What becomes of the brokenhearted?

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I'm searching though I don't succeed,
But someone look, there's a growing need.
Oh, he is lost, there's no place for beginning,
All that's left is an unhappy ending.
Witherspoon, Riser and Dean

This Motown hit by Jimmy Ruffin from the summer of 1966 is one of my all-time favorites and provides the ideal introduction, summary, and conclusion for this issue of *Heart and Metabolism* that is devoted to the subject of the prevention of left ventricular remodeling.

Remodeling of the heart is broadly divided into physiological and pathological. Physiological remodeling encompasses the normal developmental growth of the heart as the rest of the body grows (eutrophy), in addition to the hypertrophy (increase in heart muscle mass with respect to body weight) that accompanies ''healthy'' stresses such as pregnancy and frequent exercise. It is generally accepted that, during physiological remodeling, the cellular and extracellular components of the heart remain normal and the process is therefore completely reversible. Thus heart size has been documented to increase and decrease without any decrement in function during bed rest, weightlessness, and seasonal athletic training. In contrast, pathological remodeling is the term used to describe the complex alterations in the cellular and extracellular components of the heart that occur in response to pathological ''unhealthy'' stresses – predominantly, hypertension and ischemic heart disease. It is this latter form of irreversible left ventricular remodeling, characterized by interstitial fibrosis, that is the focus for this issue.

As hypertension is treated more aggressively, the etiology of pathological remodeling has changed. Thirty to forty years ago, the principal cause was hypertension. However, since the mid-1990s, the main underlying causes have been myocardial ischemia and infarction. Obviously, these conditions commonly co-exist.

In survivors of acute myocardial infarction, prognosis and the symptoms of heart failure are principally determined by left ventricular size. At any particular timepoint after infarction, left ventricular size is determined by the interplay of processes that: precede infarction (such as hypertension, valvular heart disease, and previous myocardial infarction); coincide with infarction (such as the location, size, and transmurality of the infarct, and the success/rapidity of reperfusion); and follow infarction (such as hypertension, valvular disease, and neurohormonal activation).

Largely as a result of the complexity and temporal interplay of these factors, it is difficult to separate the influence that the process of healing has on ventricular shape and size from other events occurring before, during, or after infarction. However, it seems likely that as many as 30% of patients surviving anterior myocardial infarction develop progressive left ventricular dilatation and eventual heart failure

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as a consequence of adverse left ventricular remodeling. This issue of *Heart and Metabolism* focuses on the description, measurement, and manipulation of these processes.

The new ''Hot Topics'' section includes a short summary of the features of left ventricular remodeling and the strategic points in its natural history at which interventions have been shown to be of benefit. This overview by Dr Huqi provides an excellent starting point from which to explore the role of the renin–angiotensin–aldosterone system (RAAS) that is the focus of the Main Clinical Article by Drs Morrone and Marzilli. Their article provides an excellent refresher of the basic biology, in addition to an overview of the pivotal outcome studies involving manipulation of this system early after myocardial infarction and later in the remodeling process once symptoms of heart failure are established. Although the role of the RAAS has been well established through clinical trials, there are biological processes, believed to be of crucial importance, for which there are no specific therapies.

In their New Therapeutic Approaches article, Drs Frantz and Bauersachs discuss an evolutionarily very primitive immune recognition system based on Toll-like receptors (TLRs). These receptors are present, not only on cells of the immune system, but also on cardiac myocytes, where they are designed to recognize the molecular characteristics of pathogens directly. Unfortunately, the receptors also recognize damage-associated molecular patterns and trigger responses that harm, rather than protect, the heart. TLRs have not yet been specifically targeted in patients post myocardial infarction, although some of the relevant downstream kinases, for example p38 mitogen-activated protein kinase, are under investigation in Phase 2 studies and are known to lead to programmed cell death. This is the topic reviewed by Dr Foo, who provides a very detailed overview of the processes that lead to apoptosis*. It is quite possible that β-blockers and angiotensin-converting enzyme inhibitors have an impact on apoptosis but, as yet, as in the case of TLRs, no drugs that specifically target the cell death pathway have demonstrated success in clinical trials.

It is likely that the process of remodeling shows individual variability as a result of patient-specific biology. Currently, most of these biological processes go unrecognized because we lack the tools to distinguish them. Drs Coelho-Filho, Kwong and Jerosch-Herold provide a state-of-the-art overview of cardiac magnetic resonance imaging and how it can be used to gain better understanding of the processes leading to pathological remodeling in an individual patient. One such process that can be recognized early after myocardial infarction by means of gadolinium-based contrast agents is microvascular obstruction within the zone of infarction. This seems to predict subsequent poor healing, and probably identifies patients in whom it is particularly important to uptitrate medications to their full evidence-based dose. The advantages of cardiac magnetic resonance imaging are further reinforced in the striking case report, by Drs Nijveldt and van Rossum, of a patient in whom extensive microvascular obstruction within an anteroseptal ST-segment elevation myocardial infarction predicted early and marked adverse remodeling.

As illustrated in this issue, we understand more and more about the biology underlying pathological remodeling. Moreover, imaging techniques are fast evolving, which will help us identify these processes and discover those at risk. As this story of discover unfolds . . . all that's left is a happy ending.

*see glossary for definition of this term.