transfer, we can determine whether imprinting is preserved or erased in differentiated cells. The low success rate of cloning may turn out to be due to a random loss of correct imprinting. Moreover, differentiated female cells contain one inactive X chromosome, whereas in early female embryos both X chromosomes are active. So, we can learn much about inactivation of the X chromosome by monitoring what happens to the inactive X chromosome after nuclear transfer. Cloning by nuclear transfer from established, well-characterized cell lines will be much more informative than cloning from cells that have been freshly isolated from adult or fetal tissues.

With the cloning of large farm animals, the goals become economic[10]. The profit motive has, fortunately, kept cloning research alive, despite initial difficulties. Genetically altered fibroblasts (connective-tissue cells) can now be used to clone sheep[11] and cows[12] by nuclear transfer, and this should allow us to engineer the large-scale production of useful proteins by farm animals. Obviously, cultured cells must be used for precise targeting of the desired genetic manipulation, be it the addition or deletion of a specific gene. This again highlights the need to establish well-defined, cultured cell lines to be used for cloning.

Finally, what about cloning humans? At some point we will have to determine whether and when cloning — in the sense of taking somebody's cell nucleus, transferring it into an egg and raising the embryo to term and beyond — should be attempted. But we must remember that cloning is not an instant duplication, so mad dictators will not be able to expand themselves into huge armies of doppelgängers, nor will the bereaved be able to restore their lost ones. There is, nevertheless, one area in which cloning technology can be useful to humans: cell and tissue therapy.

Practical problems notwithstanding, at present there are no theoretical obstacles to such tissue therapy. Embryonic stem cells have the ability to differentiate into any cell type and could be produced from human blastocysts (embryos at a very early stage of development). Indeed, this has been done repeatedly in mice. This means that people could provide their own cells and, by using them to replace the nuclei of their own or donor eggs, obtain stem cells in culture. These cells could then be induced to differentiate in culture, providing individually tailored cell and tissue replacements without the current problems of rejection that affect transplantation from the same or foreign species. But, as far as I know, it would be illegal in most countries to sacrifice such blastocysts by turning them into a cell line in culture, because they represent potential human beings. Moreover, many technical problems will have to be overcome before this approach can become reality, but its potential value for human medicine is enormous.

There are many other beneficial aspects of cloning — easy preservation of genetically important strains and mutants of laboratory and farm animals, preservation and propagation of endangered species (provided that interspecies nuclear transfer is biologically possible) and genetic improvements, among others. There are undoubtedly many obvious and hidden dangers as well, although these do not include the groundless fears and blanket bans that seem to be the knee-jerk reaction to any cloning news. The work of Wakayama and colleagues[6] may be the last report (or at least the penultimate, as the first cloning of humans is bound to raise a few eyebrows) to induce a media frenzy. After this, I hope that we can move towards times when cloning will become a standard and useful technique to address numerous problems in basic and applied science. ☐

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Nonlinear dynamics

Death by delay

Steven H. Strogatz

Anyone who has ever taken a shower in an old dormitory knows that time delays can cause oscillatory instabilities. First the water is too cold, so you turn up the heat. But as you stand there shivering, the water does not get any hotter, because of delays in the antiquated heating system. If you impatiently turn up the heat even more, you are in trouble — by now, your original request for heat has registered and the water is scalding. Furiously reversing the setting, you are about to trigger a series of wild oscillations.

This much is familiar. The new twist, reported in *Physical Review Letters* by Reddy, Sen and Johnston[1], is that delays can also have the opposite effect: they can damp out oscillations that would otherwise be self-sustaining. More precisely, coupled limit-cycle oscillators can drive one another to a state of zero amplitude — often called amplitude death — if their mutual interactions are suitably delayed. This 'death by delay' may affect coupled limit-cycle oscillators in physics, medicine, biology and chemistry.

In the new models, each oscillator is assumed to have a stable limit cycle (Fig. 1). This assumption is appropriate for any system that will oscillate on its own, that is, in the absence of external periodic forcing. Examples include the heart's own pacemaker cells, rhythmically chirping crickets, flashing fireflies, a pendulum clock with an escapement, aeroelastic flutter in airplane wings, oscillating chemical reactions, and Josephson junctions driven by a constant-bias current[2].

In the earliest research on limit-cycle oscillators, between about 1920 and 1970, most theorists concentrated on the behaviour of a single, periodically forced oscillator, or two coupled oscillators. The questions were prompted in part by such emerging nonlinear technologies as vacuum tubes, phase-locked loops, radar and lasers, as well as by their intrinsic mathematical interest. Nowadays, the important theoretical problems concern the collective behaviour of large arrays of oscillators[3]. Synchronization, wave propagation, spatial patterns and self-organized criticality have

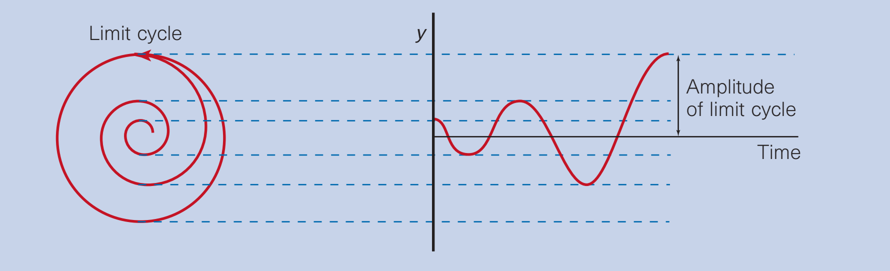

Figure 1 **A self-sustained oscillation in voltage, concentration or some other physical variable is represented geometrically by a limit cycle. Here the *y*-axis records a measurable variable, and the other coordinate represents the remaining variable (such as current, or rate of change of concentration) needed to characterize the state of the system completely. If a disturbance suddenly reduces the amplitude, the oscillation spontaneously builds back up to its standard size.**