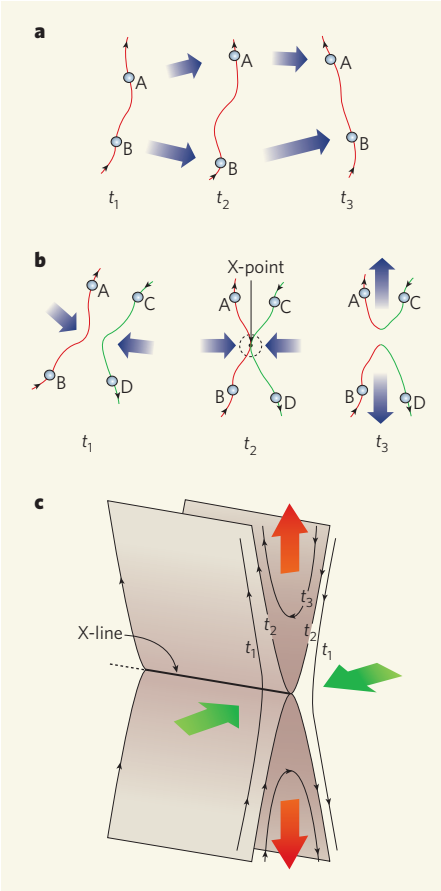

Figure 1 | The ins and outs of magnetic reconnection. **a**, Magnetic field lines are generally frozen into the plasma flow (blue arrows), so two charged particles, A and B, connected by a field line at time t_1 remain connected by the same field line at all later times. **b**, Two oppositely directed field lines, identified by particles A, B and C, D, respectively, are moving towards each other at time t_1. When they touch at time t_2, they break and cross-link (reconnect) at the so-called X-point, leaving A, C and B, D, connected at time t_3. The highly bent field lines act like a slingshot, and plasma flows out from the region at high speeds. **c**, A perspective view of magnetic field lines reconnecting along an X-line (plasma inflow, green arrows; high-speed plasma outflow, red arrows). The times t_1 to t_3 refer to the same phases of the process as in **b**. Phan *et al.*[1] investigate the length of the X-line in the solar wind.

spatial and temporal characteristics of magnetic reconnection will fuel the sometimes heated debate over what the phenomenon is like and what it can do. With the launch of NASA's STEREO mission, expected later this year, larger baselines will become available, and there is hope that the study of solar-wind reconnection can be extended to much larger scales. At the smallest scales, NASA's Magnetospheric Multi-Scale (MMS) mission, to be launched in 2013, will investigate the kinetic plasma processes near the X-line that allow the frozen field condition to be broken and reconnection to occur. The prospects for finally understanding the nature of reconnection, its ability to couple small- to large-scale phenomena, and the crucial role it plays in various cosmic settings, are excellent. ■

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MEDICINE

Politic stem cells

Irving L. Weissman

Research on embryonic stem cells holds huge promise for understanding and treating disease. Many people oppose such research on religious and ethical grounds, but two new methods may bypass some of these objections.

In this issue are two new methods[1,2] for producing pluripotent stem-cell lines — the great future hope of regenerative medicine*. Both papers report proof-of-principle tests in mice of techniques that might be used for making human pluripotent stem-cell lines. The protocols each aim to satisfy the religious, ethical and/or political objections of groups that are opposed to some of the methods used in embryonic stem-cell research.

Pluripotent stem-cell lines come from the most primitive cells in vertebrate development. They are prized because they can both renew themselves continuously in culture and, once released from this self-renewal cycle, can go on to form most mature cell types in the body (hence 'pluripotent', meaning many potentials). Their ability to make a range of functional cell types makes them crucial to the study of tissue development and degenerative diseases, and they are considered to be promising as a possible treatment for such disorders.

Pluripotent stem-cell lines can be derived from early embryos before they implant in the uterus (Fig. 1a, overleaf). These cells are called embryonic stem cells (or ES cells). The preimplantation embryo (a blastocyst) has an outer shell of cells used for uterus implantation (the trophectoderm) and an inner cell mass of pluripotent cells that will give rise to the developing embryo once it has implanted. To create ES cell lines, cells from the inner mass are removed and cultured, but this process means that the embryo cannot implant in the uterus.

To get around this, Lanza and colleagues[1] (page 216) have adapted a method commonly used in assisted-reproduction clinics for preimplantation genetic diagnosis. This involves removing a cell from the eight-cell stage of development (before the blastocyst has formed) (Fig. 1b); this 'blastomere' cell is then analysed for genetic defects. Instead, Lanza and colleagues[1] use the blastomere cell to produce ES cell lines — without compromising the embryo from which the blastomere was obtained. The single blastomeres are co-cultured with established ES cell lines, and then separated from them to form fully competent ES cell lines.

The ES cells produced using Lanza and colleagues' technique would have the same genes as the embryo, essentially a mix from the two parents undergoing *in vitro* fertilization treatment. However, the goal for many researchers is to be able to produce pluripotent cells that represent the full genetic diversity of humans, or that are genetically identical to a particular donor (a patient with a genetic disorder, for example). The production of such stem-cell lines would enable the study of the cellular and genetic bases of disease development[3]. For example, stem-cell lines generated from mice that are immunodeficient because of a defect in a single gene are themselves immunodeficient, and this might hold true for complex multigene disorders such as amyotrophic lateral sclerosis. These lines might also be 'fixed' in culture by replacing the defective gene with healthy copies, and thereby one could validate the role of particular drug targets or the efficacy of certain therapies. In the long term, healthy cells derived from repaired stem cells might aid the regeneration of tissues from the donor patient.

At present, creating pluripotent cells from a specified donor can only be achieved by a process called nuclear transfer (NT) (Fig. 1c). This involves removing the nucleus from a donor body cell (say, a skin cell) and injecting it into an egg that has had its own chromosomes removed. The egg is then encouraged to form an embryo-like, or embryoid, blastocyst, during which process the body-cell nucleus undergoes 'reprogramming', changing from expressing skin genes to expressing more

*The two papers concerned[1,2] and this article were published online on 16 October 2005. Since then, ref. 4 by W. S. Hwang *et al.* has been brought into question, and its authors have requested retraction of the paper.

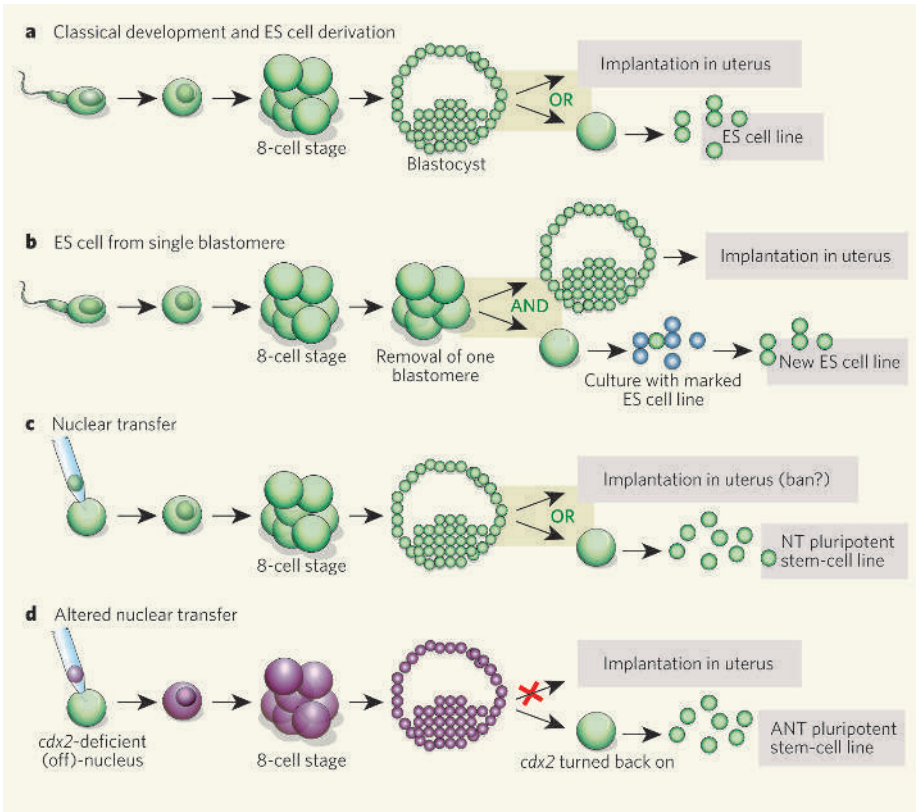

Figure 1 | Producing pluripotent stem-cell lines. **a**, The classical derivation of embryonic stem (ES) cells destroys the embryo from which they are derived. **b**, Lanza and colleagues[1] have used a modified method that does not compromise the embryo, but is not donor-specific. **c**, Donor-specific pluripotent stem cells can be made using nuclear transfer (NT) techniques. **d**, An altered nuclear transfer (ANT) method developed by Meissner and Jaenisch[2] blocks expression of the *cdx2* gene until the blastocyst stage, making it unable to implant.

pluripotent genes. Embryoid blastocysts have an inner cell mass like normal blastocysts, and these cells can become pluripotent stem cells. Such NT stem cells can, like ES cells, self-renew or differentiate to become most types of mature body cell. Technological advances[4] have improved NT in humans to the point that a single egg donor can produce enough eggs in one round of donation to ensure a patient-specific NT pluripotent stem-cell line.

Very rarely, animal embryoid blastocysts have reprogrammed enough genes to be able to implant in the uterus and complete all the developmental stages to birth. But in all species tested, more than 99% of embryoid blastocysts fail, many at later stages of pregnancy where the failure can injure or kill the mother bearing it. This has led a panel of the US National Academies to call for a legally enforceable ban on human 'reproductive cloning'[5]. Nonetheless, because human NT stem cells come from embryoid blastocysts, their derivation has raised objections on political, ethical and religious grounds. A possible solution to the controversy, proposed by many who want the medical science to progress, might be to invent a process that produces an entity that cannot implant in the uterus — termed alternative nuclear transfer (ANT) by William Hurlbut, a member of President Bush's Council on Bioethics[6].

Meissner and Jaenisch[2] (page 212) have now developed a method to accomplish ANT. Their technique builds on previous work by Strumpf *et al.*[7], who studied a gene called *cdx2* and its role in establishing the mouse trophectoderm and, later, the intestinal tract. Their results suggested that if this gene was suppressed in the nucleus of the donor cell during the NT process, it might allow the generation of NT entities that could not implant.

Meissner and Jaenisch demonstrate that this is indeed the case, using a clever method to control *cdx2* expression at various stages. They introduced into the donor cell a gene encoding an RNA that inhibits *cdx2* expression, and this gene was transmitted with the donor nucleus to the egg and continued to be active during the NT. Once they had derived the ANT pluripotent stem-cell line from the resulting embryoid blastocysts, they clipped out the inhibitor gene to enable the resulting ANT stem cells to produce mature intestinal epithelia given the right cues (Fig. 1d). These ANT pluripotent stem-cell lines can form many other mature cells, just as the classical ES and NT cell lines do.

It is highly speculative whether either blastomere-derived ES cell lines[1] or ANT pluripotent stem-cell lines[2] can also be derived from human cell sources. Nonetheless, there have already been hearings in the US Congress at

50 YEARS AGO

"Physiological control of population growth" — As Dr. Gregory Pincus, of the Worcester Foundation for Experimental Biology, pointed out, there is no doubt that progesterone can inhibit ovulation in rabbits and apparently, also, in rats. According to his own studies, the indications are that progesterone, when taken by mouth, will also inhibit ovulation in women, as determined by various indirect indices. This view was not, however, shared by Dr. Massomi Ishikawa ... nor by Dr. A. Stone ... [as was clear from all the physiological papers] the practical goal of these urgently needed researches — the discovery of a 'pill' which can be taken by mouth, and the only physiological effect of which would be that of inhibiting the development of the fertilized ovum, or of suppressing ovulation or gametogenesis at will — is so remote from realization that at this stage no one can say how, when or even whether success will ever be achieved. **Sir Solly Zuckerman**

From *Nature* 14 January 1956.

100 YEARS AGO

"The training of the body and mind" — In the afternoon Sir Lauder Brunton took the chair, and discussed education in connection with the threefold character of man. At first, he said, moral training was provided, and churches and cathedrals were built long before the people could read or write; then mental culture was considered, and became very general; and, lastly, it was being recognised that the condition of the body had considerable effect upon the morals and the mind, so that a physical training was also considered necessary. He gave some interesting instances to show how character and habits had been entirely altered by accidents to the brain, and said that while Newton was physically weak, Young, who was his superior, even in mental capacity, was a circus rider, and could perform almost any bodily feat.

From *Nature* 11 January 1906.

50 & 100 YEARS AGO

which some representatives called for a moratorium on the production of further stem-cell lines until these methods work in humans, while others declared that medical science has already gone too far, and must be reined in by laws that criminalize all such attempts. Of course, the attempts to delay or to prevent these kinds of experiment derive from the belief that preimplantation embryos, or entities with little or no potential to form a functioning organism, are human, and have the same rights as born humans. The 'non-implantable entity' is regarded by Hurlbut as a non-viable artefact, but many of his colleagues on the President's Council on Bioethics disagree[8].

So the crux of the question is when life begins, a debate that cannot be settled by science. In abstract, this would seem to be the realm of philosophy, but if such debates result in moratoria or bans on research, the medical advances that would surely come from such work will be held in abeyance, and patients with a narrow window of opportunity for treatment will be lost. Their lives are the point. Although the efforts cited here[1,2] will be criticized as a diversion of good science by politics, I believe all of these attempts to advance and translate medical science should be pursued in parallel. ■

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GLOBAL CHANGE

A green source of surprise

David C. Lowe

Living terrestrial vegetation emits large amounts of methane into the atmosphere. This unexpected finding, if confirmed, will have an impact on both greenhouse-gas accounting and research into sources of methane.

On page 187 of this issue, Keppler *et al.*[1] report the remarkable discovery that terrestrial plants emit methane into the atmosphere. Their results are startling, for two reasons. First, because the methane emissions they document occur under normal physiological conditions, in the presence of oxygen, rather than through bacterial action in anoxic environments. Second, because the estimated emissions are large, constituting 10–30% of the annual total of methane entering Earth's atmosphere.

In a series of carefully controlled experiments, Keppler and colleagues used gas chromatography and continuous-flow isotope-ratio mass spectrometry to find that methane is emitted from a wide variety of plant species under oxic conditions. Using ^{13}C-labelled acetate substrates, they ruled out the possibility that the methane is produced by anoxic microbial activity. Going further, they showed that this vegetative source depends on sunlight and temperature, with emissions approximately doubling for each rise of 10 °C. The details of the methane-production mechanism are not known, but the authors do demonstrate that emissions are related to the quantity of pectin, a cell-bonding agent, that a plant contains.

To estimate the global methane emissions from vegetation, Keppler *et al.* make two main assumptions: first, that the emission rates they measured are representative values for short-lived biomass; second, that the emission estimates can be scaled relative to annual net primary productivity, and can distinguish between different types of environment and average daily hours of sunshine, and between differences in the period of vegetation growth. This type of approach, known as a bottom-up calculation, is commonly used to estimate global emissions from various methane sources and is notorious for producing a wide range of estimates (Fig. 1)[2]. Additional constraints are applied to bottom-up estimates using methane isotopic data and inverse modelling techniques, but the errors remain large.

Most methane is lost from the atmosphere by oxidation, and estimates of this process are used in top-down calculations to deduce the amounts thus removed. For the methane budget to be balanced, the two techniques should agree when the atmosphere is near steady state. But this is rarely the case, as shown by Figure 1. The identification of a new source should prompt a re-examination of the global methane budget, and may ultimately help to reconcile the differences between the bottom-up and top-down techniques.

Meanwhile, Keppler and colleagues' finding[1] helps to account for observations from space of inexplicably large plumes of methane above tropical forests[3]. They may also explain the current puzzling decrease in the global growth rate of atmospheric methane[4,5]. Deforestation has led to a dramatic reduction in the Earth's tropical forested area (more than 12% between 1990 and 2000)[1]. Keppler *et al.* calculate a corresponding decrease in methane emissions from tropical plants of between 6 million and 20 million tonnes over the same period. During that decade, the rate of methane accumulation in the atmosphere slowed by about 20 million tonnes per year,

a

Identified methane sources	Estimates[8]	Range of estimates[2]
Total wetlands	145	92–237
Rice agriculture	60	40–100
Ruminant animals	93	80–115
Termites	20	20–20
Biomass burning	52	23–55
Energy generation	95	75–110
Landfills	50	35–73
Ocean	10	10–15
Hydrates (marine and terrestrial)	5	5–10
Total identified sources	**530**	**500–600**

b

Identified methane sinks	Estimates	Range of estimates
Tropospheric oxidation	507	450–510
Stratospheric loss	40	40–46
Soils	30	10–44
Total identified sinks	**577**	**460–580**
Total sources–sinks	**–47**	**–80 to +140**

Figure 1 | Methane sources and sinks. Numbers are millions of tonnes of methane per year. **a**, Estimates[8] and range of estimates[2] of annual emissions of methane to the atmosphere from identified sources. **b**, Equivalent figures for methane sinks. The estimates from ref. 8 imply that atmospheric methane is decreasing because identified sources are smaller than the sinks, but this is not confirmed by current measurements of methane in the atmosphere[5]. The ranges in the right-hand column show the extreme values compiled by seven different research groups, as well as estimated total sources and sinks assessed by the Intergovernmental Panel on Climate Change[2]. Note that, for statistical reasons, the sum of the individual source and sink ranges is not the same as the estimated total source and sink ranges. The wide divergence in these figures shows just how ill-defined the methane source inventory and budget are. The new source identified by Keppler *et al.*[1] — methane emitted by vegetation in oxic conditions — is estimated to produce between 63 million and 243 million tonnes per year, but potentially may double count sources listed above.