When Jan Fiolet and Michiel Janse first approached me in 1996 about the idea of putting together a focused issue of *Cardiovascular Research* on the theme of ‘Calcium and Heart Failure’, I must confess that I accepted this task with some hesitation. First of all, I thought the theme was rather narrow and doubted that there would be enough interest in the community to justify the issue. I am glad to admit that, as the present issue proves, I had severely underestimated the general level of interest in this topic. Secondly, I perceived myself as having contributed relatively little to our understanding of the topic of the proposed issue. In this regard I was comforted by the participation of two genuine pioneers in the field, Dirk Beuckelmann and Philip Poole-Wilson, as fellow Guest Editors. The success of this issue is attributable in no small measure to their outstanding efforts. Finally, I anticipated the worst in terms of deadline compliance and the many other headaches of editorship. Such fears were groundless, as the editorial team in Amsterdam served very ably and insulated me and the other Guest Editors from most of the day-to-day work.

What, then, is the state of the art with regard to calcium and heart failure? A more general way of asking the question is: How is contraction abnormal in heart failure, and what are the mechanisms that bring about and perpetuate these abnormalities of contraction? Although this issue attempts to put our understanding of this topic into a balanced perspective, it is important to recognize that there is as yet no clear and compelling answer to this central question. Human heart failure, at least in its advanced stages, produces a phenotype with many shared features (notably pulmonary congestion and decreased exercise tolerance) but also many important individual distinctions. Some patients waste away to the point of cachexia, while others remain robust. Some exhibit profound chamber dilatation and systolic dysfunction but preserved exercise tolerance, while others are crippled with only modestly reduced ejection fractions. Such differences among patients might in principle reflect individual differences in calcium cycling, although I think it is more likely that differences in systemic adaptation (or maladaptation) dominate the disease phenotype. Thus, the central issues regarding abnormalities of contraction may not be as elusive as are the differences in signs and symptoms. Unfortunately, our ability to study the fundamental biology of human heart failure is severely limited by the obvious ethical considerations surrounding access to the tissue. Virtually all the specimens available are from explanted hearts removed at the time of transplantation, a time at which cause and effect may be particularly difficult to distinguish. Nevertheless, I find it remarkable and gratifying that so much has been learned despite the obvious difficulties of accessing and working with human tissue.

Although many animal models of heart failure exist, it is fair to say that none is universally accepted as a faithful model of chronic heart failure in the human. Each model can be argued to have its own set of strengths and limitations, but eternal truths may remain elusive if we are to rely on such models.

Given these realities, what generalizations can be made? First, action potentials are prolonged in the failing heart. This is true not only in human cardiomyopathy but also in virtually every animal model of hypertrophy and failure (see the Nabhauer and Kaab review [1]). The increase in action potential duration, coupled with tissue remodelling, produces an arrhythmogenic substrate which may account for the high incidence of sudden death in heart failure. Here, Wickenden et al. [2] put a new spin on the action potential prolongation by proposing that it may actually perpetuate the heart failure process. Secondly, the prolongation of action potentials parallels (and may cause, at least partially) a general prolongation of calcium transients in failing myocardium. Most studies have found that basal calcium currents are not much changed in heart failure, although several papers in this issue (Mukharjee et al. [3] and Handrock et al. [4]; see also the review by Richard et al. [5]) challenge this conventional wisdom. Third, most observers will grant that there is something wrong with the sarcoplasmic reticulum in the failing heart; relaxation is delayed, and calcium entry may be less efficacious in evoking calcium release. This area is one of particular controversy, as summarized in various excellent reviews in this issue (Movsesian and Schwinger [6]; Hasenfuss [7]; Phillips et al. [8]; Balke and Shorofsky [9]). Fourth, virtually everyone that has looked for it has found a significant...
upregulation of the Na/Ca exchanger in failing myocardium (see Hasenfuss [7]); the functional consequences are just beginning to be explored (e.g., Mattiello et al. [10]). Finally, the myofilaments themselves may be culpable for at least part of the dysfunction, as reviewed by de Tombe [11] and by Schaub et al. [12]).

Without further ado, I am proud to introduce this focused issue. It is my sincere hope that it will help not only to synthesize our current knowledge, but more importantly that it will keep us humble. Let it inspire our rededication to exploring the vast uncertainties which remain in understanding this most lethal of modern human ailments.

Eduardo Marban, for the Guest Editors.

References