where predators are respectively too infrequent to thin their prey or so numerous that only the best-defended prey persist. Although the study of Kassen *et al.*[1] does not exclude the possibility that such mechanisms operate in other systems, it shows that neither complication is required to generate unimodal diversity–productivity curves.

Having established the minimal conditions required to produce such curves, challenges remain. It is not clear whether a single mechanistic framework can readily explain other kinds of diversity–productivity patterns. The cause of diversity patterns at larger spatial scales also remains frustratingly uncertain[2].

In particular, an especially contentious debate continues over the extent of feedback between diversity and productivity. Productivity (measured as energy or nutrient availability) can clearly influence diversity. But differences in diversity among habitats receiving similar amounts of energy can also influence productivity, when productivity is measured as the biomass of organisms accumulating on those sites[9,10]. One possible feedback mechanism is that increased productivity produces a physical scaffold to support biological heterogeneity (as, for example, in the spatial complexity of forest canopies) on which other species can build. Kassen *et al.* provide a simple example of this kind of self-organization by showing that self-supporting surface films of one bacterial morph form only at higher productivities.

Spectacularly complex natural ecosystems, such as tropical rainforests and coral reefs, have alternately inspired speculations about the causes of diversity and stymied the kinds of experiments required to sort pattern from process. Long-lived organisms, such as trees and corals, simply respond too slowly to experimental manipulations of productivity; it would take many human generations for responses to become apparent, even assuming that alterations of productivity at the appropriate scale could be engineered. That is why purpose-built ecosystems composed of short-lived organisms, such as those used by Kassen *et al.*, are playing an increasingly prominent part in tests of ecological theory. ■

Peter J. Morin is in the Department of Ecology, Evolution, and Natural Resources, 14 College Farm Road, Cook College, Rutgers University, New Brunswick, New Jersey 08901, USA.
e-mail: pjmorin@rci.rutgers.edu

1. Kassen, R., Buckling, A., Bell, G. & Rainey, P. B. *Nature* **406,** 508–512 (2000).
2. Gaston, K. J. *Nature* **405,** 220–227 (2000).
3. Tilman, D. & Pacala, S. in *Species Diversity in Ecological Communities* (eds Ricklefs, R. E. & Schluter, D.) 13–25 (Univ. Chicago Press, 1993).
4. Waide, R. B. *et al. Annu. Rev. Ecol. Syst.* **30,** 257–300 (1999).
5. Rainey, P. B. & Travisano, M. *Nature* **394,** 69–72 (1998).
6. Tilman, D. *Resource Competition and Community Structure* (Princeton Univ. Press, 1982).
7. Holt, R. D., Grover, J. & Tilman, D. *Am. Nat.* **144,** 741–771 (1994).
8. Leibold, M. A. *Am. Nat.* **147,** 784–812 (1996).
9. Tilman, D., Wedin, D. & Knops, J. *Nature* **379,** 718–720 (1996).
10. Hector, A. *et al. Science* **286,** 1123–1127 (1999).

Phase transitions

Catching crystals at birth

David W. Oxtoby

Seeing a crystal when it first appears in solution is no easy task. By the time the crystal is visible, it has already grown to macroscopic size. Using a microscope is not helpful either, because the chance that the crystal will first appear in the volume being examined is very small. Yet the earliest stages of crystallization — referred to as nucleation — usually determine the rate at which crystallization takes place, and therefore the eventual size and purity of the crystals. Since the 1930s, scientists have been developing increasingly sophisticated theories of nucleation, and have measured rates of nucleation experimentally by counting crystals once they have grown to macroscopic size, without ever actually seeing the nucleation events themselves.

On page 494 of this issue, Yau and Vekilov[1] report direct observations of small (100-nanometre scale) 'crystallites' taking part in these very first stages of crystallization. The authors look in detail at the crystallization of the protein apoferritin, which has a relatively slow timescale for crystal growth because of its large size. An ordinary ionic solid will crystallize very rapidly from solution once the first seed appears, because ions diffuse rapidly through water, but protein molecules move slowly enough that small crystallites can be caught before they have grown to macroscopic dimensions. Moreover, the molecules are large enough (a few nanometres) for their individual positions in the crystallite to be determined by modern atomic force microscopy. Proteins are thus useful models for studying crystallization, and they are also of interest in their own right — the crystallization of proteins is the key to determining protein structure by X-ray diffraction, and yet crystallization is still, in many ways, more an art than a science. Protein crystallization is also implicated in certain diseases such as sickle-cell anaemia and the formation of cataracts in the eye.

Although the first small crystallites involved in nucleation form in the bulk of the solution, Yau and Vekilov can observe them only once they have fallen to the bottom of the vessel and attached themselves to the surface there. How can the authors be sure that they are observing the critical early stages of crystallization described by nucleation? A small crystallite will tend to redissolve because it has a large surface to volume ratio; a large enough one will tend to grow in a supersaturated solution because of the thermodynamic driving force towards crystallization. The 'critical nucleus' is the size in between, where the probability of adding a particle exactly balances the probability of losing one.

Yau and Vekilov use atomic force microscopy to examine what happens to individual crystallites at the surface. They find that some (the smaller crystallites) tend to lose particles more readily while others (the larger ones) tend to grow. These measurements give a range for the size of the critical nucleus of between 20 and 50 molecules, depending on the concentration of protein in solution. Up to this point, their results simply confirm the long-held assumptions of nucleation theory, and provide some of the first direct observations of critical nuclei.

There is a surprise in the new results, however. For relatively spherical molecules, such as apoferritin, the assumption has always been that the critical nucleus would also be roughly spherical[2]: a tiny ball cut out from the bulk crystal lattice. Instead, the authors find that the critical nucleus is more like a raft, consisting of a nearly planar layer of crystal with a partial second layer on top. The shape of the critical nucleus could have a large effect on its energy and therefore on the rate of formation of crystals. If critical nuclei are not spherical, classical nucleation theory does not apply and simple prediction of nucleation rates will no longer be possible.

Yau and Vekilov build on this qualitative picture of crystallization by measuring the nucleation rates of their crystals, and show that their data are consistent with earlier light-scattering measurements of apoferritin nucleation[3]. It will be interesting to see whether these techniques can be used to determine the effect of protein concentration (and, hence, the degree of supersaturation) on nucleation rates. This would allow a direct test of the nucleation theorem[4], which is a fundamental relationship used by experimentalists to determine the size of a critical nucleus without actually seeing it.

So classical nucleation theory suggests that the critical nucleus is spherical, whereas Yau and Vekilov find a nearly planar crystalline structure. A third possibility is that the critical nucleus is not crystalline at all, but rather a disordered, liquid-like aggregate

of molecules. This last structure was predicted for the crystallization of proteins and other large molecules by computer simulations[5] and the approximate statistical-mechanical method of density functional theory[6]. These studies showed that under certain conditions the nucleation rate was significantly increased (by as much as 30 orders of magnitude). The key to the higher nucleation rates was the existence of a 'metastable' critical point at which fluctuations in protein concentration were enhanced. Under these conditions, it was predicted that the resulting critical nuclei would be highly disordered, with crystallinity appearing only at later stages in the growth process. It will be revealing to see whether this mechanism for crystal nucleation in proteins can be observed using the methods of Yau and Vekilov, by tuning the experimental conditions to bring their solutions close to a metastable critical point. ■

David W. Oxtoby is in the James Franck Institute and the Department of Chemistry, University of Chicago, Chicago, Illinois 60637, USA.
e-mail: d-oxtoby@uchicago.edu

1. Yau, S.-T. & Vekilov, P. G. *Nature* **406,** 494–497 (2000).
2. Turnbull, D. *J. Chem. Phys.* **17,** 71–73 (1949).
3. Malkin, A. J. & McPherson, A. *Acta Crystallogr. D* **50,** 385–395 (1994).
4. Kashchiev, D. *J. Chem. Phys.* **76,** 5098–5102 (1982).
5. ten Wolde, P. R. & Frenkel, D. *Science* **277,** 1975–1978 (1997).
6. Talanquer, V. & Oxtoby, D. W. *J. Chem. Phys.* **109,** 223–227 (1998).

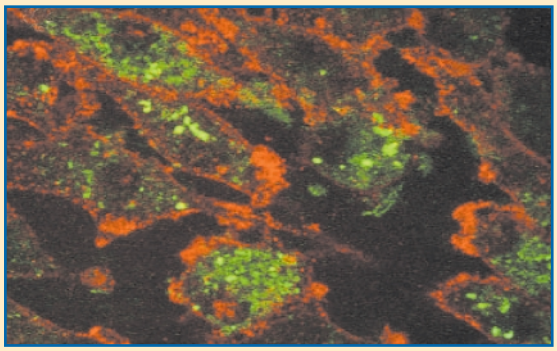
Alzheimer's disease

Plaque removers and shakers

Last year, Dale Schenk and colleagues reported (*Nature* **400,** 173–177; 1999) that Alzheimer's-like pathology in mice could be halted by vaccination with amyloid-β peptide — the main constituent of the amyloid plaques typically found in brains of Alzheimer's patients. Breathtakingly simple, but how does it work? Writing in *Nature Medicine* (**6,** 916–919; 2000), the same group now reveals that antibodies 'decorate' plaques and trigger their clearance by so-called microglial cells in the brain.

Alzheimer's disease is caused by the progressive malfunction and death of nerve cells. The gene encoding amyloid precursor protein (APP) is one of four genes with firm links to the development of Alzheimer's disease, and is mutated in certain hereditary forms of the disorder. How mutations in the APP gene result in the death of nerve cells is still a mystery, but snippets of APP, typically 42 amino acids long ($A\beta_{1-42}$), accumulate within plaques in the brains of Alzheimer's patients, and disease-linked mutations result in overproduction of this APP fragment.

Mice that carry a mutant human APP gene also develop plaques as they grow older — just like humans. Previously, Schenk *et al.* injected such mice with human $A\beta_{1-42}$, and



TERRY GUIDO

found that the animals produced antibodies against the peptide, to great effect: plaques were largely prevented from forming, and some of the pre-existing plaques in older mice were even dissolved. The same group now reports that antibodies that recognize $A\beta_{1-42}$, injected into the peritoneum, work as well as immunization with the $A\beta_{1-42}$ peptide. Apparently, the antibodies are able to penetrate the brain in low but therapeutically meaningful amounts.

The authors also show that the antibodies effective *in vivo* bind to amyloid plaques in brain tissue sections of afflicted mice and men, and to antibody receptors on microglial cells. Once activated in this way, these cells engulf and destroy the $A\beta_{1-42}$ peptide, as pictured here ($A\beta_{1-42}$ is shown in green; microglial cells are stained red).

Last week the same group announced initial results from clinical trials showing that the $A\beta_{1-42}$ vaccine is safe and well tolerated in humans. The results are promising, but these are early days and caution is warranted. First, it's not certain that humans mount as vigorous an immune response to the human $A\beta_{1-42}$ peptide as do mice. If they do not, passive immunization with antibodies may be the way forward.

Second, the mice used for these studies only partially mimic the human disease: although $A\beta_{1-42}$ accumulates in their brains, mice show neither the same loss of nerve cells nor the behavioural abnormalities associated with the human condition. And it's not yet clear whether the amyloid plaques are causing neuronal malfunction and death, or are merely a by-product of the disease, so it remains to be seen whether preventing the plaques from forming will be beneficial to Alzheimer's patients. **Marie-Thérèse Heemels**

100 YEARS AGO

Captain R. H. Elliott, who has been for some time conducting researches into the nature and action of snake venom in India, arrives at the following conclusions in the *British Medical Journal*:— (1) The snakemen of South India are certainly ignorant of any method of producing in themselves a highly-developed condition of immunity. (2) Some few of them appear to practise the swallowing of venom, or the inunction of venom into their limbs, but it is doubtful if they do so with any well-defined object. It is possible that they thus obtain some degree of immunisation. (3) They confine themselves almost exclusively to the cobra, and escape harm by their intimate knowledge of the methods of handling this snake.
From *Nature* 2 August 1900.

50 YEARS AGO

There is anxiety throughout the world concerning reserves of energy. The demand for electricity has increased of late years at an exponential rate, and if the demand for coal, oil and gas has more nearly followed a straight-line law, the slope of the line has been such as to cause concern among individual nations as to when their own supplies of fossil fuels will become exhausted, and to the world in general as to possible sources of energy when there is no more coal or oil… In consequence of this position, there is the greatest activity all over the world to eke out coal reserves by using other sources of energy. Many nations, among whom are the Norwegians, the Swedes, the Canadians, the Finns, the Poles, the Austrians, the Portuguese, the French, the Swiss, and even the Americans, are developing their indigenous sources of water-power; in many of these lands this meets most of the energy requirements. Other ideas are finding practical expression. There is a project at Abidjan on the Ivory Coast for using the potential thermal energy of sea-water existing by reason of the vertical temperature gradient of 68° F. or more over a depth of 1,640 ft. in tropical seas; a boiler heated by water at a temperature of 82° F. would supply a turbine with steam at a corresponding pressure exhausting into a condenser cooled by water at 46° F. A unique hydro-electric scheme is proposed in North Africa whereby the waters of the Mediterranean would be admitted to the Qattara Depression, providing some 300 MW. of hydro-electric capacity.
From *Nature* 5 August 1950.