**Clinical Perspective**

The Sicilian Gambit: an opening move that loses the game?

The Sicilian Gambit is the title of a review article on antiarrhythmic drug therapy published simultaneously in the *European Heart Journal* and *Circulation* in 1991. The rather peculiar name is a reference to the Queen's Gambit (an opening move in chess) and the fact that the article, considered by the authors as an 'opening move' in a new classification of antiarrhythmic drug therapy, was conceived at a meeting in Sicily. The authors of this article (Task Force of the Working Group on Arrhythmias of the European Society of Cardiology) have described themselves as 'a loosely organised group of basic and clinical investigators who met to discuss and pool their ideas about cardiac arrhythmias and their therapy and to share this information with the community'. This would seem to be a well-intentioned and admirable aim. Why then should one distinguished investigator criticise the updated, expanded version of the Sicilian Gambit article and refer to it as 'an opening move which loses the game'?

At least part of the answer lies in the history of the classification of antiarrhythmic drug actions. The earliest antiarrhythmic drugs were discovered by chance and it was only some time later that the majority of these agents were found to reduce the fast inward sodium current into cardiac myocytes. The Vaughan Williams classification of antiarrhythmic drug action and its subsequent modifications were based on clinical observations, grouping together such agents according to their predominant electrophysiological effects. For instance, quinidine, disopyramide and procainamide were all found to prolong HV and QT intervals during sinus rhythm in addition to widening the QRS complex, actions that were designated as class la. In contrast, lignocaine, mexiletine and tocainide produced none of these effects (in fact shortening the QT interval) and this action was classed as lb. In addition some drugs, such as flecainide and encainide, produced QRS widening and HV lengthening with little effect on the QT interval, hence a further class termed lc. Other drugs were found to have antiarrhythmic efficacy but did not have a prominent fast sodium current effect and the electrophysiological actions of these agents were classified as 2, 3, 4 and 5. For two decades clinical antiarrhythmic therapy was based on a combination of knowledge of the particular arrhythmia substrate in question, the Vaughan Williams classification and other information gleaned from small clinical studies.

The world of antiarrhythmic drug therapy was shaken by the publication of the large Cardiac Arrhythmia Suppression Trial in 1989, when it was revealed that flecainide and encainide were associated with an increase in mortality in patients with asymptomatic ventricular arrhythmias following myocardial infarction. Other agents with class lc activity came under scrutiny, in particular propafenone, although it was appreciated that it did possess other actions not shared by flecainide or encainide. It was against this background that the meeting in Sicily (sponsored by Knoll Pharmaceuticals) was held. The published product of this meeting, the Sicilian Gambit, opened with a fierce attack on the Vaughan Williams classification, listing and expanding on six apparent limitations. The principal objection was that it was incomplete and therefore too restrictive in terms of antiarrhythmic actions that it incorporated. The second part of the article described previously postulated mechanisms of arrhythmias and collated possible targets for antiarrhythmic therapy at molecular, cellular and 'whole organ' levels. A 'spreadsheet' listing the known actions of 22 drugs at the molecular level was provided. Finally the concept of a 'vulnerable parameter' was introduced, the authors suggesting the most appropriate targets for therapy in a number of specific clinical arrhythmias. The original Sicilian Gambit article has since spawned a number of supplementary articles and, most recently, an expanded and updated book version.*

In our view the publication of these articles has performed a considerable service for students of antiarrhythmic therapy in that it has provided the reader with easy access to a large body of up-to-date, relevant information, outlining both what is known and what is not known. In this respect it succeeds and will be a source of scientific cataloguing of progress for the foreseeable future. It seems fair to take issue, however, with...
The proposition that there is an original 'Gambit Approach' to therapy. Arrhythmologists have always striven to take a logical approach to treatment based upon the best information available and the concept of targeting the 'weak link' or 'vulnerable parameter' in an arrhythmic mechanism has been part of their thinking process for a long time. We believe that the clinical approach to antiarrhythmic therapy remains unchanged following publication of the Sicilian Gambit as, after all, it has provided no new information. Although the authors of the Gambit concede this fact in some sections of the recent versions, this is overshadowed by rather overdefensive dismissal of reasoned and invited arguments expressing this view elsewhere. Perhaps it is this point that has raised the hackles of some basic investigators and clinicians. As stated above, the Vaughan Williams classification is based on the proven effects of antiarrhythmic drugs on cardiac conduction and refractoriness and forms a significant part of the spreadsheet of information presented in the Gambit. If these effects were of no relevance to the treatment of clinical arrhythmias or if other actions at another level were shown to be more relevant, then we agree that it should be forgotten. There is considerable evidence, however, that

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**Figure 1** The 'Spreadsheet' Approach to classification of antiarrhythmic drugs. (Reproduced with permission.)

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The table and diagram illustrate the relative potency of block (Low, Moderate, High) for various drugs and their effects on different channels and receptors. The clinical effects are marked with arrows indicating their impact on parameters such as heart rate, PR interval, and QRS width.
the reverse is the case and that logically thinking clinicians, including those authoring the updated Sicilian Gambit[14,15], continue to use it.

In summary, it is clear that the original Sicilian Gambit has performed a useful function in that it catalogues in a fairly comprehensive way what is known about mechanisms of action (proven and unproven) of antiarrhythmic drug therapy. The authors should be encouraged to continue to update us within this framework[16]. They have reemphasised the 'thinking man's approach to selection of therapy', which cannot be a bad thing. It is incorrect, however, to suggest that they have invented the pathophysiological approach to drug selection or that there is such a thing as a specific or original 'Sicilian Gambit approach' to therapy. The authors are unnecessarily critical of the evidence-based Vaughan Williams classification that they themselves, or at least those that treat patients, will continue to use.

C. J. GARRATT*
M. J. GRIFFITH
*Glenfield Hospital, Leicester
Queen Elizabeth Hospital, Birmingham

References