ogies². The kinetics of fibril formation and the effect of seeding in both purified and *in vivo* preparations support the nucleation self-seeding hypothesis.

The [PSI⁺] phenotype is also dependent on the expression of a heat-shock protein (Hsp104), a chaperone that oversees protein folding, which may therefore subsume the role of protein X. It is possible that if the concentration of such a heat-shock protein were drastically increased as a result of local stress, a nucleating seed could be created. If different heat-shock proteins were to form different 'strains' of seeds, then the basis of strain variation could be found in the structural organization of this nucleating molecule. Once the formation of Sup35 fibrils is initiated, a constant morphology is maintained, so it will be interesting to see whether Hsp104 plays a part in this effect.

Further support for the nucleation hypothesis has recently come from a mammalian system in which compounds that bind nonspecifically to amyloid fibrils affect the progression of experimental scrapie¹⁰. But the discussion is by no means over. The strongest evidence for a template-directed process is found in the persistence of strain differences in the physical characteristics of PrP-res upon transmission¹¹. In the final analysis, it may be that the models are not mutually exclusive, or that both mechanisms are involved.

Has BSE crossed the species barrier into humans, and are the 'new-variant' CJD cases, few though they are, a harbinger of future trends? The new molecular *in vitro* data^{1,2} should help us understand how on the one hand we are dealing with diseases that generate high titres of infectivity, but on the other are not particularly contagious. If we're lucky, the species barrier, encoded at least in part within the amino-acid sequence of PrP, will prove to be self-limiting. But if we're unlucky ...

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Symbiosis

Making light work of adaptation

Robert W. Buddemeier

Reef-building corals are photogenic 'doe-eyed invertebrates' which form high-diversity, shallow-water communities that are often loosely analogized to rainforests. They are cnidarians — relatives of jellyfish and anemones — and are usually, but not invariably, colonial. Among their distinguishing characteristics are the algal (dinoflagellate) symbionts that live within their tissues, and the rapidity with which their calcium carbonate (aragonite) exoskeletons are formed.

Because reef-building corals are vulnerable to human-induced stress, resulting in the mysterious phenomenon of 'bleaching' (stress-induced loss of the pigmented algae, with sometimes fatal consequences)¹, international monitoring and assessment groups have been set up^{2,3}. The paper by Rowan *et al.*⁴ on page 265 of this issue now opens up new pathways to understanding this complex biological system. The authors convincingly extend previous work, showing that there is neither a single taxon of symbiotic algae, nor a uniquely obligate relationship between a host species and a single algal taxon. Rather, at least some symbiotic corals are communities, and the distribution of the various plant taxa is controlled by the levels of light that are available in the microenvironment. Moreover, a synergistic relationship between light and temperature controls the distributions of algal taxa within the coral colony. Under high-temperature stress, the algal symbionts at the upper end of their normal irradiance range are preferentially lost (bleached). And the new work implies that the relationship is somewhat symmetrical — at marginally stressful temperatures, we would expect increases in irradiance to have similar effects.

Photosynthesis by the symbiotic algae consumes carbon dioxide. Marine calcification precipitates carbonate ions, forcing a re-equilibration of the bicarbonate-dominated marine inorganic carbon system that creates a carbon dioxide source⁵. So, it has long been an article of geological faith that the coral symbiosis is intimately and causally linked to the high rates of calcification in reef-building corals, compared with the rates in asym-biotic, non-reef-building corals⁶. This is also thought to have led to the massive accumulations of carbonates in shallow-water environments, and possibly even to feedback-controls on the global carbon cycle⁷.

Coral reefs are restricted to shallow-water tropical and subtropical environments, which are characterized by warm temperatures, aragonite supersaturation (concentrations of calcium and carbonate ions that

exceed the thermodynamic mineral solubility product), and high light intensities⁸. Along with this biogeography, the fidelity with which corals' aragonite exoskeletons record the isotopic and chemical characteristics of their growth environment⁹ has made them favourites of the marine palaeoclimate research community. Because corals have been around for more than 200 million years, and seem to be relatively stable in terms of rates of speciation and extinction¹⁰, the many recognizable fossils have made a large contribution to our understanding of climates and oceans past.

The current paradox of coral-reef research is that the organisms and ecosystems involved seem to be vulnerable to environmental change in the short term, yet they have persisted over hundreds of millions of years, through rapid (and sometimes extreme) environmental change — so how do they do it?

The demonstration by Rowan *et al.*⁴, of labile and micro-adaptive symbiotic combinations, fits well with other recent revisions of the conventional wisdom regarding coral systematics. Veron¹⁰ has reported that corals undergo reticulate evolution, characterized by hybridization and a level of genetic variation that is more common in plants than in

Figure 1 Latitudinal distributions of Holocene calcium-carbonate accumulation rates and types (shading indicates the relative importance of coral-algal communities), compared with temperature, surface-water aragonite saturation ratio⁷ and photosynthetically active surface radiation (400–700 nm)⁸. The existence of a 'tunable' multi-component algal symbiosis, proposed by Rowan *et al.*⁴, suggests that all three environmental variables play interacting roles in coral physiology and biogeography.

higher animals. Fautin¹¹ points out that varied reproductive strategies and the heritability of somatic mutations may result in considerable genetic variability, even within the presumed single clone of a large colony. So, many (if not all) coral 'species' represent a palaeontologically stable 'morphospecies', with genetic, symbiotic and niche variabilities that make a mockery of attempts to apply the species concepts that are associated with higher animals and terrestrial organisms.

The significance of these findings goes well beyond the level of depressing (but enlightening) news for organismic coral researchers — whether their bailiwick is the past or the present. The mechanisms by which corals calcify are not well understood, but it has long been known, for example, that skeletal morphology changes in many species as a function of the levels of light. Moreover, the isotopic and chemical composition of the exoskeleton may vary with the rate of growth (extension). Similar variations in how the taxa of the algae that mediate calcification are distributed within a colony constitutes a map for future research — not just an interesting, but frustrating, anomaly. Even more fundamental to the relationship between light, temperature and calcification are studies that seem to uncouple coral calcification¹² or extension¹³ from symbiosis or light, despite earlier experiments which showed that light/dark calcification ratios in symbiotic corals are much greater than unity¹⁴.

The discovery of many labile symbioses by Rowan *et al.* may help to resolve the apparent paradox: if reef-building corals retain the same, genetically hard-wired calcification mechanism that allows their asymbiotic cousins to build skeletons in dark, cold, undersaturated water, this may be reflected in the 'dark calcification' that builds the skeletal template¹³. In the light, photosynthesis by a 'tunable' suite of algal symbionts helps to optimize the harvest of calcium carbonate from supersaturated waters. This calcification component may even be as important as temperature in explaining why reefs are mainly in the tropics (Fig. 1). And the concept of dual-process calcification is a diel analogue of the differential extension-thickening model that explains variations of skeletal density on a seasonal basis¹⁵.

The present spate of exciting and unsettling findings highlights the roles of acclimatization and adaptation in explaining how the consistent metabolism of coral communities over space and structure¹⁶, and the consistent structure of these communities over time¹⁷, can be achieved by evolutionarily stable taxa in a highly variable environment. And these seemingly arcane questions are central to more immediate and practical issues, such as natural controls on carbon cycles and the survival of ecosystems and

biodiversity during global change. Whether they like it or not, coral researchers are living in interesting times. □

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Immunodeficiency viruses

Spoilt for choice of co-receptors

Paul R. Clapham and Robin A. Weiss

As intracellular parasites, viruses need first to attach to and then gain entry into cells. The human and simian immunodeficiency viruses (HIV, SIV) carry out these steps through surface glycoproteins which interact with different molecules displayed by the host cell. All immunodeficiency viruses bind with high affinity to the CD4 cell-surface receptor of T lymphocytes, which attaches them to the cell under attack, but different strains use distinct co-receptors to trigger viral entry (see Fig. 1 and our previous News and Views article¹ on the topic).

In papers on pages 296 and 238 of this issue^{2,3}, and elsewhere^{4,5}, several groups announce the discovery of further co-receptors for SIV and HIV infection; indeed, a receptor molecule encoded by cytomegalovirus is also reported to serve as an HIV co-receptor⁶, although this may not hold for all cytomegalovirus strains. The ability of immunodeficiency viruses to use so many receptors has provoked much thought about HIV pathogenesis and how it might be prevented.

CD4 was identified in 1984 as the receptor for HIV, but it soon became apparent that its presence alone was not sufficient to permit viral entry. The identity of second receptors remained elusive until 18 months ago, but since then it has become clear that there is a growing family of them, used by different HIV and SIV strains. Their expression on different (but often overlapping) cell populations, along with selective use by particular virus strains, makes them a major determinant of which cells HIV can infect.

All the co-receptors so far identified are members of, or related to, the seven-transmembrane, chemokine-receptor family. These are G-protein-coupled signalling receptors which bind the chemoattractant proteins, known as chemokines, that are involved in controlling activation and

migration of various leukocytes. All HIV-1 strains so far tested use the CCR5 or CXCR4 co-receptors, or both, and therefore these two are likely to be crucial to HIV infection and pathogenesis *in vivo*. Many HIV-1 strains, however, are able to use other co-receptors — including CCR3, CCR2b (refs 7, 8) and three of the four newly identified ones (see Table 1) — as well as CCR5 or CXCR4.

The CCR5 co-receptor is targeted by the so-called non-syncytium-inducing (NSI) viruses of HIV-1, those that don't induce cell-to-cell fusion in T-cell lines. It seems crucial for viral transmission because people who are homozygous for a CCR5 gene deletion are largely protected from HIV-1 infection⁹. CCR5-using strains are usually present throughout the course of infection. Syncytium-inducing (SI) viruses, by contrast, use the CXCR4 co-receptor, and often emerge later in the course of infection; they can be isolated from about half of AIDS patients.

In the co-receptor context, SIV presented a puzzle because some strains infect several CD4-positive human and non-human cell types that are resistant to HIV-1 (ref. 10). That puzzle grew more complex earlier this year when it was found that SIV used CCR5 but not CXCR4 (refs 11–13), yet could infect the CCR5-negative human T-cell lines Hut 78 and CEM × 174, as well as the astroglial cell line U87.CD4. Clearly, these strains used different and unidentified co-receptors.

Deng *et al.*² now describe two new co-receptors for SIV. They have been identified through screening complementary DNA libraries for their capacity to allow SIV entry into cells, and are termed Bonzo and BOB (standing for 'brother of Bonzo'; alas, the names will change to the more conventional terminology when their natural ligands are identified). Both receptors were used by the