The birth of modern science was ushered in by the great intellectual revolution that occurred during the Renaissance, when irreligious thinkers began to question centuries-old dogmas imposed on the populace by an establishment of savants intent on maintaining their supremacy. The proclivity of erudite oligarchies to enforce dogmas, however, did not vanish after the Renaissance, as documented by many instances in which innovative scientists were subjected to great hardship for daring to challenge existing paradigms. Indeed, the history of science, far from being a smooth evolutionary process, has been punctuated by a series of revolutions, big and small. It seems likely that the everlasting conflict between the attempts of intellectual elites to maintain their power through the promulgation of axioms and the insuppressible drive of the free mind to verify the veracity of ideas will continue as long as human nature remains what it is.

A veritable revolution is now unfolding in the field of cardiac biology, where a fundamental tenet that has been venerated for several decades, namely, that the heart is a postmitotic organ incapable of regeneration, has come under attack of late. According to this dogma, the number of cardiac myocytes we are born with is all we will have for the rest of our lives; if myocytes die (e.g., as the result of infarction), they cannot be replaced. This rather bleak doctrine has been challenged for 20 years by the observations of Anversa et al. (1–3), which have laid the foundation and provided the ammunition for the present revolution in cardiac regeneration. The spark that ignited the fire came in 2001, at the dawn of the new millennium, when Orlic et al. (4) demonstrated that bone marrow (BM) cells can reconstitute infarcted myocardium in mice. Since then, research has moved at lightning speed. A year later, Strauer et al. (5) reported that BM cell transplantation improves cardiac function in patients with acute myocardial infarction (MI) and within months a deluge of clinical studies (6–11), including a randomized clinical trial (12), suggested that BM cell therapy exerts beneficial effects in various subsets of patients with ischemic heart disease (13). The flood gates had opened. The rapidity with which the basic observations of Orlic et al. (4) have been translated into clinical studies is unprecedented. Almost overnight, the approach to acute MI and heart failure has changed, and the focus has shifted on trying to achieve what was previously unthinkable (according to the dogma): To reconstitute dead myocardium.

In this issue of the *Journal*, Strauer et al. (14) broaden the revolution by describing the results of intracoronary administration of autologous BM mononuclear cells in 18 patients with chronic transmural MI. They found an improvement in regional and global left ventricular function and in exercise capacity, associated with an increase in perfusion and glucose uptake in the infarcted region. The first trial of BM cells in chronic ischemic cardiomyopathy was performed by Perin et al. (7). That study used percutaneous transendocardial injection of BM cells and provided encouraging results, as did other investigations (8,9). The importance of the present study (14) lies in the fact that it used the intracoronary route to perform cellular cardiomyoplasty in patients with chronic ischemic heart disease. Strauer et al. (14) did not observe any complications, such as arrhythmias, restenosis, distal embolism with microinfarction, changes in markers of inflammation, or depressed myocardial function, suggesting that the delivery of BM cells by the intracoronary route is safe. Although these observations are limited by the short follow-up (three months) and the small sample examined (18 patients), they are consonant with those obtained in acute MI, in which the experience accumulated with >170 patients enrolled in various trials worldwide (5,6,10–12,15) supports the safety of intracoronary BM and progenitor cell injection (13). Therefore, in response to those who regard human studies of BM cells for myocardial repair as premature because the mouse data are not consistent (16), one could argue that, given the evidence for safety and feasibility and the preliminary evidence for efficacy (13), it would be unethical to withhold such studies, which have the potential to offer a revolutionary treatment for heart disease, simply because some investigators have reported negative results in the mouse. Even in the mouse, the preponderance of the evidence supports the feasibility of BM cell-mediated cardiac regeneration (13). Besides, as a brilliant thinker once put it, “mice are not people.”
Despite the novelty and potential impact of the observations of Strauer et al. (14), a number of limitations must be recognized. First and foremost, their investigation was not randomized. Because of this, and because of its small size and short-term follow-up, this study is far from providing conclusive evidence for efficacy. It is also unclear whether the analyses of cardiac function and metabolism were blinded. Because patients were not blinded, the results of exercise spiroergometry could have been biased in favor of treatment. Additional assessment of ventricular function by echocardiography or magnetic resonance imaging would have strengthened the conclusions. It would be important to know the exact frequency distribution of various cell types (CD45+/CD14−, AC133+, CD34+) in the mononuclear BM cell preparation that was injected. Finally, it would have been useful to specify the extent of the initial metabolic and perfusion defects (assessed by fluorodeoxy glucose and tetrofosmin uptake, respectively) in the control and treated groups; this would have clarified whether the two groups were comparable before treatment.

The mechanism for the salutary effects of BM cells observed by Strauer et al. (14) remains a matter of speculation. The comparatively greater increase in fluorodeoxy glucose uptake vis-a-vis the increase in perfusion (assessed as tetrofosmin uptake) strongly supports regeneration of myocytes as the basis for the improvement in function. Of the four possibilities put forth by the authors (14) (i.e., transdifferentiation of BM cells into cardiac myocytes, activation of resident cardiac stem cells by BM-derived cytokines, proliferation of residual viable myocytes induced by BM-derived cytokines, and fusion between BM cells and surviving myocytes), the first two appear to be the most plausible. Cardiac stem cells, characterized by Beltrami et al. (17) both in vitro and in vivo and also described by others (18–20), can affect cardiac repair and improvement in function when delivered by the intramyocardial (17) or the intracoronary (21) route and could be activated by BM cells via paracrine mechanisms (e.g., release of growth factors). On the other hand, it is implausible that the fusion between a BM cell and a preexisting myocyte will result in improved function; there is no evidence or theoretical reason to support this conjecture. An additional mechanism to be considered is based on the recent work by Kucia et al. (22), who have found in the BM a pool of CXCR4+/Lin−/CD45−, nonhematopoietic stem cells that express early cardiac lineage markers (Nkx2.5/Csx, GATA-4, and MEF2C) and therefore appear to be committed to differentiation into the cardiac lineage. Kucia et al. (22) proposed that these cardiac progenitors contribute to BM-dependent cardiac regeneration by differentiating into cardiac myocytes and vascular cells, a paradigm that involves neither cell fusion nor transdifferentiation of hematopoietic stem cells.

Asides from their obvious therapeutic implications, the new ideas that are emerging from the current stem cell revolution may explain why the BM is the most protected organ in the body, even more than the brain. It is located deep inside our bones, and as if this were not enough, it is spread in multiple locations so that loss of one bone will not cause loss of function. Why is nature so compulsive in protecting the marrow? Why does hematopoiesis have to be performed inside the bone rather than in the liver or spleen, where it occurs during fetal development? Nature always does things for a good reason. The studies reviewed in this article (5–12,14) support the concept that the BM is a reservoir of stem cells that have the potential to differentiate into cardiac lineage and that may be continually released into the peripheral blood to reach the heart where they contribute to its physiological turnover. Similarly, the BM may be responsible for the turnover of other tissues as well. In this scenario, the BM would be truly our most important organ, the one that needs to be protected most jealously.

In summary, Strauer et al. (14) have made an important contribution to the field of myocardial regeneration by providing evidence that intracoronary administration of BM cells improves cardiac function in patients with chronic ischemic cardiomyopathy. These observations, although intriguing, are still preliminary and need to be validated in future studies. The results of Stau er et al. (14) provide a rationale for more definitive clinical trials, which should have the following features: 1) they should be randomized, double-blind, controlled, and adequately powered; 2) a long follow-up period should be used to document persistent beneficial effects and possible chronic untoward effects (such as neoplasms); and 3) cardiac function should be assessed with state-of-the-art imaging modalities, such as magnetic resonance imaging, in conjunction with assessment of myocardial metabolism and perfusion with positron emission tomography. Despite these notes of caution, however, let us not lose sight of the enormous progress that has been made in just four years since the report by Orlic et al. (4). These are truly momentous times. Old dogmas are crumbling while new ideas are spreading like wildfire. The outcome is uncertain, but we can be assured that in the end the truth will prevail, as it always does in science. If cardiac regeneration is indeed possible, the stem cell revolution will prove to be one of the most significant, if not the most significant, conceptual and therapeutic advances in cardiovascular medicine.

Reprint requests and correspondence: Dr. Roberto Bolli, Division of Cardiology, 550 South Jackson Street, 3rd Floor, Ambulatory Care Building, Louisville, Kentucky 40292. E-mail: rbolli@louisville.edu.

REFERENCES