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Stem-cell therapy: hope and hype

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In the fifth year since human cloning to generate stem cells was legalised in the UK, what progress has been made towards taking stem-cell therapy from laboratory to clinical practice? In 2000, articulating robust UK Government support, then Health Minister Yvette Cooper proclaimed that stem cells from cloned human embryos "could prove the Holy Grail in finding treatments for cancer, Parkinson's disease, diabetes, osteoporosis, spinal cord injuries, Alzheimer's disease, leukaemia and multiple sclerosis . . . transform[ing] the lives of hundreds of thousands of people".[1] But 4 years later, the technical difficulties and biological hazards inherent in cloning human embryos and developing treatments from their stem cells led Richard Gardner, Chairman of the Royal Society Working Group on Stem Cells and Therapeutic Cloning, to doubt whether this would ever be "a procedure that becomes widely available . . . There are concerns about the efficiency and elaborateness of the procedure, and it's going to be very time-consuming and very expensive".[2] So, to paraphrase May 25th's *Saving Faces* event in London, UK, are stem-cell therapies hype, or hope, or substance?

Only two UK groups currently seek to clone human embryos, both with immediate aims not of developing therapies but of improving understanding of embryonic development or specific diseases. Techniques for culturing human embryonic stem cells have advanced—eg, allowing them (like adult stem cells) to be grown[3]—but an increasing appreciation of the hazards of embryonic stem cells has rightly prevented the emergence or immediate prospect of any clinical therapies based on such cells. The natural propensity of embryonic stem cells to form teratomas, their exhibition of chromosomal abnormalities, and abnormalities in cloned mammals all present difficulties.[4,5]

The prospect of having to clone (to obtain embryonic stem-cells) every patient requiring therapy is surely unrealistic (the Korean report of cloning human embryos for stem cells used almost 250 human eggs in generating a single stem-cell line[6]). If cloning is unrealistic and/or too hazardous, the autologous advantage of (cloned) embryonic stem cells vanishes: and immune rejection of embryonic stem cells generated from "foreign" in-vitro fertilisation or abortion presents further problems.

These biological problems only add to the ethical objections. *The Lancet* declared in 2001 that: "the creation of embryos solely for the purpose of producing human stem cells is not only unnecessary but also a step too far".[7] Semantic questions about embryology and personhood are interesting, if unprovable, but what is unarguable is that the human embryo is alive and is human, and intentionally ending the life of one human being for the potential benefit of others (ie, for research) is not territory to which mainstream clinical researchers have hitherto sought claim—or which ethically conscious objectors could ever concede.

So is stem-cell research a damp squib, another overhyped funding gambit? Far from it, for the embryonic stem-cell story forms only one aspect. Excitement about the potential of adult stem cells was tempered by reports in 2002 that in some circumstances such cells can fuse.[8] Fusion might give a false appearance of metadifferentiation, the argument ran, therefore adult stem cells are not really multipotent, and are a non-starter as an alternative to embryonic stem cells.

Fortunately, for the now highly expectant patient, reports of the death of adult stem cells were greatly exaggerated. Much research (some indeed antedating the fusion excitement) clearly shows that although fusion can and does occur in certain tissues, adult (say)

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Researcher at Seoul National University prepares to inject somatic cell (monitor) into bovine enucleated egg

bone-marrow-derived stem cells can also generate multiple lineages without cell fusion.[8] Interestingly, fusion may be an unexpected mechanism of achieving repair, and could additionally offer means of delivering gene therapy.[9] Normal (bone-marrow-derived) donor nuclei were found in the muscle of a patient with Duchenne muscular dystrophy, over a decade after bone-marrow transplantation for immune deficiency, offering proof of principle for fusion of bone-marrow-derived stem cells as gene therapy, and presenting tantalising therapeutic prospects.[10] Also, it is now clear that aneuploidy represents a not uncommon, spontaneous, and normal process, rather than necessarily carrying sinister implications, as speculated.[11,12]

Suggestions of low rates of differentiation of bone-marrow-derived stem cells and integration in situ, and of questionable differentiation, have also been addressed.[12-14] Perhaps the most compelling (and extraordinary) evidence unambiguously confirming the ability of adult bone-marrow-derived stem cells not only to metadifferentiate but also to integrate fully into adult (human) organs, and survive for decades, comes from postmortem studies of sex-mismatched recipients of bone-marrow transplants, showing donor-derived fully differentiated neuronal cells of a highly complex morphology apparently fully functionally established within the host brain,[15,16] with no evidence of fusion.

We now know that bone marrow-derived stem-cells circulate systemically and actively migrate into damaged tissue to contribute to spontaneous repair.[17–19] Experimentally, therapeutic benefit occurs in numerous disease models[20,21] but, importantly, repair by bone-marrow-derived stem cells does not stop at the laboratory door. Safety data from 50 years of clinical bone-marrow transplantation, during which non-haemopoetic stem cells have inadvertently also been transplanted, and the accompanying clinical expertise in collecting, handling, freeze-storing, thawing, and delivering marrow, have safely allowed a rapid translation of bone-marrow stem-cell science from laboratory to clinic. Controlled trials have shown significant benefit of marrow-derived stem-cell therapy in myocardial infarction,[22] and trials are planned or underway in chronic cardiac failure, stroke, and other diseases: reports of successful adult stem-cell therapy in patients with corneal disease have just appeared. The next few years, not decades, will show whether adult stem-cell treatments are to join the mainstream therapeutic arsenal.

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I declare that I have no conflict of interest.

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AIDS in Uganda: the human-rights dimension

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Much has been written about Uganda's successes in HIV prevention. The United Nations estimates that HIV prevalence in the country has declined from about 15% in the early 1980s to 6% today. Beyond this, there is little on which experts agree. In particular, the respective roles of abstaining from sex, being faithful to one's partner, and using condoms (the ABC approach) in this decline has generated extensive and at times ideological debate. At stake in this debate are not only scientific inquiry and substantial US AIDS funding, but also potentially the health and lives of millions of people. The assumption is that if abstinence were responsible for Uganda's HIV decline, funding for abstinence-based programmes should be at the centrepiece of the global anti-AIDS effort.

This is a dangerous assumption. First, US-funded abstinence programmes have a track record of censoring or distorting information about any other method of HIV prevention beyond abstinence, placing young people at needless risk of HIV infection. In 2002, we documented numerous cases of censorship and misinformation about condoms (or exaggeration of their failure rates) in "abstinence only" programmes in Texas.[1] Reviews of abstinence-only curricula in US-funded programmes have found similar problems.[2,3] It should come as no surprise that abstinence-only programmes have proven ineffective and potentially harmful. Studies have consistently found that these programmes are ineffective in reducing risky behaviours, and might increase HIV risk by discouraging the use of contraception.[4–6] Comprehensive programmes that include information about condoms and safer sex alongside abstinence messages have, by contrast, proven effective.[7,8]

The unproven abstinence-only approach is now being exported to Uganda as part of US President George W Bush's Emergency Plan for AIDS Relief (PEPFAR). In a recent investigation, we found that US contractors discouraged teachers in Uganda from discussing condoms with students because the new policy was abstinence-only.[9] A draft secondary-school HIV/AIDS curriculum (funded by PEPFAR) states that "condoms are not 100% perfect protective gear against STDs and HIV infection. This is because condoms have small pores that could still allow the virus through".[10] At one PEPFAR-funded HIV/AIDS rally, participants were told that "using a condom with a person with these [sexually transmitted] diseases is like using a parachute which opens only 75% of the time".[11]

This strategy cannot plausibly be described as ABC, as the Ugandan and US Governments now describe their anti-AIDS approaches. But there is a second problem with focusing on the respective roles of A, B, and C in Uganda's HIV decline. For too many Ugandans, especially women and girls, ABC is not enough. In 2003, we interviewed Ugandan women who described how domestic violence caused or contributed to their HIV infection.[12] These women could not "abstain" from being raped by their spouses, much less insist on their fidelity or condom use. Nor is ABC an effective strategy for girls who face rape or sexual coercion, sex workers who face violence from police and clients, or children who rely on "sugar daddies" for their basic necessities. Programmes should focus on empowering vulnerable populations to achieve economic independence, protecting their legal rights, and providing them with the information and tools they need to prevent HIV—not preaching "abstinence until marriage."

The exhortation to abstain until marriage not only ignores the plight of women who contract HIV in marriage, but also discriminates against lesbians and gay men, who cannot legally marry in Uganda. But abstinence-until-marriage programmes are merely the tip of the iceberg of extreme state-sponsored prejudice and