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SUCCESSFUL, NEUTRAL, OR NEGATIVE?

To the Editor:

Noiseux and colleagues¹ have reported the successful completion of the coronary artery bypass grafting (CABG) study Implantation of Autologous CD133+ Stem Cells in Patients Undergoing CABG (IMPACT-CABG), in which 19 patients underwent CABG combined with intramyocardial injection of CD133+ bone marrow cells and 14 underwent CABG combined with placebo treatment. The trial is considered a success because cell isolation and delivery were safe and feasible. Although left ventricular function was not influenced by cell therapy, a larger-scale trial with a higher cell dose is planned to demonstrate therapeutic efficacy. In addition, Menasché² provided an elegant commentary, in which he identified lessons that we can learn from this “neutral” outcome.

I have been involved in clinical evaluation of this concept since 2001, and I thank Noiseux and colleagues¹ for acknowledging these efforts. Through the years, however, I have come to view the “success” of this therapeutic approach differently. Clearly, no harm is done by injecting CD133+ cells, and the isolation process has become even simpler and quicker with the CliniMACS Prodigy system (Miltenyi Biotec Inc, Somerville, Mass).³ Ultimately, however, a complex and costly novel therapy should also have a relevant impact on patient fate. In my group’s initial trials at Rostock University,⁴ we indeed observed a difference in left ventricular function between the treatment and control groups. In those early days of cardiac cell therapy, however, with the local ethics board faced with something entirely new and potentially very dangerous, placebo injection was not performed and control patients did not undergo bone marrow aspiration (so that the trial was not blinded), and the random stratification process was modified during the enrolment phase. Subsequently, we conducted another similar trial in Berlin, this time

with a true randomized, controlled trial design, and no longer was any effect on global left ventricular function observable.⁵ Some incremental changes in regional perfusion were detected by magnetic resonance imaging, and some in wall motion were detected by echocardiography; however, these changes clearly did not influence the overall outcome.

Personally, I believe that this concept should not be pursued further. The cardioregenerative potency of bone marrow cells expressing this antigen does not suffice. Results of the multicenter Intramyocardial Transplantation of Bone Marrow Stem Cells in Addition to Coronary Artery Bypass Graft (CABG) Surgery (PERFECT) trial, which was terminated early, and a trial from Tehran still await publication, but even if those happened to show a small difference in left ventricular ejection fraction with a matching *P* value, I would not be convinced. As discussed by Moyé,⁶ the “Proteus effect” describes the situation in which “early results in a new field commonly overstate the true effect size, which is itself moderated in subsequent research efforts.”⁶ If the early results are at best “neutral”, if not negative, how would larger trials change that? How long should we continue to promote an experimental therapeutic concept that appears conceptually attractive but lacks solid evidence of therapeutic efficacy? This kind of investigator-driven research is extremely arduous, and I congratulate Noiseux and colleagues¹ for pulling it through and adding to the “neutral” evidence. At some point, however, we should just cut our losses and move on to testing more promising concepts.

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