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EDITORIAL

George Ralph Mines (1886–1914): the dawn of cardiac nonlinear dynamics

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On 6–7 November 2014, a symposium entitled *Cardiac Arrhythmias: Challenges for Diagnosis and Treatment*, organized by the authors of this editorial (Fig. 1), was held at McGill University in Montreal to commemorate the centenary of the death of George Ralph Mines (Fig. 2), a Cambridge graduate who at the time of his death, on 7 November 1914 at the age of 28, was the Professor of Physiology at McGill. Inspired by Mines's seminal papers published in 1912–1914, the symposium focused on identifying areas in which basic physiology and theoretical modelling are defining new approaches to clinical cardiac electrophysiology. This special issue contains 11 papers contributed by speakers at this symposium, as well as three other contributed papers and one perspective.

Despite his early death, Mines made transformational contributions to cardiac electrophysiology. His research concerning induction of tachycardia and fibrillation provides much of the basis for our current understanding of these phenomena. Mines's papers contain other insights concerning cardiac dynamics that have particular significance in light of subsequent developments in studies of cardiac electrophysiology and dynamics. In this essay, we briefly review Mines's contributions to the study of cardiac electrophysiology and nonlinear dynamics, including some of his lesser known, but very relevant, findings.

The mechanisms by which cardiac arrhythmias are initiated, maintained and terminated can be understood in terms of the four basic phenomenological properties of excitability, refractoriness, automaticity and conduction. The heart is thus fundamentally a nonlinear system, since the first three of these properties arise only in nonlinear systems. One of the characteristic properties of many nonlinear systems is bistability, in which at any given time the system can show one of two possible stable behaviours. We describe below Mines's work on three different forms of bistability that appeared just over a hundred years ago in a pair of remarkable articles, one of them in this journal (Mines, 1913, 1914). We then indicate how Mines's pioneering ideas are of relevance to work carried out on cardiac arrhythmias during the century following his death.

The vulnerable period and the induction of re-entrant rhythms

In his 1914 article, which appeared after his death, Mines showed that the delivery of a premature stimulus to the ventricles of a Langendorff-perfused rabbit heart at room temperature could throw the ventricles into fibrillation for a period lasting 'from a few seconds up to over three hours'. Mines noted that the stimulus had to be 'properly timed'. Figure 3 reproduces Mines's kymograph recording of ventricular contraction, with the white spots indicating the times at which an electrical stimulus was applied to the ventricle. While the first six stimuli did not provoke ventricular fibrillation, the last one, arriving at the 'critical instant' did induce fibrillation. Mines noted that 'stimuli too early or too late are ineffective in producing fibrillation' and that 'the critical instant for the production of fibrillation is immediately after the close of the refractory phase.' This period was later termed the 'vulnerable period' and the clinical correlate of this behaviour is the 'R-on-T-phenomenon', when a premature stimulus or a premature ventricular contraction that induces ventricular fibrillation falls during the T-wave of a normal sinus beat on the electrocardiogram (Ferris *et al.* 1936; Wiggers & Wégria, 1940; Smirk, 1949).

The ventricles of the heart thus support two stable behaviours (normal sinus rhythm and ventricular fibrillation) and there is thus bistability. Injection of a much larger electrical stimulus can defibrillate the heart, i.e. get rid of ventricular fibrillation, thus restoring normal sinus rhythm (Prevost & Battelli, 1899; Gurvich & Yuniev, 1947). This result provides another demonstration of the underlying bistability but in the reverse direction.

Two definitions are needed in order to appreciate the major mechanism for the induction of tachycardia and fibrillation. If a stimulus is delivered to a ring of excitable tissue, then in some cases the circulation of excitation may block in one direction, but not the other, leading to unidirectional block. Re-entry refers to a circulating excitation where the period of the rhythm is set by the time it takes to traverse a circuitous path, rather than the period of a pacemaker. A re-entrant rhythm can be generated not only by excitation traveling in a one-dimensional ring, but also by spiral waves circulating in a two-dimensional surface, or wavefronts of more complicated geometries (e.g. scroll waves) circulating in three dimensions.

Mines also showed that a circus movement could be produced in rings of cardiac tissue (Mines, 1913, 1914). Mines explained: (i) why unidirectional block was required to start up re-entry, (ii) why there was a vulnerable period during which a well-timed stimulus would initiate re-entry, (iii) why the circumference of the ring had

Figure 1. Photograph of the organisers of the Mines Centennial Symposium
Left to right are Dr John Orlowski, Dr Leon Glass, Dr Michael Guevara, and Dr Alvin Shrier.

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to be shorter than the 'wavelength' of the circulating impulse, and (iv) how a well-timed stimulus could abolish the re-entrant motion (see Boukens & Janse (2013) and Aguilar & Nattel (2016), in this issue, for a review). In the case of circus-movement re-entry taking place in the intact heart, one would have bistability between two periodic rhythms: normal sinus rhythm and the re-entrant rhythm that produces a monomorphic tachycardia. As in the case of circus-movement re-entry, the start-up of spiral-wave re-entry by a premature stimulus hinges on there being unidirectional block (Frazier *et al.* 1989). (See, e.g. movie at http://www.medicine.mcgill.ca/physio/guevaralab/Xu_Movies/homog.mpg, which shows the start-up of a spiral wave by a premature extrastimulus in an ionic model of a two-dimensional sheet of ventricular cells.)

While Mines is generally credited with the discovery of circus movement re-entry in cardiac tissue, the first, albeit brief, description of this phenomenon in the heart was in fact by Alfred Mayer, a marine biologist who is widely credited for his systematic studies of the same phenomenon in the jellyfish (e.g. Mayer, 1906, 1908). This fact has been only very occasionally noted in the literature (e.g. Rytand, 1966). Mayer initiated re-entry in ring-shaped strips cut from the turtle ventricle using electrical or mechanical stimulation, and clearly stated the requirement of producing unidirectional block to initiate re-entry (Mayer, 1908). Also, Garrey, in his 1914 report on fibrillation, expressly mentioned that he had conducted public demonstrations in Woods Hole of 'circus contractions' in rings of tissue cut from turtle ventricles before the appearance of Mines's 1913 paper (Garrey, 1914).

Clinical cardiac electrophysiology identifies physiological and anatomical factors that lead to the induction, stabilization, destabilization and termination of re-entrant tachyarrhythmias. Atrial fibrillation refers to the rapid disorderly activation of the atria leading to a loss of atrial pumping activity. While atrial fibrillation itself is not fatal, its incidence in the population increases with age and it is the most common cardiac arrhythmia requiring medical attention. In this issue, as Haissaguerre *et al.* (2016) and Narayan & Zaman (2016) discuss, although it is generally accepted that atrial fibrillation is due to re-entrant rhythms, it is controversial whether there is a single 'mother rotor' (Jalife *et al.* 2002), multiple re-entrant wavelets (Konings *et al.* 1994), or multiple transient spiral-waves (Haissaguerre *et al.* 2016, in this issue). Since a major clinical objective is to develop techniques to treat atrial fibrillation by ablating atrial tissue, the distinctions are not only of academic interest. Early surgical methods for treating atrial fibrillation, which have also been theoretically modelled (Dang *et al.* 2005; Jacquemet 2016 in this issue), involved disrupting anatomical regions that could support re-entrant circuits. Noting that the junctions between the pulmonary veins and the left atrium often display rapid activity, Haissaguerre pioneered techniques of ablation to isolate the electrical activity in the pulmonary veins from the atria. More recently, as Narayan & Zaman (2016) discuss in this issue, it has been found that ablating atrial tissue at the central 'core' of atrial spiral waves can abolish atrial fibrillation. Whereas Mines observed re-entry by seeing the circulation of a wave of contraction in a ring of cardiac tissue, new technologies that enable mapping the electrical activity in the atria provide an important direction for current work (see Proietti *et al.* 2016 in this issue).

Ventricular tachyarrhythmias, rapid rhythms originating in the ventricles, provide a different set of challenges to clinicians and basic scientists. In patients who have had a myocardial infarction, ventricular tachycardia is often mediated by anatomically defined re-entrant pathways. There are however other possibilities, as discussed by Narayan & Zaman (2016) in this issue. If a wave of excitation leads to a sufficiently strong cardiac contraction, the heart may still pump enough blood to the body so that the arrhythmia would not be fatal, and patients could seek medical treatment. If there is a well-defined anatomical circuit, an appropriate ablation could eliminate the possibility of re-entry and thus prevent the initiation of the arrhythmia (Aliot *et al.* 2009). In this issue, Proietti *et al.* (2016) review current approaches and provide a prospective towards ablation of ventricular tachycardia. In contrast with atrial fibrillation, ventricular fibrillation, an irregular rhythm believed to be associated with multiple re-entrant waves, is invariably fatal. Since ventricular fibrillation can often be converted to normal sinus rhythm by

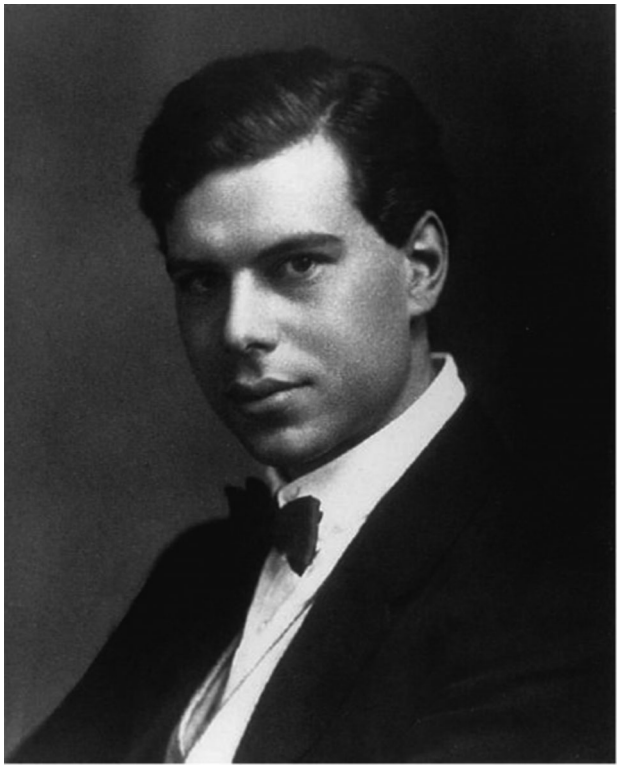

Figure 2. George Ralph Mines at the age of about 27
Photograph reproduced from DeSilva 1997. Original photograph reprinted with permission from the Physiological Laboratory, University of Cambridge, UK.

delivering an electrical shock, e.g. with an implantable cardioverter-defibrillator, a major question is how to improve methods for risk stratification so that implantation is relegated to patients who would have a benefit, as discussed by Lerma & Glass (2016) in this issue. In patients, there can be a direct transition from sinus rhythm to ventricular fibrillation, or there can be a preceding ventricular tachycardia. Theoretical and experimental studies are now being directed towards improving techniques for defibrillation by optimizing the waveform or by delivering multiple low voltage pulses (Fenton *et al.* 2009; Li *et al.* 2011; Trayanova & Rantner 2014).

1:1 and 2:1 bistability and hysteresis

Although Mines's discoveries on the induction of re-entrant rhythms have had great impact, his findings in other areas are much less appreciated, but are likewise important. In this section we summarize his findings about stable rhythms observed during periodic stimulation of cardiac tissue. We characterize observed rhythms by the ratio of the number of stimuli to the number of contractions (e.g. each cycle of a 2:1 rhythm consists of two stimuli and one contraction). Mines discovered that there could be bistability and hysteresis involving 1:1 and 2:1 rhythms in the periodically stimulated ventricle of the frog (Mines, 1913). He demonstrated hysteresis by showing that there was a range of stimulation frequencies over which one could observe either a 1:1 or a 2:1 rhythm, depending on whether the stimulation frequency was increased or decreased to end up within that range (Fig. 4). When a 2:1 rhythm was established within this range, interpolating a single well-timed extrastimulus could flip the rhythm from a 2:1 rhythm to a 1:1 rhythm. When a 1:1 rhythm was established within this range, dropping two or three stimuli from the stimulus train caused a 2:1 rhythm to emerge upon the resumption of stimulation. In the words of Mines: 'It is seen that over a quite considerable range of frequencies of excitation, there exist two possible equilibria, stable so long as the heart continues beating regularly and without interruption.' Mines based his explanation of both the bistability and hysteresis on the concept of the refractory period and the fact that the duration of the contraction decreases with an increase in heart rate.

Recording of action potentials in single ventricular cells many years later ultimately provided experimental support for Mines's explanations for 1:1 and 2:1 bistability and hysteresis (Yehia *et al.* 1999). In these single-cell experiments, one could in addition flip the 1:1 rhythm to a 2:1 rhythm by a well-timed premature stimulus. The 1:1/2:1 hysteresis can also be seen when one gradually increases and decreases the stimulus amplitude instead of the stimulation frequency (Purkinje fibre: Lorente & Davidenko, 1990; single ventricular cells: Yehia *et al.* 1999). There is at least one case in a patient showing that a properly timed atrial or ventricular extrastimulus can elicit flips from normal sinus rhythm to 2:1 atrioventricular block and vice versa (Pruvot *et al.* 1999). We now discuss how the above phenomena may be playing an important but underappreciated role in the induction of ventricular tachycardia and fibrillation.

Alternans, bifurcations and the onset of ventricular tachyarrhythmias

In 1913, Mines wrote in his article in this journal, 'The condition in which cardiac muscle acted upon by evenly-spaced stimuli (either natural or artificial) responds with alternate large and small contractions, has been of late the subject of much discussion.' The same could be said today. Since rhythms displaying alternating morphologies of ventricular complexes or segments of the electrocardiogram (alternans rhythms) often precede the induction of ventricular fibrillation, they remain the subject of intensive experimental, theoretical and clinical study (Weiss *et al.* 2006; Wilson & Rosenbaum, 2007; Verrier *et al.* 2011). We first discuss several different mechanisms for alternans studied by Mines.

Alternans resulting from spatially heterogeneous 2:1 block. In some of his experiments on increasing and decreasing stimulation frequency, Mines noted that 'the transition from whole to half-rhythm [i.e. from 1:1 to 2:1 rhythm] is not always so simple', in that '... the condition of alternation makes its appearance and complicates matters to some extent' (Fig. 5). Mines's explanation for alternans was that 'the refractory phase of some portions of the muscle differs from that of other portions, and therefore the frequencies at which they adopt the new manner of response are different.' Thus, by Mines's explanation, at the first arrow in Fig. 5 (top), during a time at which the stimulation frequency was being gradually increased ('accel'), some cells began to make the transition from 1:1 to 2:1 rhythm, while other cells remained in 1:1 rhythm, thus producing the beat-to-beat alternation in the overall force of contraction of the ventricle that is seen between the times indicated by the first two arrows. Following a phase of irregular rhythm containing many 2:1 cycles, Mines increased the stimulation frequency further (second 'accel'), which resulted in the immediate establishment of an overall 2:1 rhythm of contraction (third arrow), with presumably a large majority or all of the cells that were in 1:1 rhythm up until that point in time converting to

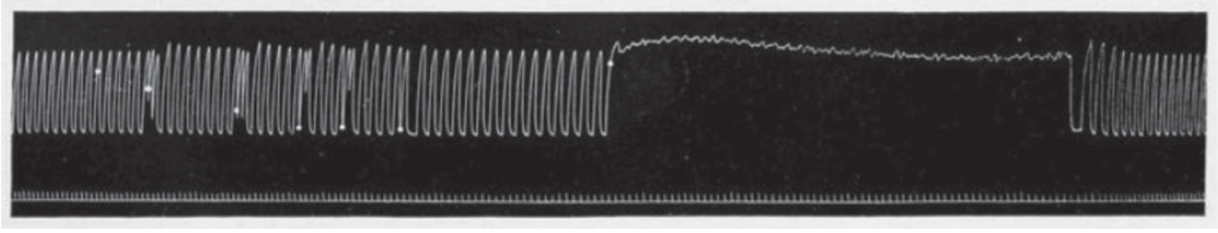

Figure 3. Kymograph recording of contractile activity in the ventricles of a Langendorff-perfused rabbit heart (22.5°C)
The white spots show the moments of electrical stimulation of the ventricle at different phases of the cardiac cycle. In this and subsequent figures, tic-marks at bottom are at 1 s intervals. Figure 5 of Mines (1914).

2:1 rhythm. In Fig. 5 (bottom), Mines then decreased the stimulation frequency ('ritard') until the time came when the 2:1 'half rhythm' converted into an alternans rhythm (fourth arrow), because of the reversion of some cells to 1:1 rhythm. By the end of the trace, the alternans was only barely perceptible, with a 1:1 rhythm presumably being attained not too long after the end of this trace.

Mines adopted his explanation for alternans as given above from Gaskell (1882), who wrote: 'the most probable explanation is that a larger amount of tissue contracts when the beats are large than when they are small, and that, therefore, in all probability, certain portions of the ventricle respond only to every second impulse while other portions respond to every impulse.' Mines went on to note that while 'Gaskell's hypothesis does not require that the portions of muscle which fail to respond to alternate excitations shall be visibly separated', it would be much easier to determine what is going on should such a spatial separation exists.

So Mines next went on to investigate Gaskell's hypothetical mechanism for alternans by purposely constructing a preparation that would allow such a spatial separation. This consisted of a ring of tissue taken from the auricles of a tortoise (Fig. 6, top), tied around its top with a thread to produce block of propagation, so that there are thus two spatially separated parts of the ring (branches A and B in Fig. 6). A lever was attached to the thread to record the overall mechanical contraction of the ring, and the ring was electrically stimulated using the pair of electrodes at the bottom of the ring. As the frequency of stimulation was increased, there was a transition from a global 1:1 rhythm throughout the entire ring to a 2:1 rhythm in both branches. We refer to this as a spatially concordant 2:1 rhythm, since the 2:1 rhythms in the two branches are in phase with one another. Mines showed that a well-timed extrastimulus applied to either branch during the concordant 2:1 rhythm would produce a new rhythm in which branches A and B of the ring contract on alternate stimuli; i.e. there were two spatially discordant (i.e. 180 degrees out of phase) 2:1 rhythms in the two branches of the ring. Since branches A and B were not identical, they contracted with different strengths and there was, looking at the overall contraction of the ring, a 2:2 or alternans rhythm. Figure 6 shows Mines's recordings of contractile activity in the ring during concordant 2:1 block (bottom left) and discordant 2:1 block (bottom right) at the same stimulation frequency. Mines also mentioned that another well-timed stimulus (or dropping of a few successive stimuli) during the spatially discordant 2:1 rhythm would then re-establish the spatially concordant 2:1 rhythm. There was thus bistability between concordant and discordant 2:1 rhythms. Mines did not report any hysteresis involving these two rhythms.

Concordant and discordant alternans can also both be seen in the mammalian ventricle with the same intervention that Mines used, incremental fast pacing. In a study using optical mapping of the action potential in a mammalian epicardial-rim ventricular preparation, as stimulation frequency was increased concordant alternans occurred first and was later replaced by discordant alternans (Pastore *et al.* 1999; Pastore & Rosenbaum, 2000). Unidirectional block of propagation occurred during discordant alternans in a neighbourhood of the 'nodal line' demarcating the border between the two regions showing out-of-phase alternans, where there are steep gradients of repolarization, initiating tachycardia or fibrillation in all the hearts studied (Pastore & Rosenbaum, 2000). Ventricular fibrillation, which occurred in 93% of the hearts, and tachycardia (7%) were always preceded by discordant alternans, never concordant alternans (Pastore & Rosenbaum, 2000). A later study using perfused wedges of full-thickness ventricular myocardium has shown that as stimulation frequency was increased concordant alternans could occur on occasion after discordant alternans, and that that there could be multiple nodal lines present (Gizzi *et al.* 2013). When a transmural structural barrier to propagation was created using laser ablation – producing a preparation reminiscent of that of Mines in that there are spatially separated active regions – only discordant alternation was seen in 80% of the hearts studied (Pastore & Rosenbaum, 2000). Ventricular arrhythmias once again started up only if discordant alternans had appeared, being again initiated in areas neighbouring the nodal line, but with the incidence of ventricular tachycardia now predominating over that of ventricular fibrillation (70% *vs.* 30%). In 14/19 patients without structural heart disease who underwent electrophysiological testing for supraventricular arrhythmias, recordings from two sites showed concordant alternans during incremental

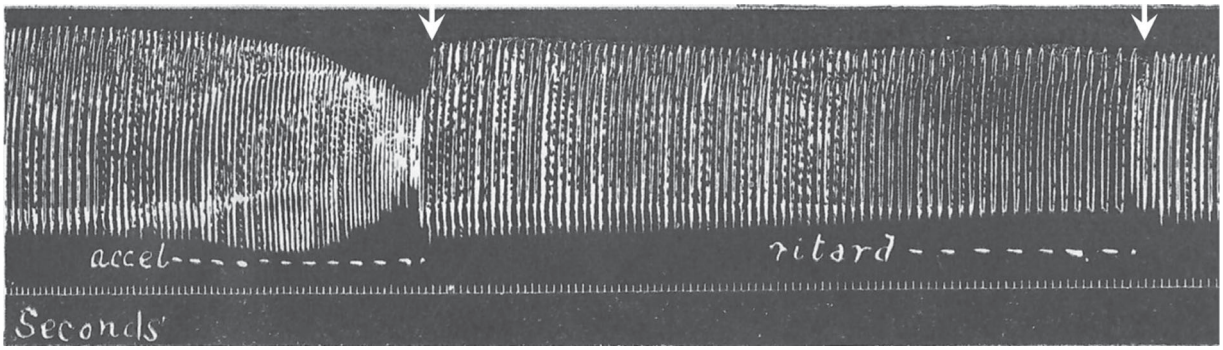

Figure 4. Kymograph recording of contractile activity in atropinized frog ventricle
Conversion of 1:1 rhythm into 2:1 rhythm (first arrow) as stimulation frequency increases ('accel'), followed by conversion back to 1:1 rhythm (second arrow) as stimulation frequency decreases ('ritard'). The stimulation frequency at which 1:1 rhythm is lost is higher than that at which it is regained, thus demonstrating hysteresis. Figure 16 of Mines (1913) with arrows added.

fast atrial pacing (Hiromoto *et al.* 2005). Moreover, in 13 of these 14 patients, discordant alternans was seen with a further increase in pacing frequency, and 8 of these 13 patients then went on to show atrial fibrillation.

In this much more recent work on fast pacing, there is no mention of the existence of 2:1 block, as in Mines's work – instead, there is a beat-to-beat alternation in the morphology of the action potential at each site mapped in the ventricle. While Mines did make several electrogram recordings of alternans in an earlier paper (Mines, 1912), electrical activity was not recorded in the experiments of Figs 4–6 above, and so the mechanisms at the cellular level underlying the various 2:1 and 2:2 rhythms seen by him are not at all clear. Mines himself had appreciated that mechanical and electrical responses could be quite different, mentioning, e.g. that there were occasions when there was electrical alternans, but no mechanical alternans (Mines, 1912). In the discordant 2:1 rhythm of Fig. 6 (bottom right), the most likely possibility is that there was decremental conduction of the action potential in branch A or B on alternate stimuli, with concurrent successful conduction down the other branch. In that case, in the branch with decremental conduction, there is a fall in the size of the action potential as one progressively moves down the propagation pathway, culminating in block. One would therefore see an alternans or 2:2 rhythm in which the action potential morphology alternates from beat to beat at sites more proximal in the pathway of block, and a 2:1 rhythm of block at sites more distal. In this scenario, had Mines been able to record action potentials along branches A and B during discordant 2:1 rhythm, he would have seen a discordant 2:2 rhythm proximally in branches A and B, and a discordant 2:1 rhythm more distally.

Alternans and period-doubling bifurcations. At the very start of the section on 'Alternation' in his 1913 article, Mines pointed out that Gaskell's mechanism to generate alternans (a portion of the heart being in 1:1 rhythm, with another portion being in 2:1 rhythm) does not imply that all the cells in 2:1 rhythm need to be in phase with one another, and went on to design an experiment to confirm this contention (Fig. 6). But neither Mines nor Gaskell entertained a competing hypothesis, that there might be intrinsic alternation in a single cell.

Perhaps the first clear evidence pointing towards the possibility of alternans in a single cell became available with the advent around 1950 of recording of the action potential with a sharp glass intracellular microelectrode in a multicellular preparation: such a recording can show beat-to-beat alternation of action potential morphology (e.g. Hoffman & Suckling, 1954). However, this is not firm proof of 'intrinsic' or 'primary' alternans, since there is electrotonic communication between cells in multicellular tissue. Mines had quoted Gaskell: 'Owing to some cause which affects the ventricle unequally, the excitability of the ventricular muscle is at the time not absolutely the same throughout, so that,

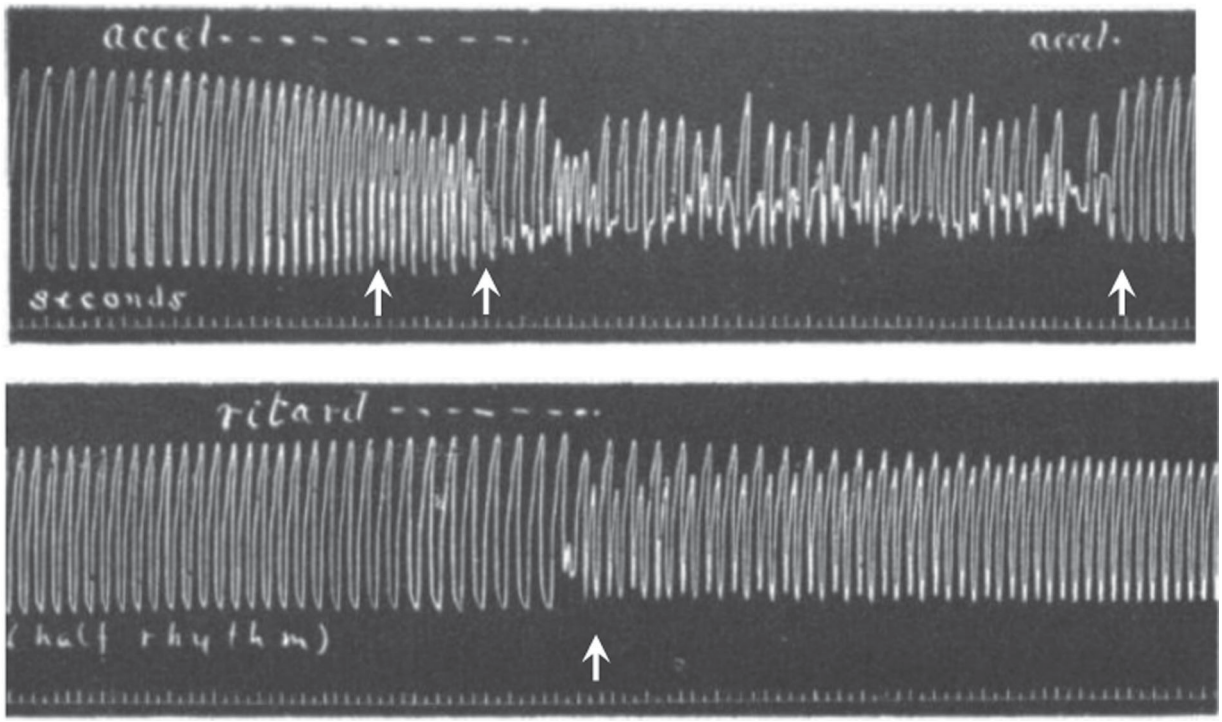

Figure 5. Kymograph recording of contractile activity in atropinized frog ventricle (bottom trace continuous with top trace)
Top, as stimulation frequency is gradually increased (first 'accel' annotation), there is a transition from 1:1 rhythm to alternans or 2:2 rhythm (first arrow), which persists until the second arrow. A second brief phase of further increasing the stimulation frequency (second 'accel' annotation) leads to a 2:1 rhythm (third arrow). Bottom, as stimulation frequency is decreased ('ritard'), the 2:1 'half rhythm' suddenly converts to a 2:2 rhythm (arrow), with the degree of alternation becoming increasingly less pronounced as time proceeds. Modified from original single trace of Fig. 18 in Mines (1913) by splitting into two traces and adding arrows.

although the impulses remain the same in strength, yet certain parts which possess a lower excitability are able to respond only to every second impulse while the rest of the tissue responds to every impulse.' However, if 2:1 block exists, there will be retrograde electrotonic flows of current from the distal segment of the conduction pathway back into the medial part of the pathway that could help to induce alternans there, since that retrograde current flow would be alternating in amplitude and duration from beat to beat due to the presence of a 2:1 rhythm as its source (Guevara, 1988) – i.e. the 'impulse' of Gaskell in the central part of the pathway would itself alternate in strength from beat to beat.

Proof of the existence of alternans in single cells came many decades after Mines's experiments, only after it became possible in the late 1970s to isolate single calcium-tolerant cardiac cells and record their action potentials with suction micro-electrodes. In single rabbit ventricular cells at a high stimulus amplitude, there is a direct 1:1 $\rightarrow$ 2:2 transition and then a direct 2:2 $\rightarrow$ 2:1 transition as stimulation frequency is increased, with 1:1/2:1 and 2:2/2:1 bistability (Guevara *et al.* 1989). At lower stimulus amplitudes, there is a direct 1:1 $\rightarrow$ 2:1 transition, again with bistability and hysteresis, and there can be a transient phase of drifting alternans, reminiscent of Mines's results in Fig. 5 above (Yehia *et al.* 1999). At even lower stimulus amplitudes, there is a transition from 1:1 to n+1:n Wenckebach rhythms and then to 2:1 rhythm (Yehia *et al.* 1997).

Given the above possibilities in terms of the transitions in single cells, and the dependence of the nature of the transition on the stimulus amplitude, the situation in a multicellular piece of tissue offers up the opportunity for very complicated behaviours. For example, should the alternans in the middle part of an inhomogeneous pathway during overall 2:1 block not be in some sense intrinsic to these cells (i.e. not be 'primary alternans'), but due to electronic interactions with more proximal cells in 1:1 rhythm and more distal cells in 2:1 rhythm (i.e. 'secondary alternans'), we are then back to a variant of Gaskell's original hypothesis of a spatially heterogeneous response, with a 1:1 rhythm in some portion of the tissue and a 2:1 rhythm in some other portion of the tissue. Indeed, there is even evidence for a subcellular organization to alternans, with, e.g. spatially discordant alternans of internal calcium level, a prime driver of electrical alternans, being seen within a single ventricular cell (Cordeiro *et al.* 2007). Applying a control method, a single ventricular cell showing a 2:2 electrical rhythm and global concordant alternans of internal calcium level can be turned into a cell showing a 1:1 electrical rhythm but with subcellular discordant alternans of internal calcium level (Gaeta *et al.* 2009).

Nonlinear dynamics provides an alternative interpretation of alternans as resulting from a bifurcation – a qualitative change in the dynamics (i.e. the rhythm) seen as a bifurcation parameter (e.g. the stimulation frequency) is changed. In a space-clamped situation, assuming only the action potential duration (APD) restitution curve, and using an iterative procedure, one can predict that a 2:2 rhythm, in which the action potential alternates on a beat-to-beat basis, will arise out of a 1:1 rhythm as stimulation frequency is increased (Nolasco & Dahlen, 1968). A similar analysis has also been carried out for mechanical alternans (Mahler & Rogel, 1970). Indeed, using this mathematical analysis, both the 1:1/2:1 and the 2:2/2:1 bistabilities mentioned above had been predicted to exist in the quiescent embryonic chick heart-cell aggregate (Guevara *et al.* 1984), but these behaviours were not searched for in that multi-cellular preparation. Using the APD restitution curve and the iterative procedure, and assuming spatial inhomogeneity, one can predict that concordant alternans will be bistable with discordant alternans, in that a well-timed premature stimulus within the 'discordance window' would flip the concordant rhythm to the discordant rhythm (Pastore *et al.* 2006; see also Rubenstein & Lipsius, 1995).

In mathematical terms, the 2:2 rhythm is a periodic orbit that arises out of the 1:1 rhythm via a period-doubling bifurcation (Guevara *et al.* 1984). Such period-doubling bifurcations also occur in extensions of the simple APD restitution model that include 'memory' terms (e.g. Fox *et al.* 2002) and in models in which the alternans hinges on internal calcium cycling (Shiferaw *et al.* 2003). In multicellular preparations in which there is conduction of the action potential, the interactions between restitution of the conduction velocity and the restitution of APD can lead to a wealth of complex dynamic phenomena, many of which have been observed in experimental and theoretical models (Courtemanche

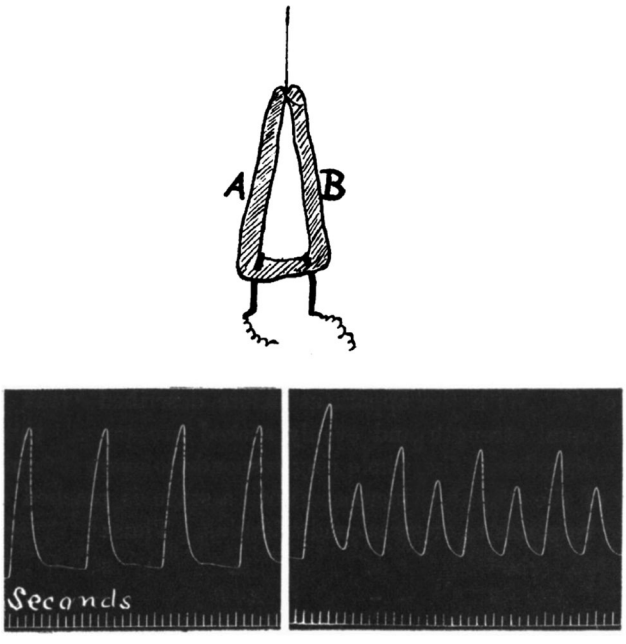

Figure 6. Kymograph recording of contractile activity in a ring of tortoise auricle
Top, the ring of tortoise auricle. Bottom, a kymograph recording of contractile activity in the ring shows that a well-timed extrastimulus flips the spatially concordant 2:1 rhythm (left) into a spatially discordant 2:1 rhythm, producing a 2:2 or alternans rhythm in the ring (right). Top and bottom panels are Figs. 20 and 21 respectively in Mines (1913).

et al. 1993; Echebarria & Karma, 2002; Weiss *et al.* 2006). In particular, the discordant alternans provoked by fast pacing of the ventricle can be due to various combinations of several factors: APD restitution, conduction velocity restitution, memory effects, calcium cycling, and tissue heterogeneity (Hayashi *et al.* 2007; Mironov *et al.* 2008). Strong supporting evidence for dynamic instabilities associated with period-doubling bifurcations has also been provided by experiments in which stimulation schemes have been devised that control experimentally observed alternans rhythms based on the assumption that a period-doubling bifurcation is responsible for generating alternans (Hall *et al.* 1997; Christini *et al.* 2001; Gaeta *et al.* 2009). In experiments involving fast pacing, 4:4 and 8:8 rhythms have been described (see Gizzi *et al.* 2013 and references therein) leading to the suggestion that ventricular fibrillation might be chaos arising from a cascade of period-doubling bifurcations.

Alternans and the onset of ischaemic ventricular tachyarrhythmias. Alternans is very commonly seen in the ventricle following acute coronary artery occlusion and following reperfusion, and frequently precedes malignant ventricular arrhythmias. There has thus been great interest in using various indices of T-wave alternans as a predictor of cardiovascular risk (e.g. Quan *et al.* 2014; Verrier & Malik, 2015). Recording of the action potential reveals areas of the ventricle in which there is a beat-to-beat alternation in the morphology of the action potential (Downar *et al.* 1977; Hashimoto *et al.* 1984*a*,*b*; Carson *et al.* 1986; Abe *et al.* 1989; Martišienė *et al.* 2015). During acute myocardial ischaemia, a premature ventricular contraction (PVC), the compensatory pause following such a PVC, or an intentional pause in stimulation can initiate a phase of alternans or make alternans cease (Hellerstein & Liebow, 1950; Kataoka & Yoshimura, 1979, Dilly & Lab, 1988). Both spatially concordant and spatially discordant alternans can be seen at different times as ischaemia progresses in a given ventricle (Hellerstein & Liebow, 1950; Downar *et al.* 1977; Hashimoto *et al.* 1984*a*,*b*; Konta *et al.* 1990; Martišienė *et al.* 2015). Concordant alternans, and more so discordant alternans, presages the transition to malignant ventricular arrhythmias such as ventricular tachycardia and fibrillation (Downar *et al.* 1977; Konta *et al.* 1990; Tachibana *et al.* 1998; Nearing & Verrier, 2002). As in the experiments on fast pacing of the non-ischaemic ventricle summarized above, the site of conduction block that initiates re-entry during discordant alternans lies close to the nodal line separating the two regions of out-of-phase alternans, where there are steep repolarization gradients (Konta *et al.* 1990; Tachibana *et al.* 1998). The sudden increase in alternans magnitude that is seen following a suitably timed spontaneous or induced PVC, after the subsequent compensatory pause, or after an intentional pause in stimulation is due to a flip from discordant to concordant alternans (Downar *et al.* 1977; Hashimoto *et al.* 1984*a*,*b*; Dilly & Lab, 1988). As ischaemia progresses, the alternans initially seen at sites lying deeper within the ischaemic zone typically progresses on to 2:1 block (Downar *et al.* 1977; Hashimoto *et al.* 1984*a*; Carson *et al.* 1986; Abe *et al.* 1989; Martišienė *et al.* 2015). There is thus a very close connection between the concordant alternans, the discordant alternans, and the bistability between these two rhythms that is seen during ischaemia and that which was described by Mines. This contribution of Mines has passed completely unrecognized. There is also beginning to be an accumulation of evidence for alternans playing a role in the initiation of atrial fibrillation (Hiromoto *et al.* 2005; Narayan & Zaman, 2016 in this issue).

Long QT syndrome

The long QT (LQT) syndrome refers to the situation in which the QT-interval is abnormally prolonged. This is significant clinically because patients with a prolonged QT-interval have an increased risk of sudden cardiac death. The recognition of the significance of the LQT syndrome came first in 1957 (Jervell & Lange-Nielsen, 1957) and then in 1963 (Romano *et al.* 1963), long after Mines's death (for reviews see Morita *et al.* 2008; Roden, 2008; and Schwartz *et al.* 2012). The LQT syndrome may occur as a consequence of mechanisms that increase the inward sodium and calcium currents during the action potential or decrease the outward potassium currents that lead to the repolarization of the cardiac cells. Drugs that lead to decreased potassium currents and consequently longer APDs are potentially arrhythmogenic. Since many drugs potentially have such effects, this places a large burden on drug developers and government entities that certify the safety of new medications (Nachimuthu *et al.* 2012). As reviewed by Roden (2016) and by Foo *et al.* (2016) in this issue, mutations that lead to decreased functional expression of potassium channels, particularly the hERG channel, have now been identified. The possibility of identifying genetic abnormalities provides a new prospective for diagnosis and therapy, especially as it is likely that some mutations may lead to lethal arrhythmias only in particular contexts. For example, genetic mutations may lead to arrhythmias after administration of only certain specific drugs, during increased sympathetic activity or exercise.

There are several different mechanisms by which the LQT syndrome could lead to lethal arrhythmias. As discussed above, the APD plays a key role in the determination of 2:1 block and alternans via a period-doubling bifurcation, and discordant alternans is seen in animal models of LQT2 and LQT3 syndromes (Chinushi *et al.* 2003; Ziv *et al.* 2009). Although alternans is often observed in patients with LQT syndrome, understanding the physiological mechanisms underlying this phenomenon remains an important research direction (Chinushi *et al.* 1998). In experimental work, prolongation of the APD can also lead to early afterdepolarizations of the action potential. If an early afterdepolarization in a region of the heart leads to a PVC, this might play a role in the induction of arrhythmia (Weiss *et al.* 2010), via the re-entrant mechanisms described by Mines. Limited analysis of the patterns of PVCs in patients with sudden cardiac death are consistent with this possibility (Lerma *et al.* 2007).

Emerging areas and prospects

The Mines symposium also addressed emerging areas in which new technologies are offering prospects of advances that were not anticipated by Mines. We briefly discuss personalized medicine, genomics, optogenetics and stem cells.

The term personalized medicine generally refers to the application of genomic data to help individualize diagnosis and therapy. In many situations, single gene mutations are associated with disease. In the context of the LQT syndrome, genomics is also having an impact on clinical cardiology (Roden, 2016 in this issue). We anticipate that further advances will help identify

additional mutations that predispose to arrhythmias or other types of heart disease. Improved genetic knowledge may also prove useful in identifying appropriate drugs for a given individual. The concept of precision medicine can also be extended to analyse the dynamics of arrhythmias in individuals, with a view to improving diagnosis and therapy (Lerma & Glass 2016, this issue).

The development of powerful means for data collection, analysis and simulation offers the possibility for the development of insight into the physiological and anatomical substrates for arrhythmias in individual patients. Using computed tomography scans of the thorax and electrocardiographic body surface mapping, Wang *et al.* (2011) gained insight into the anatomical circuits underlying tachycardias in individual subjects. This approach provides methods for targeting sites for ablation that are complementary to traditional mapping techniques. In a similar vein, in this issue Trayanova & Chang (2016) describe how one can use MRI mapping, combined with computer simulation, to determine the risk for ventricular tachycardia and fibrillation and to help guide ablations in the clinic, while Jacquemet (2016) discusses modelling of six different targets for ablation in atrial fibrillation. The increased fluctuations seen as one approaches a period-doubling bifurcation have been very recently considered in two situations using interventions that are capable of provoking arrhythmias: fast pacing (Prudat *et al.* 2016 in this issue) and administration of a potassium channel blocker (Quail *et al.* 2015). In a perspective on the former article in this issue, Vandenberg & Hill (2016) suggest that analysis of cardiac alternans might be useful in improving management of patients at risk for sudden cardiac death.

The characterizations of cardiac electrophysiological activity at the tissue or cellular levels have long depended upon the use of extracellular, intracellular and patch electrodes. However, these techniques tend to be invasive with limited or no spatial resolution, and recording typically cannot be carried out repeatedly over extended periods of time. Over the past two decades the study of cardiac electrical activity and the generation of arrhythmias in the intact heart and in model cardiac systems have greatly benefited from the implementation of optical mapping of excitation using voltage- and calcium-sensitive dyes. However, there are limitations with this approach due to the properties of these dyes and a lack of our ability to perturb the dynamics of these systems by precisely modulating electrical activity. Recently, the 'optogenetics' approach has been introduced, which involves the genetic modification of tissue to express light-sensitive ion channels that can perturb membrane potential (Boyden *et al.* 2005; Nagel *et al.* 2005; Deisseroth *et al.* 2006). In parallel, genetically encoded calcium and voltage sensors have been developed that permit repetitive high-resolution recording of electrical activity from cardiac tissues. As discussed by Entcheva & Bub (2016) in this issue, the combination of new methods for optogenetic actuation and simultaneous fast, high-resolution optical imaging offers the potential for unprecedented insights into cardiac excitation wave dynamics. In modelling work, estimating parameters of ionic models has always been a challenge. In this issue, Krogh-Madsen *et al.* (2016) describe the use of specially designed experimental protocols and global search heuristics to tease out relevant model parameters. The personalization of electrophysiology is a natural extension of the work already performed on personalization of anatomical structure.

While there has been considerable progress in treating heart disease, the challenge of managing heart failure remains enormous. Stem cell therapy has emerged as a potentially exciting approach to achieve human heart regeneration and treat heart failure, but there remain numerous unresolved matters concerning optimal therapeutic strategies. Ischaemic cardiomyopathy is involved in the most common form of heart failure in which myocardial infarction compromises cardiac function. As Mount & Davis (2016) discuss in this issue, there have been multiple candidate stem cell types used in an attempt to regenerate damaged tissue in ischaemic cardiomyopathy. While they point out the pitfalls encountered with the regenerative approach, they also highlight the exciting potential for the next generation of cell therapies.

In conclusion, in the hundred years since Mines's death, there has been a great deal of progress in our understanding of cardiac electrophysiology and of cardiac arrhythmias. While Mines's ideas about the vulnerable period and re-entrant rhythms permeate the literature, his findings on 1:1/2:1 bistability and on concordant/discordant 2:1 rhythms and alternans are much less well known. With the recent upsurge of interest in alternans (especially that of the much more arrhythmic discordant type), we have come full circle, at least in terms of the dynamical underpinnings of these rhythms, and Mines's long forgotten insights might very well guide future studies to improve our present understanding of these behaviours.

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Additional information

Competing interests

None.

Author contributions

The majority of the first draft of the MS was written by M.R.G. with subsequent additions and editing by L.G., A.S. and J.O. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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