular nodal tachycardia

The pharmacology and physiological roles of adenosine have been recurrent themes in the *BJP*. In the atrioventricular node, the actions of adenosine are almost identical to those of acetylcholine or verapamil as are other pharmacological actions such as vasodilation. However, these actions *in vivo* are very brief because of high-capacity adenosine-uptake mechanisms. Adenosine, acetylcholine and verapamil all reduce calcium currents in the atrioventricular node. Given such facts, plus adenosine's extremely short duration of action and tolerable side effects of transient hypotension or occasional bronchoconstriction, it made sense to introduce intravenous adenosine for the termination of supraventricular nodal tachycardia. The success rate for such use is as high as 95% and so it has displaced the less efficacious verapamil whose success rate is $\sim$75%. Whereas the antiarrhythmic actions of adenosine were not a topic of papers in the *BJP*, the multiple pharmacological actions of adenosine were. The latter studies were important for the successful use of adenosine as an antiarrhythmic drug.

Other arrhythmic drug – related research

In addition to describing the antiarrhythmic actions of older and newer antiarrhythmic drugs, the *BJP* was a vehicle for related activities such as antiarrhythmic classification systems, drug-induced torsades de pointes, arrhythmic mediators and mechanisms, as well as the search for new antiarrhythmic drugs.

The search for a mechanistic classification of antiarrhythmic drugs

As described above, Vaughan Williams' Oxford group created a classification system for antiarrhythmic drugs that is still in

use. As with any drug classification system, it is inherently subject to problems stemming from the fact that many drugs lack both specificity and selectivity. In the 1960s, antiarrhythmic researchers were trying to bring order to the varying effects different antiarrhythmic drugs had on cardiac intracellular potentials. The Oxford group was a leading proponent of such studies, many of which were reported in the *BJP*. They realized that the antiarrhythmic action of some drugs was related to their direct effects on cardiac action potentials (Vaughan Williams & Szekeres, 1961). Thus some of the new beta blockers had cardiac electrophysiological actions not related to blockade of beta adrenoceptors. Such observations could be resolved by ascribing to all beta blockers an antiarrhythmic action due solely to beta adrenoceptor blockade, unlike drugs that reduced cardiac action potential height. The latter had been given the label Class 1 and so the beta blockers were classed as Class 2 antiarrhythmic drugs (Dohadwalla *et al*., 1969).

Extensive investigations of amiodarone and sotalol's ability to prolong action potential duration was the basis of Class 3 actions. Amiodarone, an iodine containing compound was originally introduced in 1960s as an antianginal drug, but because of the Oxford group's studies it eventually came into clinical use as an antiarrhythmic. Amiodarone's entry into North America was delayed. This was partly because of its confusing pharmacology, toxicity and a pharmacokinetic profile that included an extremely long duration of action and accumulation in tissue. The next important step in the classification system of Vaughan Williams was the identification of calcium current blockade as a fourth class of antiarrhythmic action. Later modifications of the classification system included sub-typing Class 1 into a, b and c subtypes on the basis of whether drugs also widened action potentials (1a), had marked (1b), or no (1c) frequency dependent sodium current blocking actions. Harrison devised a clinical addition to the classification on the basis of ECG and electrophysiological effects in man. Finally, in 1979, a fifth class (Class 5) was proposed by Vaughan Williams for drugs with specific bradycardic actions on the sinus node (e.g. alinidine; see Vaughan Williams, 1992).

The hunt for torsadogenic drugs

The discovery of Class 3 actions led to new drugs and the realization that many different drugs, from a variety of therapeutic classes, had Class 3 actions and that this caused torsades de pointes. Even the oldest antiarrhythmic, quinidine, had this action as a Class 1c drug. The Class 3 action also explained cases of 'sudden' deaths seen with 'safe' drugs. The classic case was with 'second generation' antihistamines (e.g. astemizole). Subsequently, many other drugs displayed the same Class 3 action, and their use was also causally associated with sudden death. Such discoveries were made as a consequence of long-term monitoring of ECGs and better post marketing surveillance.

Our understanding of Q-T widening (Class 3 actions) on the ECG, whether due to iatrogenic or genetic causes, is now reasonably complete. We now know which drugs widen the Q-T interval, and cause torsades, as well as the genetic aberrations that widen the Q-T interval. Genetic causes relate to mutations of potassium channels (iKr) or, in some cases, sodium channels. Such knowledge is invaluable to drug researchers and regulators as they seek to ensure that new drugs do not have the potential to induce torsades, especially drugs used in non life-threatening conditions.

Members of the BPS and the *BJP* have played their part in the above studies. Much of the relevant data has been reported in other journals, but applications of such knowledge to drugs now appear often in the *BJP*. The aim of researchers and regulators is to avoid drugs with lethal adverse effects; any drug should save far more lives than it takes. On a quizzical note, it is possible that some drugs provide so much comfort to patients with non-lethal medical conditions, that some patients would accept a very small chance of death in order to achieve such comfort. After all, we routinely accept a chance of death in a road accident for the comfort and convenience of easy travel. It must also be remembered that the majority of drug related deaths are the result of inappropriate therapeutic drug use.

The search for mediators of arrhythmias and arrhythmogenic mechanisms

In the search for a better understanding of arrhythmias, the *BJP* has published a number of contributions. These often involved papers related to the search for putative mediators of arrhythmias. In some cases, such studies were part of series that systematically attempted to unravel arrhythmogenic mechanisms, whereas, in other cases, single papers centred on whether a particular mediator is, or is not, involved in the arrhythmias induced by a particular stimulus (e.g. ischaemia). A classic example is beta adrenoceptor stimulation as discussed above. Other examples include the arrhythmic mediator roles of eicosanoids or particular receptors.

The search for new antiarrhythmic drugs

Members of the BPS, and the *BJP*, have played various roles in the search for new antiarrhythmic drugs. These included introducing new antiarrhythmic drugs, examining the actions of existing antiarrhythmic drugs, or explaining the mechanisms underlying arrhythmias. For example, the Vaughan Williams classification, especially Class 3, stimulated much new drug research as discussed above. The ultimate aim of our laboratory was always the discovery of new drugs for the prevention of fatal acute myocardial infarction-induced arrhythmias. This has resulted in a new antiarrhythmic drug (see below).

Role of particular groups and laboratories

The above discussion illustrates, in a general manner, the part that BPS members, and the *BJP* have played in antiarrhythmic drug research. The following substantiates some of the claims made above in terms of the laboratories that have published a number of papers (see Table 2) in the *BJP*.

The Oxford Laboratory – Vaughan Williams, Singh and others

Much of this group's work has been described above, but particular landmarks which should be recognized include Sekiya & Vaughan Williams' (1963) use of intracellular

potential measurements in isolated rabbit atria, a preparation used to describe the electrophysiological action of disopyramide, quinidine, and the beta blocker pronethalol. All of these drugs reduced action potential height while altering responses to electrical stimulation – the membrane depressant or local anaesthetic effect. The same preparation was also used with other sympatholytic drugs. As described above, such studies led to the postulation of two classes of antiarrhythmic drugs, namely, those with membrane depressant actions (Class 1) due to inhibition of cardiac action potentials (sodium channel blockade), and those due to blockade of cardiac sympathetic nerve activity (Class 2).

Once Classes 1 and 2 had been defined, Singh & Vaughan Williams (1970a, b) quickly defined a third class of antiarrhythmic action based on drugs that selectively widened cardiac action potentials. A useful description of Class 3 actions (Singh & Vaughan Williams, 1970a) was made with the beta blocker, MJ1999. This compound, unlike its comparator beta blocker, AH3474, widened the rabbit atrial action potential. By 1971 there was a clear description of three classes of antiarrhythmic drugs. By 1972 a fourth class (Class 4) was added to accommodate calcium channel blockers.

This classification system, augmented by further subclassifications of Class I as well by Harrison's translation into clinical utility, was readily accepted in Europe, but more slowly in the U.S.A. The new and improved classification system still has both clinical and experimental utility. Furthermore, with improvements in our understanding of the ionic current basis of cardiac electrophysiology, it has become possible to provide a molecular underpinning to the classification. Classification is also pivotal in detecting and delineating the electrophysiological toxicities of antiarrhythmic drugs. Without the Vaughan Williams/Harrison classification it would not have been so easy to unravel the lethal actions of Class 1c antiarrhythmics, or to solve the problem of Q-T widening and torsades de pointes.

The Vancouver Laboratory – Walker, Curtis and others

The Vancouver group's focus was always on drugs that prevent ventricular arrhythmias due to acute myocardial infarction (maintained ischaemia). It had the ultimate aim of discovering antiarrhythmic drugs, which would selectively prevent such arrhythmias. The work began as an exploration of the antifibrillatory actions of different drug types, including nitroglycerin, prostaglandins and propranolol, as well as different anaesthetics (Au *et al*., 1983). The antiarrhythmic actions of beta blockers were investigated in considerable detail as discussed above. Interestingly, a tangential series of studies, reported in other journals, showed a direct antiarrhythmic effect of halothane. The beta blocker story included CNS ablations studies (Curtis *et al*., 1985) and was finalized by Paletta *et al*. (1989) who concluded, ''These results suggested that antiarrhythmic effects … unrelated to cardiac beta-blockade … could be attributed to elevations in serum potassium concentration''.

In addition, Classes 1, 3 and 4 were also investigated for their actions against ischaemia-induced arrhythmias. All three Classes demonstrated antiarrhythmic protection but this protection was severely limited by adverse effects on the heart, and/or the rest of the cardiovascular system. Animals saved from ventricular fibrillation died from the drug (Curtis *et al*., 1984; Curtis & Walker, 1986). Tedisamil, a Class 3 drug in rats, was antiarrhythmic, but only at doses that profoundly increased action potential duration (Beatch *et al*., 1991).

Such results, published in the *BJP*, and in other journals, substantiate a view that for an ion channel blocking drug to prevent acute infarction-induced arrhythmias, it had to act selectively within the ischaemic myocardium, probably via mixed ion channel blockade as shown by Sarraf *et al*. (2003). A direct result of the above studies was the formation of a biotech company, now known as Cardiome Pharma Corp., whose goal was to discover selective antiarrhythmics. One such drug, RSD1235, is currently in Phase III clinical trials for the in-hospital termination of atrial fibrillation.

The Madrid Laboratory Valenzuela/Delpon/Tamargo

This Spanish group has published at least 11 papers in the *BJP* since 1989 After an initial report (Delpon, Valenzuela & Tamargo, 1989), they performed many intracellular electrophysiological studies, using guinea pig ventricular and papillary muscle, or new antiarrhythmic compounds and related drugs. They have also investigated the vascular actions of current antiarrhythmic drugs with a view to explaining their adverse vascular effects.

In recent papers, the group used single channel techniques to study potassium current blockade. Longobardo *et al*. (2000) examined the actions of a quaternary derivative of the local anaesthetic bupivacaine on hKv1.5 channels, expressed in *Ltk*$^-$ cells, using whole-cell patch-clamp techniques. Related studies followed with other local anaesthetics in a study of mechanisms underlying channel blockade. In a recent paper, Caballero *et al*. (2003) used standard molecular biology techniques to study the positional importance of valine in the amino-acid sequence of the wild-type Kv4.2 (HERG) channel.

The Glasgow laboratory – Parratt and others

The Glasgow group of Parratt has a long standing interest in the mechanism underlying arrhythmias due to ischaemia and reperfusion, as well as the actions of antiarrhythmic drugs. The Glasgow group has extensively used rats for their studies. A typical example of their work in the 1980s was with reperfusion arrhythmias in the rat and their sensitivity to various antiarrhythmic drugs (Kane *et al*., 1984). Jim Parratt has extensive interaction with the group at Szeged, Hungary. Later work used dogs, and pigs to study various aspects of ischaemic and reperfusion arrhythmias. For example, they made interesting observations regarding bradykinin's ability to reduce arrhythmias (Vegh *et al*., 1991; 1993). They further suggested that, ''it might be a 'primary mediator' of the protective, antiarrhythmic effects of ischaemic preconditioning''. One of their more recent publications has described how sildenafil is antiarrhythmic after oral administration in dogs (Nagy *et al*., 2004).

The Hungarian (Szeged) group

As noted above, this group has connections with Parratt who has often published in the *BJP* with the group. Much of their work involves the use of dogs, as for example, studies with bradykinin. Dog cardiac tissue was also used to study antiarrhythmic drug, dronedarone, a derivative of amidarone

with lesser toxicity (Varro *et al*., 2001). More recent studies have used dog cardiac tissue to study the action of drugs on potassium channels, their characteristics as well as their role in repolarization reserve (Biliczki *et al*., 2002 and Lengyel *et al*., 2004) These latter studies all originated in Szeged laboratories with Varro as the senior author.

The Bristol group – Witchel/Hancox and others

A group from Pharmacology and Physiology at Bristol has been contributing to the *BJP* over the last 6 years. The group's interests include HERG (iKr) channels and the actions of the antidepressant drugs that cause Q-T prolongation (Teschemacher *et al*., 1999), as well as drug effects mediated via the Na/Ca exchanger. Recently, they have been studying the effect of point mutations in the HERG channel. They were able to show that fluvoxamine (a SSRI) is quite distinct in its mode of blockade of HERG and thus distinct from related drugs they had previously studied (Milnes *et al*., 2003).

The King's (London) Group – Curtis and others

This group studies ischaemic and reperfusion arrhythmias in isolated hearts, using rats as well as rabbits. Their studies included the effects of potassium and potassium current blockers (e.g. Rees & Curtis, 1993) as well as studies with mibefradil. They have continued to investigate the role of catecholamines in ischaemic arrhythmias but were unable to induce late phase arrhythmias in isolated hearts by infusion of catecholamines, even when blood was used to perfuse isolated hearts (Clements-Jewery *et al*., 2002).

The Liverpool Group – Coker and others

Susan Coker's group in Liverpool has studied a number of different aspects of the action of drugs on ischaemic arrhythmias by using rabbits and rats. Some of their work centred around phosphodiesterase inhibitors, including zaprinast and rolipram, and the relationship between arrhythmias and its effect on platelets (Holbrook & Coker, 1991). Later studies have encompassed effects of drugs acting on autacoids and neurotransmitters with a more recent interest in the Q-T prolonging actions of different drugs, including antimalarials (Batey & Coker, 2002).

The Sydney group – Campbell and others

Campbell worked with Vaughan Williams in Oxford (Campbell & Vaughan Williams, 1982) and since has worked in Physiology & Pharmacology at the University of New South Wales. Using intracellular potential techniques in guinea pig tissue, the group has investigated such factors as the influence of potassium concentration on Class 1 antiarrhythmic (Wyse *et al*., 1993) as well as drug effects on potassium current including the antimalarial drug, halofantrine (Tie *et al*., 2000).

Conclusions

This brief history outlines the type and depth of antiarrhythmic drug studies reported in the *BJP*, most of which were performed by members of the BPS. Over time, papers in the *BJP* have moved from qualitative and quantitative descriptions of the electrophysiological and functional effects of antiarrhythmic drugs to their use as tools in the elucidation of the intimate details of molecular structure and function in ion channels. The current endeavour of many studies in the latter area, it is hoped, will ultimately lead to new, more efficacious, specific/selective and less toxic antiarrhythmic drugs. With the passsage of time, this could become reality, but in the meantime, more functional studies might provide newer drugs sooner. Thus, the biological complexities of arrhythmias and antiarrhythmic drugs will continue to fascinate us. Let us hope that we all continue to be published in the *BJP* as members of the BPS.

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