histamine, serotonin and calcium. These ions bind tightly to and neutralize the fixed charge groups, causing the granule network to shrink. Shrinking is favoured when the counterion is polyvalent or partially hydrophobic.

If a secretory granule consisted only of a charged network, it would not hold its payload very long in the intracellular or the extracellular environment. Sodium and potassium ions would invade the granules and rapidly 'exchange out' the incorporated species. Because these metal ions do not bind to the fixed negative-charge groups, they would establish an osmotic pressure inside the granule, causing it to swell and release its contents. To prevent this, the granule is coated with a lipid membrane that blocks ion transport. Secretion of the stored contents requires electrochemically stimulated fusion of the granule's membrane with the cell membrane, which exposes the matrix to the extracellular medium, triggering ion exchange and swelling.

If nature can do this, why can't we? That was the question asked by Needham and colleagues, and their response is outlined in Fig. 2 of the paper on page 459. Using technology that had already been developed[5], they synthesized crosslinked polymethacrylic-acid microgels that had a swollen diameter of 6.5 μm at pH 7.4. They then incorporated the hydrophobic, cationic, anticancer drug doxorubicin hydrochloride at pH 5.0, which neutralized the acid groups, causing the gel to shrink. As a final step, they used a newly devised process to coat the collapsed gel with a lipid bilayer, and showed that the lipid was present exclusively at the surface. The lipid coating all but prevents dissipation of pH gradients, and the acidified construct remains stable in pH 7.4 phosphate-buffered saline, a proxy for body fluids, for at least 48 hours. By this means they mimic the storage aspect of a granule.

To demonstrate 'quick release', the authors exposed microspheres in phosphate-buffered saline at pH 7.4 to electroporation fields that were strong enough to breach the lipid coatings. A brief electroporation pulse led to rapid swelling of the gels which was complete within seconds, and all the incorporated doxorubicin was released within minutes. Although these processes take somewhat longer than they do in nature, the times concerned are more than acceptable for many drug-release purposes.

How might such a system be used in practice? The particles are of such size that they will be rapidly cleared by the reticuloendothelial system, which consists of scavenger cells that continually patrol the body. So, without modification, the system is probably best suited for local administration, be it subcutaneous, intramuscular or intraperitoneal. The authors suggest, however, that the synthesis can be altered to make much smaller particles that will avoid the reticuloendothelial system and can also leak through the porous capillary walls of tumours, providing targeted delivery of anticancer agents. The practicality of the system might be further improved by tethering certain molecules, ones which bind specifically or nonspecifically to target cells or extracellular matrix, to the lipid coating, thus localizing the microspheres at a particular site and perhaps preventing side-effects. Collagen, peptides containing arginine–glycine–aspartate sequences and Fab fragments of antibodies are logical candidates. This strategy has been investigated with liposomes, another type of drug carrier[6].

Needham and colleagues' prototype system triggers drug release by electroporation, which may be difficult to effect *in situ*, and the authors point out that modifications to the lipid coating may make it sensitive to stimuli such as temperature or ultrasound. Work with liposomes also points to a second, potentially powerful, refinement of the system[7,8]. By anchoring suitable stimulus-sensitive polymers in the membrane, one can destabilize the lipid coating, and therefore trigger drug release, by changes in local temperature, pH and glucose concentration, or by illumination at a particular wavelength. Even more sophisticated systems can be envisaged in which lipid-coated, bioadhesive microgels that respond to different stimuli, each type of microgel containing a different agent, are mixed together and delivered locally or regionally. Such a system could permit localized combination therapies, in which the delivery of the different agents occurs according to a predetermined sequence.

These kinds of elaborations would add further complexity to Needham and colleagues' system — the combinatorial possibilities are numerous, and would require a great deal of further development and testing. Moreover, the effectiveness of the original concept needs to be tried out in an animal model. At the least, however, the authors have succeeded in showing how some cunning chemistry can be used to emulate a physiological process for the purposes of improved drug delivery. □

Ronald A. Siegel is in the Departments of Biopharmaceutical Sciences and of Pharmaceutical Chemistry, School of Pharmacy S-926, University of California at San Francisco, San Francisco, California 94143-0446, USA.
e-mail: ras@rebus.ucsf.edu

1. Kiser, P. F., Wilson, G. & Needham, D. *Nature* **394,** 459–462 (1998).
2. Langer, R. S. & Peppas, N. A. *Biomaterials* **2,** 201–214 (1981).
3. Tanaka, T. & Fillmore, D. *J. Chem. Phys.* **70,** 1214–1218 (1979).
4. Fernandez, J. M., Villalon, M. & Verdugo, P. *Biophys. J.* **59,** 1022–1027 (1991).
5. Kashiwabara, M., Fujimoto, K. & Kawaguchi, H. *Coll. Polym. Sci.* **273,** 339–345 (1995).
6. Yerushalmi, N. & Margalit, R. *Archiv. Biochem. Biophys.* **349,** 21–26 (1998).
7. You, H. & Tirrell, D. *J. Am. Chem. Soc.* **113,** 4022–4023 (1991).
8. Meyer, O., Papahadjopoulos, D. & Leroux, J. *FEBS Lett.* **421,** 61–64 (1998).

Daedalus

A chance of justice

A legal verdict, says Daedalus, pretends to be a certainty; but in truth it is merely a probability. Consider, for example, those plaintiffs who claim to have been made ill by silicone breast-implants, radioactivity or tobacco. Clearly it is impossible to be sure that they would not have got just as ill if they had never encountered these perils.

So Daedalus is musing on the character and process of a truly scientific court. If, for example, epidemiological evidence shows that passive smoking in the workplace increases your chance of getting lung cancer by 1%, then the judge could decide the case won if the number 100 turns up on his random number generator, but lost if 1–99 turn up. Chancy or vexatious litigants would be strongly discouraged.

It might be fairer, however, to allow an openly statistical verdict. A defendant found 'probably guilty' (perhaps set at 91.7% if 11 jurors out of 12 reckon he did it) might incur a fine or punishment reduced in proportion. A defendant found 'probably innocent' (say, 8.3% or 16.7%) might leave the court unpunished, but with a definite 'stain' on his character. Thereafter, until the stain was declared spent, or expunged by good behaviour, he would be literally 'a suspicious character' — which would tell against him if he came up again on a similar charge.

This approach would fit well into British society. British motorists already accumulate 'stains' on their driving licences for each small offence. Enough staining cancels the licence. The British honours system awards a 'shine' on the character of good eggs and praiseworthy types; if they later go to the bad, the shine can be withdrawn again. Affirmative action gives whole groups a collective shine, entitling them to jobs, presumptions of virtue or innocence, and so on.

Such an open system of honours and dishonours is much fairer than the 'dossier societies' run by dictators. Secret dossiers, for some reason possibly connected with the second law of thermodynamics, only accumulate evidence against their subjects. Only those faceless apparatchiks who never put a foot wrong or do anything original, flourish under them. Ominously, dossiers are now growing fast even in the democracies, in the form of credit ratings, referees' reports, compulsory secret reporting of 'suspicious' bank deposits, and so on. An open, numerical 'stains and shines' system might just stop the rot.
David Jones