one more predictable transcription factor, NANOG, and a fourth largely unconsidered gene encoding Lin28, a protein thought to be involved in RNA processing (*15*). This combination shares only two of the factors reported by Takahashi *et al.*, raising the question of redundancy among genes that can reprogram cells. Perhaps one master gene upstream of the six now described opens the gate to pluripotency. Yu *et al.* avoid expressing c-*Myc*, which can act as an oncogene and cause cancer, and improve gene delivery by using lentiviral vectors. It is possible that c-Myc promotes the proliferation of induced pluripotent stem cells until the stochastic and progressive process of dedifferentiation has progressed sufficiently to allow self-renewal. c-Myc could be functionally redundant with NANOG, which maintains embryonic stem cell pluripotency. Yu *et al.* further show that from the eight induced pluripotent stem cell lines generated, two expressed Oct4, Sox2, and NANOG alone. It is extraordinary that just three exogenously expressed transcription factors can completely reprogram a cell.

Finally, Hanna *et al*. show that symptoms of sickle cell anemia can be ameliorated with induced pluripotent stem cells in a mouse model of this human disease. Adult somatic cells taken from the tail of a mouse bearing a mutated version of the human β-globin gene were converted into induced pluripotent stem cells. The mutation was then repaired and through expression of the HoxB4 transcription factor, the cells were differentiated into hematopoietic progenitor cells and transferred back into the affected animals. All three animals treated with the induced pluripotent stem cells survived up to 20 weeks, whereas untreated animals died before the seventh week of age. The treated animals also showed increases in red blood cells and hemoglobin. Although it is premature to extrapolate these experiments to humans (we have yet to obtain mature blood cells from human embryonic stem cells), Hanna *et al.* have shown that induced pluripotent stem cells are more than a laboratory amusement: They may not only treat, but potentially cure diseases, at least in an animal model (and for the limited time of the study).

These three reports come on the heels of the announcement by Byrne *et al.* that nonhuman primate embryonic stem cells can be derived from adult fibroblasts using somatic cell nuclear transfer (*16*). The next logical step will be to compare the cells obtained by Byrne *et al.* with those generated using the suite of transcription factors implicated in cell dedifferentiation. Such a comparison is necessary to determine whether the reprogramming process and function of induced pluripotent or somatic cell nuclear transfer-derived cells are equivalent or not. We may not be able to resolve these questions anytime soon, not only because the mechanism of somatic cell nuclear transfer has yet to be described in detail, but more because we can as yet only follow the transformation of a given somatic cell into an induced pluripotent stem cell when embryonic stem cell–like colonies first emerge, and not any earlier.

The current breakthroughs raise exciting questions. Some are technical, such as whether viral vectors can be replaced with other agents that facilitate transient expression of delivered genes. Others are mechanistic, such as whether the conversion of cells is due to epigenetic modifications of key genetic elements or to a genetic event that has yet to be identified. Another question is whether several events must occur in a given sequence, with a precise amount of each transcription factor at a particular time, for cell dedifferentiation to occur and be sustained. This also raises the issue of whether the converted cell that gives rise to an induced pluripotent cell colony is somehow predisposed to "stemness," given that, in the context of somatic cell nuclear transfer, it is clear that pluripotent cells, such as embryonic stem cells, are easier to reprogram into viable animals than are somatic cells.

Is human therapeutic cloning no longer needed? The short answer is no, but it is likely a matter of time until all the hypothetical advantages of therapeutic cloning will be implemented with induced pluripotent stem cells. More importantly, the controversial issues (ethical and technical) specific to human therapeutic cloning may well be left behind along with the procedure itself, a refreshing change for the field, indeed.

References and Notes

1. R. Edwards, P. Steptoe, *A Matter of Life* (Hutchinson, 1980).
2. I. Wilmut, A. E. Schnieke, J. McWhir, A. J. Kind, K. H. S. Campbell, *Nature* **385**, 810 (1997).
3. J. A. Thomson *et al.*, *Science* **282**, 1145 (1998).
4. R. P. Lanza, J. B. Cibelli, M. D. West, *Nat. Med.* **5**, 975 (1999).
5. T. Wakayama *et al.*, *Science* **292**, 740 (2001).
6. W. M. Rideout 3rd, K. Hochedlinger, M. Kyba, G. Q. Daley, R. Jaenisch, *Cell* **109**, 17 (2002).
7. J. Yu *et al.*, *Science* **318**, 1917 (2007).
8. J. Hanna *et al. Science* **318**, 1920 (2007).
9. K. Takahashi *et al.*, *Cell* **131**, 861 (2007).
10. K. Takahashi, S. Yamanaka, *Cell* **126**, 663 (2006).
11. M. Wernig *et al.*, *Nature* **448**, 318 (2007).
12. K. Okita *et al., Nature* **448**, 313 (2007).
13. A. Meissner *et al., Nat. Biotechnol.* **25**, 1177 (2007).
14. R. Blelloch, M. Venere, J. Yen, M. Ramalo-Santos, *Cell Stem Cell* **1**, 245 (2007).
15 E. Balzer, E. G. Moss, *RNA Biol.* **4**, 16 (2007).
16. J. A. Byrne *et al.*, *Nature* **450**, 497 (2007).

17. Thanks to S. Suhr for helpful comments.

10.1126/science.1153229

MATERIALS SCIENCE

The Flow of Glass

Michael L. Falk

Experiments on colloidal glasses quantify how glass structure accommodates flow.

How does glass bend and flow? This question may seem odd to most people, given that in our common experience glass is something hard and brittle. But for those who have seen a glassblower at work, it is clear that the ability of glass to change shape when heated is crucial to its utility and beauty (see the first figure). The flow of glass is the subject of a revealing set of experiments published by Schall *et al.* on page 1895 of this issue (*1*).

The authors performed their experiments on a system composed of colloids—beads smaller in diameter than a human hair suspended in solution. To appreciate the connection between colloids and glassy materials, it is important to understand that in addition to soda-lime glass (the material composed primarily of silica that constitutes our housewares and windows), glasses can also be made from nearly every other kind of material, including plastics and even metals. So what makes something a glass?

To a large extent, a glass is defined by what it is not: a well-ordered crystal. The vast majority of engineering materials are crystalline, that is, they have an underlying repetitive structure from which they derive their electrical, mechanical, thermal, and optical properties. This structure typically arises when the material is created from a liquid. As the liquid cools, the atoms find an arrangement that optimizes their bonding, giving birth to small crystallites that grow into the final material structure.

Glasses, in clear contrast to their crys-

The author is in the Department of Materials Science and Engineering, University of Michigan, Ann Arbor, MI 48109, USA. E-mail: mfalk@umich.edu

The art of glassblowing. When glasses are heated to very high temperatures, they become highly viscous. Upon cooling, the glass rigidifies. The processes that govern flow in the cooled glass are elucidated by Schall *et al.* in this issue.

talline cousins, are models of disorder. As a glass is cooled, its atoms retain the same disorder that they exhibited as a liquid. The motions of the atoms slow down, resulting in a material just as solid as any crystal but without a crystal's obvious structural order. For this reason, glasses have often been referred to as amorphous (literally "shapeless") solids, but recent investigations have indicated that these materials have their own unique, if subtle, structure (*2*). This structure may explain why a glass, a material with a structure so similar to that of a liquid, does not flow in a liquid-like manner. When simple liquids flow, they tend to do so a little bit at a time everywhere, such that their flow is more-or-less uniform. However, studies like those by Schall *et al*. clearly demonstrate that in glasses, flow is not so simple.

Crystals do not flow naturally, but if you apply enough force to them, you can make them flow. On the atomic scale, this is accomplished by a misalignment in the crystal lattice known as a dislocation (see the second figure, top panel). You can think of it as a bump in a rug. It is possible to get a rug, even a very heavy one, to move a small amount by creating a bump on one end and pushing the bump along the rug. Similarly, once a dislocation is created it can glide through the crystal. As a result, the crystal undergoes an internal slip that changes its shape.

Is there a defect that could act as a dislocation for glasses? Spaepen, one of the authors on the current investigation, theorized in 1977 that "flow defects" were responsible for plastic flow in glasses (*3*). Dislocations can be directly imaged in crystals using transmission electron microscopy (*4*), but such characterization techniques are considerably more difficult to apply to glasses.

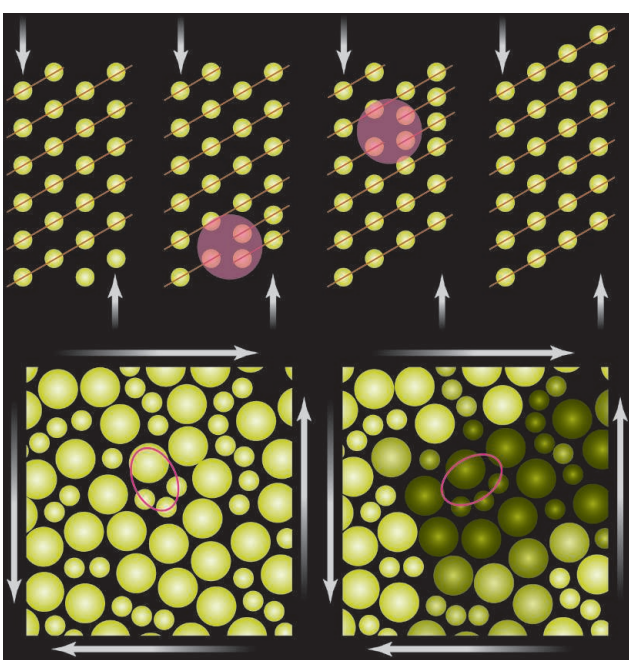

PHOTO CREDIT: NIKLAS BERNSTONE/GETTYIMAGES

The role of defects. (**Top**) In crystals, flow is determined by dislocations, defects in which the planes of the crystal are shifted relative to each other. These defects change the shape of the material by gliding through the crystal. The arrows denote the applied forces and the red circle shows the location of the dislocation. The diagonal lines emphasize the crystal planes in the atomic arrangement. (**Bottom**) In glasses, a different type of defect—a shear transformation zone—accommodates the flow. When a shear stress is applied in the direction of the arrows, the atoms rearrange from the positions on the left to those on the right. The darker colors denote which atoms on the right have had the most rearrangement in their vicinity. The ovals illustrate the approximate internal rearrangement associated with the shear transformation zone. [Adapted from (*8*)]

For this reason, similar but larger-scale systems have long been used to elucidate flow in glasses. Some early investigations were performed in sheared bubble rafts, in which a single layer of millimeter-sized soap bubbles floats on water (*5*, *6*). Based on these experiments, Argon proposed that regions in the glass undergo "shear transformations" (*7*); theories that posit shear transforming flow defects commonly refer to these as shear transformation zones (see the second figure, bottom panel) (*8*). Computer simulations have shown that these zones are associated with regions of enhanced structural disorder (*9*) and are sensitive to pressure (*10*). Schall *et al.* now confirm the existence of shear transformation zones in their colloid system. They also show that they are irreversible and thermally activated, and that their transformation can induce the formation of new shear transformation zones. Furthermore, they quantify the stress needed to cause a shear transformation zone to transform.

There are some important differences between the current work and the model bubble raft systems studied in the 1970s. First, the colloidal system is three-dimensional, providing a more realistic model for a real glass. Second, the authors reveal the detailed dynamics of their system, by means of confocal microscopy and digital data analysis.

These investigations are particularly relevant to understanding the formability, fracture, and failure of an emerging type of material, metallic glasses. While glasses have been made out of metal since the 1960s (*11*), the cooling rates required were so fast that only thin ribbons could be manufactured. It is only in the past two decades that these materials have been produced at moderate quench rates at thicknesses that lend themselves to a broader array of engineering applications (*12*, *13*). Metallic glasses are exceptionally strong and elastic, but when their strength is exceeded they typically fail catastrophically (*14*).

Investigations like those presented by Schall *et al.* provide valuable insights that can provide the underpinnings for predictive theories of glass flow and failure. Such theories are needed to pave the way for new materials that take advantage of the disorder inherent in glasses, which may in the years ahead provide as rich a source of new materials advances as crystals have to date.

References

1. P. Schall *et al*., *Science* **318**, 1895 (2007).
2. H. W. Sheng, *Nat. Mater.* **6**, 192 (2007).
3. F. Spaepen, *Acta Mater. Acta Metall.* **25**, 407 (1977).
4. S. M. Ohr, J. Narayan, *Philos. Mag. A* **41**, 81 (1980).
5. A. W. Simpson, P. H. Hodkinson, *Nature* **237**, 320 (1972).
6. A. S. Argon, H. Y. Kuo, *Mater. Sci. Eng.* **39**, 101 (1979).
7. A. S. Argon, *Acta Metall.* **27**, 47 (1979).
8. M. L. Falk, J. S. Langer, *Phys. Rev. E* **57**, 7192 (1998).
9. D. Deng *et al*., *Philos. Trans. R. Soc. London Ser. A* **329**, 549 (1989).
10. C. A. Schuh, A. C. Lund, *Nat. Mater.* **2**, 449 (2003).
11. W. Klement *et al*., *Nature* **187**, 869 (1960).
12. A. Inoue *et al*., *Mater. Trans.* **31**, 177 (1990).
13. A. Peker, W. L. Johnson, *Appl. Phys. Lett.* **63**, 2342 (1993).
14. C. A. Schuh *et al*., *Acta Mater.* **55**, 4067 (2007).

10.1126/science.1150919

The Flow of Glass
Michael L. Falk (December 21, 2007)
Science **318** (5858), 1880-1881. [doi: 10.1126/science.1150919]

Editor's Summary