Selected Article

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Don't go breaking my heart

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Doctors are rushing to test a new treatment for heart disease that seems to give miraculous results. But are they courting disaster? Lisa Melton finds out

IAN ROSENBERG ought to be dead by now. By July last year the cocktail of pills that had been keeping the 68-year-old former businessman alive was losing its punch. His ailing heart, scarred and weakened by a massive heart attack 25 years ago, was giving up and he was facing death. "I only had months to live," he says. "I couldn't even walk up two steps - not two flights, two steps."

Rosenberg was rescued by his own stem cells, taken from his bone marrow and injected into a vessel feeding his heart, in an experiment at the Johann Wolfgang Goethe-University Hospital in Frankfurt. Over the next couple of months Rosenberg began to recover, and for a near-dead person, he is now very much alive. He has returned to playing golf and in July he took a trip to Venice. "For years, at the airport I always had a wheelchair," he says. "This time, I ran up the stairs."

The treatment that Rosenberg received is one of the most promising areas of medical research right now, and yet it is highly controversial. Stem cells are seen as the medicine of the future. Once we fully understand what they are and how to manipulate them, over the next decade or two, they are expected to provide a cure for many of humanity's ills. But in one field, cardiology, doctors are already rushing to the clinic to test them out.

Some of the early results have seemed spectacular, with patients like Rosenberg pulled back from the brink of death. But amid the excitement, scientists are warning that the research is progressing way too fast. There is much we still do not understand about stem cells, and there are reasons to suspect that some of the early cardiac research was flawed. Some patients receiving a related therapy have suffered potentially fatal heart rhythm problems. Is the field a disaster waiting to happen? "I think the risk is very high," says Jürgen Hescheler at the University of Cologne in Germany, a renowned critic of the trials. "It's too early to go into humans."

Better therapies for heart disease are certainly needed - the condition is one of the west's biggest killers, accounting for about one in five deaths. Heart attacks occur when one of the organ's blood vessels suddenly becomes blocked, usually by a fatty plaque or blood clot. The muscle supplied by that vessel is starved of blood and starts to die, causing the heart to lose pumping power. About half of heart attack victims never make it past the hospital's A&E department.

Patients who survive the initial trauma face an uncertain future. The dead heart muscle becomes scar tissue, which cannot contract. The surviving muscle must work harder to compensate for the lost tissue, and these muscle cells start to exhaust themselves and die, compounding the damage. The outcome, as in Rosenberg's case, is slowly worsening heart failure: the heart cannot pump blood round the body forcefully enough, which can lead to fluid collecting in the lungs, making it hard to breathe. Many patients develop irregular heartbeats or suffer further heart attacks. Medicines can help to some extent, but the only hope is a heart transplant. Due to a lack of donors, however, most people die on the waiting list. Heart failure is a debilitating and relentlessly progressive disease: once heart muscle cells die, they cannot be renewed.

At least, that's what the textbooks say. But in recent years there has been a surge of interest in the potential of stem cells to regenerate various organs. Unlike the vast majority of cells in the body that are "specialised", for example as skin, muscle or bone, stem cells are blank slates that have the potential to become several different kinds of tissue. Soon after conception the developing embryo consists of a ball of stem cells. As they repeatedly divide, more and more specialise into the various tissue types and lose their stem-cell status. But some organs retain small numbers of "semi-specialised" stem cells into adulthood which can regenerate that particular tissue type.

Bone marrow is a rich source of adult stem cells that normally give rise to the

cells of the immune system and red blood cells, which need to be replenished throughout life. There are indications that bone marrow stem cells may develop into other tissues too, as they have been found in various organs around the body, perhaps in a repair role. Scientists have been trying to boost this putative regenerative function in various ways.

In 2000, a ground-breaking experiment suggested that bone marrow stem cells could develop into heart muscle, in mice at least. Researchers led by Piero Anversa at New York Medical College in Valhalla gave the animals heart attacks, then injected bone marrow cells into their heart muscle. The damaged area was rebuilt by a spectacular 68 per cent and heart function improved dramatically, according to the paper published in *Nature* the following year (vol 410, p 701). The team used a staining technique with fluorescent antibodies to show that the bone marrow cells had turned into new heart muscle cells and blood vessels.

Cardiologists wasted no time. While the results were still being confirmed in larger mammals, within about a year of Anversa's study, three separate groups of German doctors had started setting up human trials. Other groups around the world joined the field, investigating several strategies. Some have been using neat bone marrow, while others have been trying to isolate the stem cells from it and grow them in culture to increase their numbers. Another technique is to isolate bone marrow stem cells from the blood. To increase the efficiency of this approach, patients can be injected with a biological signalling molecule called G-CSF, which encourages bone marrow to churn out more stem cells into the blood.

Although the trials were not placebo controlled, early results were encouraging. In a Frankfurt-based study, for example, the 40 patients who received the stem cell therapy had their heart's pumping capacity boosted by an average of 8.5 per cent. That might not seem much, but it could give someone the ability to walk up a flight of stairs, for example.

Cardiologists in Germany and elsewhere were upbeat, bordering on euphoric, and quickly began planning larger placebo-controlled trials. The largest one up and running is being carried out by the Frankfurt team and will involve 200 patients. There are plans for a 600-patient trial at Barts and the London Hospital, and one involving up to 1000 patients in Germany, the UK, Italy, Poland and Spain.

One of the main constraints is lack of funding, as pharmaceutical firms have little interest. "There is no intellectual property in bone marrow," says John Martin, a cardiologist at University College London, who is running the 1000-patient study. On the plus side, however, that may result in a relatively cheap treatment for one of the western world's biggest killers. "For the first time academics are in charge of the whole thing," he says.

Unusually, the US is lagging behind Europe in this field, mainly because its regulatory agency, the Food and Drug Administration has been more cautious about letting trials proceed given the paucity of animal data.

But FDA officials are not the only ones to be worried. What cardiologists are ignoring, say the critics, is that stem cell science is still in its infancy: we know little about which cells can develop into which tissues, under which conditions. It is theoretically possible that the bone marrow cells injected into the heart could develop into other tissues, such as bone, skin, or even tumours. Or if they turn into immune cells, their original fate, they could produce chemical signals that promote inflammation, already a problem in the damaged heart. While no such side effects have been seen so far, who knows how long they may take to develop?

Stem cells have reached early human trials for other conditions such as Parkinson's disease and spinal cord injury, but in no other field has the pace of research been so fast. "People are going ahead saying it is safe," says Hescheler. "For me this is not proven." It is no accident that this is happening in cardiology, where doctors are renowned for their risk-taking. "Sometimes it is warranted to push the envelope," says Emerson Perin at the Texas Heart Institute in Houston, who got the go-ahead for the first US trial this year. "We are not going to sit around and watch patients die."

The problem with risk-taking, however, is that it is, well, risky. Not all the studies have produced positive results. In one study where patients were given G-CSF, two people had heart attacks and one person died. And in April two separate studies seemed to refute the conclusions of Anversa's study in mice (*Nature*, vol 428, p 664, p 668). The researchers tried to replicate the original experiment but used a genetic labelling method that is probably more accurate than the fluorescent antibody approach. They found no evidence that bone marrow cells were transformed into heart muscle and blood vessels. "We stand 100 per cent - 1000 per cent - by what we published in 2001," insists Anversa. But the new results have raised eyebrows. "There is a technical flaw in the original study," claims Hescheler.

If that's the case, why did the patients in the German trials appear to benefit? It could have been that the bone marrow cells released chemicals that encouraged blood vessels to sprout, helping to feed the heart. It could even have been a mechanical effect from sticking needles into the organ. Without proper placebo controls, it is hard to say what caused the results, or even if the results were real. Scientists doing basic stem cell research fear that if patients start dying it could set back the field for many years - as seems to be happening in gene therapy at the moment. It is not even clear if

bone marrow is the best source of stem cells for the heart. There are two other potential sources of stem cells, although both are at a much earlier stage of research (see Figure).

One is the heart itself. For a long time it has been assumed that heart muscle cells are incapable of self-renewal. But over the past few years, evidence has grown that there are cells in the heart with the expected characteristics of cardiac stem cells that seem to have some regenerative capacity. In time we may learn how to boost this artificially, says Anversa, perhaps by injecting the right biological signalling molecules. "I think we will be able to do that," he says. "In the next decade tremendous progress will be made."

Alternatively, embryonic stem cells, present in the early developing embryo, are probably the most versatile stem cells of all. Animal studies suggest that when injected into the heart they fuse with the muscle cells, taking on a cardiac identity. But we are a very long way from being able easily to create and manipulate human embryonic stem cells, not to mention some people's ethical objections.

To complicate matters further, a fourth way of using cells to mend broken hearts has reached human trials, although this does not involve stem cells. This involves taking a small sample of muscle from the thigh, growing the cells in culture for about three weeks, then delivering them into the heart. This method has attracted more interest from the private sector, as the cells have to be grown in the lab to boost their numbers, and the culture medium can be patented and commercialised.

In contrast to the bone marrow approach, there was a decade of painstaking animal research before this technique was tested on the first patient in 2000 (*Lancet*, vol 357, p 279). The results were encouraging: the transplanted cells fused with the heart cells, strengthening the damaged areas. The first study suggested it improved the ability of the heart to pump by up to 30 per cent.

But this technique is not without its critics either. The type of muscle that moves our limbs, known as skeletal muscle, is distinctly different to that in the heart. Some scientists think that skeletal muscle cells and cardiac muscle cells may not properly couple electrically, leading to potentially fatal heart rhythm problems. The field went on red alert when 4 of the first 10 patients did indeed develop arrhythmia. Philippe Menasché, a cardiologist at the Georges Pompidou European Hospital in Paris who pioneered the technique, points out that in heart failure patients, "half the deaths are due to arrhythmia anyway". It is impossible to say whether there was a higher than normal incidence as the trial was so small and not placebo-controlled.

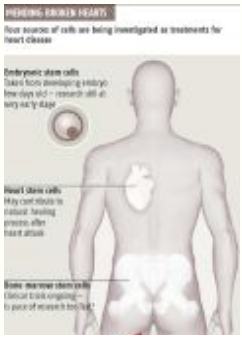
These problems have not put a stop to the development of Menasche's approach, however. With backing from the US biotech firm Genzyme, he is carrying out a 300-patient placebo-controlled trial across Europe. Crucially, one of the entry criteria is that all subjects must already have had a defibrillator implanted, in case arrhythmias develop.

Other biotech firms, for example Bioheart of Weston, Florida, and GenVec of Gaithersburg, Maryland, have also started small trials of the technique. Frank Young of Bioheart rejects the accusation that the field is moving too fast. "Most question why we are not going faster," he says.

The bone marrow researchers don't want to slow down either. "If we were to wait for the mechanisms of every drug to be worked out, we would be withholding a lot of wonderful treatments that are currently in use," points out Anthony Mathur, a cardiologist who is running the 600-patient Barts trial.

Stopping trials would also be unpopular with patients. Ian Rosenberg is so grateful for the treatment he received in Frankfurt that next month he will launch the Heart Cells Foundation, a charity to raise the £6 million needed to fund the Barts trial. "We have people waiting for cell therapy," says Rosenberg. "Unfortunately, they are dying before it becomes widely available. The funding should be there - stem cells are too important."

But some would argue that it is precisely because stem cells hold so much potential for the future of medicine that we should proceed more cautiously. Otherwise the field could be set back many years. "Stem cell therapy does have a future, but nobody benefits by blazing a trail early on," argues Michael Marber, a cardiologist at St Thomas' Hospital in London. "It artificially raises people's hopes. "There needs to be a period of realism."



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