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Rogue research in the guise of stem cell therapy

By Sandhya Srinivasan

The stem cell therapy industry is booming in India, without regulation of any kind. Unorganised, unscientific 'research' is being passed off as therapy. Some of those offering stem cell therapy in India today may be preying on the desperation of seriously ill patients likely to agree to unknown risks

The newspapers are filled with reports about the miracle cures of stem cell therapy. In November 2005, former Chhattisgarh Chief Minister Ajit Jogi declared that he felt a "remarkable improvement" after the first course of stem cell therapy. What is this treatment, what stage of development is it at, and where does India stand? And what does it say about the kind of research that is being done in this country?

Perhaps we should take heed of the warnings in an editorial entitled 'Stem cell therapy: Hope or hype?' The drive to make the most of the stem cell "boom" may lead to disaster, note Stephen L Minger, Peter Braude and Ruth Warwick in a May 21, 2005 editorial in the ***BMJ.***

What is stem cell therapy all about?

Most cells in the body multiply to form the same kind of cell, such as skin, blood, kidney, and so on. Stem cells are special cells that have the capacity to multiply and differentiate into various types of cells with different functions. Researchers are trying to use this quality to get stem cells to repair tissues in various parts of the body. Stem cells can be obtained from foetuses (through medical termination of pregnancy or miscarriage) and embryos (through fertility techniques). They can also be obtained from other locations such as the umbilical cord of a newborn, and bone marrow. Stem cells can be obtained from, processed and used on the same person (autologous stem cell therapy) or on another person (allogenic stem cell therapy).

This seems to offer the prospect of a miracle cure. New cells regenerate diseased organs. Patients bound to their wheelchairs because of spinal cord injury could walk again. Those suffering from terminal illnesses or degenerative diseases might recover completely. Stem cell therapy could offer the prospect of renewed life to the seriously ill

or dying.

When desperate people are given this hope they are especially vulnerable to exploitation. The stem cell therapy industry is booming in India, without regulation of any kind. Further, while specialists indicate that work is at the very preliminary stages in India, all kinds of procedures are being promoted as cures. In effect, unorganised, unscientific "research" is being done in the guise of therapy. Some of those offering stem cell therapy in India today may be preying on the desperation of patients with serious illnesses who may agree to unknown risks.

Unregulated

In recent years there have been a number of press reports of unethical practices in stem cell therapy or research in India.

Private hospitals have offered stem cell therapy to treat conditions such as damaged heart muscle, liver cirrhosis and diabetes and promise to treat many more.

The stem cell boom is not confined to private clinics. More recently, doctors at the Institute of Immunohaematology, an ICMR centre, used stem cell therapy developed by a UK-based company, Tristem, to treat four patients with aplastic anaemia at Mumbai's KEM hospital. White blood cells were taken from each patient, "transformed", and then re-infused into the patients. The problem: this, too, was an experimental treatment developed abroad, and was being tested exclusively on Indian patients.Further,poor patients in public hospitals were being subjected to questionable research.The trial was stopped after the ethics committee found out that patients' photographs and other details were posted on the company's website. After the press controversy, the company, Tristem, moved to Pakistan where it has been advertising stem cell therapy to treat thalassaemia and other diseases. Such advertisements contribute to the hype "generally nurtured by commercial interests" about this technology, noted Dr Farhat Moazam, chairperson of the Centre of Biomedical Ethics and Culture, Sind Institute for Urology and Transplantation, Karachi. "In the absence of ethical guidelines, Negligible oversight processes at institutional and national levels, and lack of regulation of healthcare services, it is not difficult to imagine a proliferation of clinics and hospitals promising desperate patients treatments for all manner of illnesses by using stem cells," she wrote in a letter to the newspaper ***Dawn***.

"We want to promote stem-cell technology but not in this scandalous way," said Vasantha Muthuswamy, head of basic medical sciences at the Indian Council of Medical Research to ***Nature*** magazine, referring to the mushrooming of clinics offering stem cell therapy, without any evidence that they were following basic ethical guidelines and scientific practice.

The new wave

Guidelines are also becoming necessary as the government starts funding stem cell research in India. For example, in January 2006, KEM hospital in Mumbai announced the imminent opening of a stem cell centre with a grant of Rs 2 crore from the Union department of biotechnology. The centre plans to do work in orthopaedics, anatomy and cardiology. Clinical trials of stem cell therapy will be conducted for patients with certain cardiac problems. According to newspaper reports, stem cells from the patient's bone marrow will be injected into the patient just before the surgery.

Private hospitals have also been announcing departments of stem cell therapy. In Mumbai, the Asian Heart Institute specialising in cardiac care announced its stem cell department as well. And a Mumbai-based institution doing eye surgery announced a tie-up with a Japanese institution for retinal stem cell research focusing on age-related macular degeneration.

In July 2005, a US-based company, Histostem, announced a tie-up with the Maharashtra government to set up a national cord banking centre in Mumbai. The centres reportedly promised to offer "the latest stem cell-based medical treatment in India at affordable rates." The chief executive office of Histostem said the company planned to invest $ 20 million over the next three years. "We intend to offer medical facilities using stem cell technology for spinal cord injuries, brain strokes, diabetes and bone cancer at much lower costs." Industries secretary V K Jairath is reported to have said that the Maharashtra Industrial Development Corporation would have an equity partnership with the company, and the company would be entitled to various concessions such as subsidised land, stamp duty concessions and additional floor space index, "the same announced under the government policy". Histostem also announced a tie-up with the New Delhi-based Apollo Hospitals to jointly develop new therapies using umbilical cord stem cells. Apollo's inputs include assistance in obtaining umbilical cord blood. According to the news report, over 50,000 people donated cord blood for the company's $80 million stem cell therapy centre in Korea.

ICMR guidelines

In 2002, the Indian Council of Medical Research drew up draft guidelines for stem cell research /regulation in India. This was partly in response to the controversies of stem cell therapy and partly in response to the anticipated growth in international collaborations in this field. The ICMR's guidelines were preceded by guidelines from the Department of Biotechnology in the previous year, and there has been some confusion on which one of the two apply. However, it is understood that the two departments plan to cooperate to ensure ethical research and practice. Since 2000, the ICMR has had guidelines on all biomedical research; the new guidelines would supplement this earlier document.

The ICMR draft guidelines discuss stem cell therapy in terms of the source of the stem cell ' adult (in bone marrow and certain other tissues), cord blood (in the umbilical cord), foetus and embryos.

"Realising the potentials of this new technology in modern therapeutics and biomedical research, it is strongly recommended that stem cell research and its clinical applications be promoted in the country."

However, it should be regulated properly and new research examined carefully before being approved. There is a need for regulation, and a regulatory body. A central committee will clear all research projects involving embryonic stem cells in the country. This will also survey and approve laboratories where embryonic research will be allowed, and IVF centres from where embryos are sourced.
The ICMR draft guidelines note that since medical termination of pregnancy is legal in India, foetal stem cells can be obtained easily from MTP clinics, but termination for the purpose of obtaining stem cells is not permitted. Likewise, spare embryos for embryonic stem cells can be obtained from IVF clinics, but embryos should not be produced for the sake of stem cell therapy /research. (In fact, this is a real danger ' that women will be coerced or paid to undergo risky procedures in order to produce spare material for stem cell research and therapy, and a simple ban on such practices may be insufficient.)

The draft guidelines are reasonably general. Among the issues to be considered are whether the product has been obtained with the donor's informed consent, whether research proposals are reviewed by an ethics committee, the possible commercial value of the product of research, and so on.

Safety is a major issue, and the guidelines mention regulation of centres doing stem cell work to ensure that they are registered and follow standard practices for preservation of the tissue. As the writers of an editorial in the ***BMJ*** in May 2005 note, "The lessons of the premature application of gene therapy, the devastation caused by HIV transmission to people with haemophilia, the clinical and legal problems resulting from hepatitis C infection through blood transfusion, and the crisis caused by bovine spongiform encephalopathy should all be learning opportunities. Expansion of stem cell cultures could allow a single stem cell line to be used for many hundreds, if not thousands of patients, exponentially amplifying the potential risk of disease transmission from a single infected donor."

Even these very general guidelines are yet to be finalised. They would be read along with the ICMR's more detailed guidelines for biomedical research, finalised in 2000. However, the 2000 guidelines are not legally binding, and in any case, there is little or

no real regulation of medical practice in India. As a result, public and private hospitals around the country seem to be offering stem cell "therapy". But is this therapy or some kind of research in the guise of therapy? Do patients know what they're going in for?

According to Dr Muthuswamy (as quoted in ***Nature),*** since the guidelines were issued, the ICMR has been receiving notification of various stem cell research projects. But many private clinics offering such procedures reportedly did not contact the ICMR at all.

The ***BMJ*** editorial writers mentioned earlier point out that in countries like Russia and India "intervention by the governments may be needed to limit or prevent the escalating numbers of clinics offering stem cell cures for all sorts of ills." They note that "despite inadequate preliminary data on clinical safety or from animal experiments, trials using cells derived from autologous bone marrow samples are already being conducted on patients with heart disease, with urgency and therapeutic need being cited as the reasons for immediate implementation. However, urgency is not an excuse for bad science."

AIIMS and its 'global first'

On February 25, 2005, ***The Times of India*** reported that doctors at the All India Institute of Medical Sciences, a central government institution, had "marked a global first in pioneering stem cell medicine by 'injection method', placing the institute right at the top of the world's medicine map." The article was carried on the front page with more reports on the inside pages. The headline read: 'AIIMS scripts stem cell success story: injects new life into diabetics; seriously sick patients'.

In an 'exclusive' to the newspaper, Dr P Venugopal, director of AIIMS, said that he was finally in a position to report the results of his work. Starting in February 2003, 35 patients with end-stage cardiac disease had been given stem cell therapy through a technique developed at the institute, he said. They had been monitored over six-month intervals and the majority had improved.

Another press report one month later indicated that AIIMS was "all set to prove to the world the efficacy of its stem cell therapy conducted over the last 18 months on heart patients, with the help of Positron Emission Tomography technique." The machine was to be installed in the next month, Dr Venugopal was reported as saying, after which "we will get the final proof of our work on heart patients." The institute would soon "be offering the service to patients with muscular dystrophy, neurological disorders, cornea treatment and other ailments".

But Dr Venugopal's work has not been published in a peer-reviewed, scientific journal. It has not been presented before, and evaluated by, the scientific community. His colleagues do not comment on whether his work was scientifically sound, correctly

carried out, and proven to be effective. But the press reports ' really a form of advertising -- generated hope for seriously ill people and their families, desperate for a cure

It didn't help that the director general of the Indian Council of Medical Research said that he stood by the authenticity of the work by the institute. "We will leave it to the medical profession to maintain a strict code of ethics," he is quoted as saying in a report in ***The Hindu***, April 6, 2005.

At the same time, Vasantha Muthuswamy of the ICMR, who is in charge of developing ethical guidelines for stem cell research and treatment, was expressing her helplessness. "We are only a block away from AIIMS and we did not know this was happening there," she is quoted as saying, in ***Nature.*** "If the nation's premier medical institute did not ask our permission for such therapy, how can we blame private clinics for what they do?"

A patient's story Sounak Banerjee was ten years old when he was diagnosed with Becker's muscular dystrophy, a progressive disease affecting the muscles. This was in 1987. Shocked by the initial diagnosis, his father, a retired government official, took Sounak to the best doctors they knew of. "But they told us that there was nothing to be done," says Banerjee. The only advice was to do physiotherapy to reduce the effect of the disease.

When he read the ***Times of India*** story Banerjee dashed off to Delhi and found his way to the department of stem cell therapy at AIIMS. The crowds at the waiting room provided the confirmation he needed. "We spoke to so many patients there, who said they felt better, and we were convinced," he says. "We also asked around to evaluate the treatment. We could not meet Dr Venugopal though we tried."

In all, the Banerjees made three trips to Delhi, first to get an appointment, then for Sounak to undergo a muscle biopsy, and then finally for the treatment itself, which was scheduled on September 22, 2005. Each appointment was obtained with much difficulty, as the waiting list was so long. Though he was reluctant to "use influence", Banerjee was forced to speak to former colleagues in the government to somehow get an early appointment. "We were desperate for Sounak to get this treatment." One of his government friends indicated that there were problems of some kind with the treatment.

On September 22, 2005, when the Banerjees arrived at the department of stem cell therapy, they were prepared for a waiting room packed with patients and their relatives. Instead they found an empty hall. They managed to speak to the doctors who had earlier seen Sounak but they were only told: "We are unable to take up this treatment

at this point." Slowly, it became clear to the Banerjees that the department of stem cell therapy had been pressurised to shut shop. Presumably the government had put pressure on the doctors to stop work ' at least publicly ' until the guidelines were finalised.

When the dejected family went back to their hotel, just around the corner from AIIMS, they were in for another surprise. "A stranger came up to me and said, 'I hear your son has muscular dystrophy and you didn't get treatment at AIIMS. My children too have the same problem but they are being treated at a private clinic nearby.' The only difference: the clinic was charging Rs 150,000. AIIMS had offered it for Rs 3,000."

The Banerjees later read newspaper reports about a clinic in Delhi offering stem cell therapy. They were furious at the idea that private doctors were being permitted to offer stem cell therapy for large sums of money when a government hospital which had been charging much less had been banned. They also came across an advertisement for stem cell transplants, in an Indian publication. The advertisement was by a Singapore-based institution with tie-ups to Indian clinics.

Report of a hundred cures

In November 2005, Dr Geeta Shroff announced that her clinic, Nutech Mediworld, had helped 100 patients suffering from Alzheimer's disease, paralysis and Parkinson's disease using embryonic stem cell therapy. Also present at the clinic at the time of Dr Shroff's announcement was Union Health Secretary P K Hota, Prime Minister Manmohan Singh's wife Gursharan Kaur, and former Chhattisgarh Chief Minister Ajit Jogi. Jogi had apparently received the therapy for paralysis.

According to press reports, the health secretary said, "My presence does not mean I support it....Human life should not be toyed with. We are worried...we will set up a system...No proven medical therapy using embryonic stem cells is available."

Dr Shroff is reported to have said that the clinic's doctors have followed existing government guidelines in the use of stem cell therapy ' though there are no finalised guidelines for stem cell research in India. "We have been in touch with ICMR and submitted our protocol to ICMR. Details of all cases are sent to them before the therapy is started," she said. She is also quoted as saying that there had been no need to do animal studies before undertaking the work.

ICMR officials are reported to have said that there was nothing to substantiate Dr Shroff's claims that 100 patients were benefited by stem cell therapy, including former Chhattisgarh CM Ajit Jogi. "Stem cell research is still in an experimental stage the world over. Initially there can be some improvement but follow-up studies have to be

done to substantiate whether it is efficacious," the official stated.

This time around, the ICMR seems to have taken a firmer stand; in April, its director general actually supported the announcement made by AIIMS doctors.

According to press reports from the time of the announcement, ICMR received only a sketchy corporate proposal for funding in 2003 ' two years after Dr Shroff says she started the work ' and she did not respond to their request for further information. But in any case, the ICMR cannot take action until the guidelines for research become law. The Medical Council of India is entitled to act against malpractice, but the secretary has said "We cannot take any action as no complaint has been forwarded to us."

In fact, what AIIMS was doing, and what Nutech Mediworld and numerous other similar institutions are doing is not "therapy" but what might be described as "rogue research".

The real picture in India

There are very few established stem cell therapies, says Dr Manorama Bhargava, senior consultant and head of the department of haematology at Sir Gangaram Hospital in New Delhi. While Dr Bhargava is not currently involved in stem cell research and therapy she initiated bone marrow transplantation at Sir Gangaram hospital.

"Adult stem cell work like bone marrow transplantation has been going on for 10-12 years; it is one of the few established therapies for haematological diseases. The therapy uses stem cells from the bone marrow for treatment or replacement. It can be based on autologous donation as well as allogenic (from an HLA matched donor)."

Dr Bhargava feels that the current publicity given to stem cell therapy is unwarranted. "Results in stem cell research are almost experimental in India," she notes. It must be based on proper animal studies, and the procedures themselves are very delicate, and must be documented carefully.

"The reason why AIIMS had to withdraw is that they simply went ahead and did the procedure without peer review publication."

"The AIIMS doctors have made claims that this happened and that happened. All path-breaking scientific work has to be open to scrutiny by the peer scientific community. The AIIMS work has not been published. Adult stem cell therapy has a very promising future -- if done properly, with proper guidelines."

Note: this article has referred to reports by Ganpati Mudur in the BMJ ***and*** Telegraph, ***by KS Jayaraman in*** Nature***, and to various bureau reports.***