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## Bone marrow transplantation for the heart: fact or fiction?

See pages 45, 47

Substantial advances in the past three decades, including risk-factor modification, use of anticoagulants and antiplatelet agents,  $\beta$  blockers, angiotensin-converting-enzyme inhibitors, and effective percutaneous and surgical revascularisation, have reduced the mortality and morbidity of ischaemic heart disease and resulting left ventricular dysfunction. However, heart disease remains the leading cause of death in the west. Furthermore, the progressive nature of ischaemic heart disease, late failures of venous bypass grafts, and restenosis after percutaneous intervention have resulted in an increasing number of patients who are no longer candidates for standard percutaneous or surgical revascularisation yet remain symptomatic on maximum medical therapy. Therapeutic angiogenesis or myogenesis may have a role in these patients who have exhausted all available treatment options, the former aimed at restoring blood flow to ischaemic myocardium and the latter at repopulating contractile elements of the myocardium.<sup>1</sup>

A significant body of in-vitro and preclinical data suggests that angiogenesis and myogenesis are feasible and indeed occur spontaneously. However, clinical trials to date using protein or gene therapy to deliver angiogenic cytokines, such as members of the fibroblast growth factor and vascular endothelial growth factor families, have been disappointing. Although the results of early studies appeared promising, a larger randomised double-blind study showed no benefit over placebo.<sup>2–7</sup> This brought to light several issues: first, angiogenesis may be too complex a process to be stimulated effectively with a single angiogenic cytokine; second, angiogenesis and myogenesis therapies may result in small benefits that may not be detectable using currently available outcome measures, necessitating the development of novel endpoints; third, delivery strategies have to be optimised and tailored for individual agents and cells to which they are delivered; fourth, and most importantly, the placebo effect is very powerful in end-stage ischaemic heart disease and has a physiological effect seen as improvement in myocardial perfusion and function.<sup>2,3</sup> The perceived complexity of the angiogenic process prompted the evaluation of master-switch molecules such as the hypoxia inducible factor (HIF)-1 $\alpha$  transcription factor and the investigation of cellular therapies using skeletal myoblasts, bone marrow, and bone-marrow-derived, circulating, or embryonic stem cells.<sup>8–12</sup>

The use of bone-marrow-derived cells as stimulators of angiogenesis or myogenesis is the focus of two reports in

this issue of *The Lancet*. The two research teams used different bone-marrow populations and different delivery methods to conduct feasibility studies of this strategy. Hung-Fat Tse and colleagues studied percutaneous delivery (via the Biosense Electromechanical NOGA mapping catheter) of autologous bone-marrow-derived mononuclear cells as sole therapy in eight patients with stable angina. Christof Stamm and colleagues injected AC133+ cells (obtained by magnetic cell separation and which contain a sub-population of CD45– stem cells with angiogenic potential) along the infarct border zone at the time of coronary artery bypass in six patients with recent myocardial infarction.

Only preliminary conclusions can be derived from these studies at present. The number of patients is too small to derive any meaningful efficacy and definitive safety data. However, intracardiac injections of autologous bone marrow appear to be feasible and relatively safe. As expected from previous studies, most patients had significant improvement in symptoms and many had improvement in physiological variables such as regional wall motion and target area perfusion. Although the sole therapy study of Tse and colleagues is not confounded by revascularisation of adjoining areas seen with the coronary artery bypass-plus study of Stamm and colleagues, the placebo effect in both studies precludes any conclusions about efficacy. No data are available about cell survival following intra-myocardial needle injection, and if the implanted cells did survive whether they differentiated along the cardiac myocyte or endothelial lineage. The cellular composition of bone-marrow-derived cells is quite variable, an issue that needs to be taken into account in assessing the results of future studies. Finally, additional significantly larger randomised placebo-controlled double-blind studies with mechanistic and clinical endpoints are warranted.

Cell-based investigational therapies for ischaemic heart disease and congestive heart failure have come of age. The promise of such therapy lies in the use of stem cells (circulating or bone-marrow-derived, pluripotent or endothelial progenitor cells) to promote angiogenesis or myogenesis. Cell transplantation may also provide a potential mechanism for gene transfer, enabling regulatable and sequential expression of transgenes of interest. However, additional pre-clinical studies are also needed to define which cell types are administered, the extent to which these therapies truly lead to angiogenesis or myogenesis, and the optimal delivery method. One particular limitation of using autologous adult stem cells in the setting of myocardial infarction is the delay associated with harvesting, and re-administration of the cells, which may significantly diminish the likelihood of a therapeutic benefit in the infarcted tissue. Wherever this field takes us, it is likely to follow the well-known pathway of incredible results in the setting of unrealistic expectations followed by disappointments and cautious optimism.

There is the opportunity with stem-cell therapy to alter this pathway at its onset by prescribing a healthy dose of scepticism to accompany a realisation of the promise of such therapies for patients with cardiovascular disease.

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## Nestlé's own goal

The Swiss multinational food giant, Nestlé, committed last week what may become known as the public-relations blunder of the decade. Nestlé shocked many by demanding from Ethiopia return of US\$6 million that the company feels it is owed as “a matter of principle”. In 1986, Nestlé had bought the parent of a German company which the Ethiopian Government had nationalised in the 1970s. The Government had offered Nestlé US\$1.5 million (at today's exchange rates) as compensation, but the company, using the exchange rate at the time of nationalisation, says the debt is now US\$6 million.

The furore began on Dec 18 in an Oxfam press release highlighting Nestlé's demand for the US\$6 million. Seemingly, this led to a mellowing from the company, who responded by saying that they are “very flexible about timing, the amount, and modalities, but are not flexible about the principle”. Nestlé also said that it will invest the proceeds in Ethiopia in a project that will benefit the country. A Nestlé spokesperson told *The Lancet* that the news release by Oxfam was “totally unfair” and that it was the Ethiopian Government who had raised the issue in 2001, before when the company had not made any claim.

In Ethiopia (see *Lancet* 2002; **360**: 1952), one of the world's poorest countries, the gross national income per head is US\$100, life expectancy is 44 years, and the infant mortality rate per 1000 livebirths is 117. Oxfam says that the US\$6 million Nestlé wants would provide safe water for 1.5 million families or anti-diarrhoeal medicines for 750 000 children in Ethiopia. Nestlé made profits of US\$3.9 billion last year. Christmas comes but once a year, Nestlé.

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## Lancet Correspondence: old letters, new rules

Why does a letter to the editor pertaining to a paper published in April appear in the last issue of October? This is frustrating for authors and editors alike.

We receive up to 60 letters per week, about a third of which can be squeezed into the columns of the journal. Most of these letters are commenting on a paper published in the journal in recent weeks, and many warrant some sort of response from the authors of that paper. We currently allow correspondents 8 weeks to submit their letters after publication of an article, and 2 weeks for original authors to submit a response. Add to that reading, editing, and administration of galley proofs, and 3 months have gone by.

So, with a new volume and updated Information for Authors (see end of issue) comes a set of tough new rules for Correspondence. We will give correspondents 2 weeks from publication in which to submit their letter to [correspondence@lancet.com](mailto:correspondence@lancet.com). Submissions by mail or fax are discouraged since these formats cannot be processed quickly in our electronic office. Letters submitted later than 2 weeks after publication are likely to be rejected.

By restricting the number of letters we accept in this way, we will ensure that those ready for publication will not have to wait long for a space in the journal. We cannot publish everyone's letter, but those we do publish should reach their audience in a timely manner.

Zoë Mullan

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## Changes in the dissecting room



Change always seems fitting at the start of the year and so we introduce new features to a redesigned Dissecting room. In addition to many of our regular items, there will be a page dedicated to the medical humanities. Three new columns, Conduct and compassion, Education and debate, and Physician writers, will address issues in medical ethics, medical education, and medicine and literature, respectively, and are intended for practising physicians and those involved in medical education. Occasional interviews will also appear in Dissecting room. Marilyn Larkin continues to cover websites but adds software reviews to the mix. Greater variety comes to the back page with Mike Fitzpatrick's column, Doctoring for a risk society, in which he reflects on issues that arise in medical practice in a society where aversion to risk has become all-pervasive. Lunch with *The Lancet*, which will intermittently replace Jabs & Jibes, is a place to satisfy your appetite for engaging interviews with interesting individuals. We hope these changes will inform, entertain, and delight you in 2003.

Joanna Palmer

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