the resolution of this region of the protein structure is not high enough to be completely certain.

When Coscia and co-workers replaced all eight hormonogenic tyrosine residues with a different residue, they could not detect any thyroxine production from the resulting mutant in their *in vitro* assay. The authors therefore conclude that only these residues are hormonogenic, out of 67 tyrosine residues in each monomer. However, it could be that the lack of hormone was due to other, unidentified sites ceasing to produce thyroxine as a result of conformational changes induced by the tyrosine substitutions.

So, do the eight identified tyrosine residues have anything in common that explains their hormonogenic activity? They are all at least partly exposed to the solvent around thyroglobulin, and the side chains of the donor–acceptor pairs formed by these residues face each other in an approximately antiparallel configuration. These residues are also all in highly mobile regions of the protein — presumably to enable the substantial bond rearrangements that need to take place to generate thyroxine.

The authors went on to show that thyroxine can be produced *in vitro* from a bacterial protein (maltose-binding protein; MBP) that has nothing to do with thyroid-hormone production. They found that either a pair of tyrosine residues found naturally in MBP, or a pair that was specifically introduced to have the same geometric arrangement and flexibility as the hormonogenic residues in thyroglobulin, produced thyroxine in the presence of an I^--oxidizing system and a peroxidase enzyme. Lactoperoxidase could be used instead of TPO, which is consistent with the previously reported observation that lactoperoxidase can promote the synthesis of thyroxine from thyroglobulin[9]. The observation that thyroxine can be produced using TPO and MPB indicates that the key requirement for generating thyroxine is the production of DIT, rather than the existence of a particular protein scaffold for the hormonogenic residues.

For reasons that are unclear, Coscia *et al.* did not detect the generation of triiodothyronine in any of their *in vitro* experiments. An earlier study[10] reported that triiodothyronine can be produced from thyroglobulin *in vitro*, and that the main site of hormonogenesis was Tyr 2766. It remains to be seen whether triiodothyronine was not observed in the current study because of the experimental conditions or because of the sensitivity of the assay used. More experiments are needed to understand not only normal triiodothyronine production, but also the mechanism that causes an increase in triiodothyronine biosynthesis in several situations: in Graves' disease (an autoimmune disease that affects the thyroid); in I^- deficiency; in people who have activating mutations of the TSH receptor; and when thyroid cells in culture are stimulated with sera from people with Graves' disease[1].

In addition to shedding light on details of the biosynthesis of thyroid hormones, Coscia and colleagues' determination of the 3D structure of thyroglobulin will probably also lead to a more thorough understanding of the effect of thyroglobulin mutations that cause congenital hypothyroidism — a deficiency of thyroid-hormone biosynthesis. It is a breakthrough as impressively big as the protein itself.

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Materials science

Metallic glasses that harden under strain

Frans Spaepen

Metallic glasses are much stronger than conventional metals, but form certain instabilities under stress that lead to fracture. A process known as rejuvenation has been shown to solve this problem. **See p.559**

Metallic glasses are formed by cooling melted alloys under conditions that prevent the melt from crystallizing[1]. They have remarkable mechanical properties — in particular, they can be subjected to high forces and undergo a large amount of deformation before they stop behaving elastically and start to deform permanently (plastically). However, they have one key weakness: they are prone to catastrophic failure under stress because they soften during plastic deformation, rather than hardening, as crystalline metals do. On page 559, Pan *et al.*[2] report a method for preparing metallic glasses that causes them to harden during plastic deformation, thereby avoiding the instabilities that lead to failure.

If you take a paper clip and bend it, you'll find that more force is needed as you bend it to an increasingly sharp angle. This is an example of work, or strain, hardening — the strengthening of a material through plastic deformation. At the atomic scale, the plastic deformation of metallic crystals in the wire is caused by the motion of 'dislocations'. These linear defects in the crystal structure multiply, intersect and entangle as deformation proceeds, thereby getting in each other's way and strengthening the material[3]. This makes work hardening one of the most complex problems in science: it needs to be understood at many length scales, from the atomic-scale lengths of the dislocation cores, through the nano- and micrometre scales involved in dislocation interactions and structures, to the macroscale lengths associated with crack propagation and the structural stability of bulk materials.

The mechanical behaviour of metallic glasses is fundamentally different. Because their atomic structure is not periodic, there are no dislocations. Plastic deformation instead occurs through shear, a mode of deformation that affects small groups of atoms (known as shear transformation zones; STZs) throughout the glass[4]. This shearing loosens (dilates) the atomic structure, and the resulting increase in volume facilitates the formation of new STZs. If the rate of deformation is sufficiently high, the atomic structure does not have time to relax and densify again. As a result, the local deformation rate continues to rise and finally becomes unstable, forming a narrow zone of intense shear strain (a type of deformation) known as a shear band.

Shear bands are macroscopic phenomena. They cause steps to form on the surfaces of materials and can therefore be suppressed by applying appropriate constraints — for example, by sandwiching metallic-glass layers

between conventional hard metals[5]. Pan *et al.* accomplish this suppression by cutting a deep, narrow notch around the circumference of a cylindrical glass bar, and compressing it in the direction of its axis (see Fig. 1a of the paper). The central region of the bar near the notch undergoes extensive plastic deformation, during which shear bands are suppressed by the constraints exerted by the outer parts of the bar. The authors then cut out the central part and deformed the unconstrained sample under tension or compression. Remarkably, the resulting material exhibits properties similar to those of conventional crystalline metals: it undergoes work hardening and does not form shear bands.

The mechanism responsible for this hardening, however, is far from conventional. To explain why, let's consider the ground states of crystals and glasses. A crystal in its undeformed ground state has the lowest possible flow stress (a measure of the force needed to sustain plastic deformation). The introduction of dislocations during deformation costs energy, and their entanglement raises the flow stress[3]. A glass in its ground state, however, has the highest possible flow stress because it has the lowest number of STZs. Deformation of this state costs energy, but through shear-induced dilatation introduces new STZs that lower the flow stress (see ref. 6, for example).

All glasses are in non-equilibrium states. When they are heated (annealed) to a temperature at which their atoms can move, the process tightens up their atomic packing and lowers their energies towards a ground state[7]. This process is called structural relaxation, or ageing, and it changes the properties of glasses[8]. For example, it can increase the density by a few tenths of a per cent; raise the elastic stiffness by a few per cent; increase viscosity by many orders of magnitude; and sometimes cause ductile glasses to become brittle.

Reversal of this ageing process is called rejuvenation, and can be achieved in several ways. The simplest is to heat a glass until it becomes a liquid again, and then rapidly cool it[1]. Another approach is to 'shake up' the structure, for example by ion irradiation[9] or plastic deformation[10]. By heavily deforming samples of metallic glasses under constrained conditions, Pan *et al.* raise the energies of the glasses far above the energy of the ground state, rejuvenating them and loading them up with STZs. When the authors then deform them under the less-constrained conditions of a tensile or compressive test, structural relaxation sets in: the atomic packing increases and the volume introduced by the earlier deformation disappears; the number of STZs drops, causing the flow stress to increase; and work hardening is achieved.

The practical implications of this work are clear: if metallic glasses can be treated so that the threat of shear-band failure is greatly reduced, then they can be more fully exploited for structural applications. However, this will require the development of methods for rejuvenating large volumes of metallic glasses — Pan and colleagues' rejuvenated samples are only 3 millimetres long and 1.5 mm in diameter. Large-scale rejuvenation will require the deformation of large quantities of alloys under constrained conditions, which could be achieved using methods such as confined cold rolling[10] or equal-channel angular extrusion[11].

The authors' rejuvenation technique might also advance glass science. Because glasses are not in equilibrium, their properties depend on the processing path by which a particular state is reached. For example, in their experiments, Pan *et al.* measured the heat of relaxation of their glasses (a measure of the glasses' internal energy) after rejuvenation and after various stages of subsequent deformation. It would be interesting to know how the structure and other properties of their glasses compare with those of glasses that have the same heats of relaxation, but which were obtained by the cooling of melted material and annealing. In other words, what makes the authors' rejuvenation technique attractive is that it opens up many more paths for exploring the complex relationship between structure and properties in glasses.

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In retrospect

Turning connective tissue into neurons for 10 years

Giacomo Masserdotti & Magdalena Götz

A method for directly converting connective-tissue cells into neurons opened up a new branch of research into cell-based therapies and called into question long-held beliefs about how development affects a cell's identity.

Our bodies rely on specialized cell types: brain cells compute information, red blood cells bind oxygen, and so on. Because almost all our cells have identical DNA, different patterns of gene and protein expression are needed to define these cell types. The selection and maintenance of these expression cascades were once thought to be irreversible after development. Over time, it emerged that cell identity could be changed, but it was often assumed that a cell could be converted into another cell type only if the two had a similar developmental origin. Ten years ago, Vierbuchen *et al.*[1] overthrew this idea, by showing that connective-tissue cells called fibroblasts could be converted into functional neurons — which have a very different developmental origin — if they were engineered to express just three extra transcription factors.

This achievement was built on almost a century of visionary experiments in manipulating cell identity. In 1927, Hans Spemann showed that it was possible to change the fate of cells in a salamander embryo. The embryologist grafted 'organizer' cells (which drive early development of the body plan) from a donor embryo into a host embryo[2], triggering the formation of a second embryo from the host cells. In 1962, the biologist John Gurdon showed that development can also be returned to the start[3] — the nucleus of an adult cell can reacquire a state similar to that of cells in the earliest stages of development, and in this state it can give rise to an entire embryo.

In the 1980s, it became clear that cells can also be directly converted from one specialized cell type to another (Fig. 1a). The first example[4] was the conversion of fibroblasts into muscle cells by inducing the cells to express the transcription factor MyoD. Some