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Figure 1 **Decline and fall — this tree frog (*Litoria caerulea*) is one of the amphibian species that Berger *et al.*[4] have found to be infected with the chytrid fungus.**

violet radiation[8]. Amphibian declines seem to have many causes, and it is vital that scientists do not relax their attempts to investigate these other factors — for which there is mounting evidence — in the mistaken belief that this new study has solved the puzzle.

The significance of Berger and colleagues' discovery[4] may go beyond the mystery of amphibian declines — this is the first time that an infectious disease pandemic has been implicated in the decline and possible extinction of animals. Moreover, if the chytrid pathogen was accidentally introduced into previously naive populations, as measles was to South America, we may be seeing a new kind of anthropogenic insult to the environment. This threat may be more insidious, and difficult to control, than existing environmental problems such as chemical pollution or habitat destruction. □

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Superconductivity

Strain yourself

Ivan K. Schuller

On page 453 of this issue[1], J.-P. Locquet and colleagues show that the superconducting transition, or critical, temperature (T_c) of a particular copper oxide can be doubled by the clever use of epitaxial strain. Increases in transition temperature using pressure have been accomplished before, but the increase obtained here is much larger than any achieved by using standard pressure techniques.

Thin solid films have been used for many years to study materials under physical conditions that cannot be achieved in the bulk. Very large pressure can be applied, and the intrinsically different behaviour of lower-dimensional systems can be observed, for example. Films have shown us many new phenomena, including giant magnetoresistance, dimensional crossover in superconducting multilayers, competition between superconductivity and magnetism, and the high reflectivity of X-ray mirrors[2–4]. The properties of thin films are different from those in the bulk largely because films are grown artificially, under conditions far from equilibrium (usually using a variety of sophisticated, high-vacuum techniques).

But quantitative structural and chemical characterization of a thin film is difficult, and many studies fail because defects such as roughness or interdiffusion of atoms invalidate the conclusions obtained. Locquet and collaborators have avoided these problems in a systematic and thorough fashion. Their films produce clear, sharp peaks in X-ray diffraction, and atomic-resolution electron microscopy shows a low defect density. (Generally, defects tend to depress the superconducting transition temperature, especially in the high-T_c oxides.)

Locquet and colleagues have grown films of $La_{1.9}Sr_{0.1}CuO_4$ on substrates carefully chosen to be of slightly smaller lattice constant (atomic spacing) than the natural value for $La_{1.9}Sr_{0.1}CuO_4$. Because the layers are very thin, the $La_{1.9}Sr_{0.1}CuO_4$ adopts this lattice constant, putting itself under considerable compressive strain to do so. It is not surprising that strain should affect T_c, because pressure has a measurable effect on ceramic superconductors. But the size of the increase in $La_{1.9}Sr_{0.1}CuO_4$ is striking. The authors measure a factor-of-two change in the superconducting T_c of their films, compared with that of the bulk alloy — an increase from 25 to 49 K.

The strain-dependence of T_c has opposite signs along different crystallographic orientations, so applying hydrostatic pressure (which is necessarily isotropic) may not increase T_c, and could even decrease it. But by an appropriate choice of the substrate material and growth temperature, Locquet and co-workers could apply uniaxial strain only in the directions that increase T_c.

In addition, this work may help to determine the critical structural parameters that control superconductivity, and perhaps even to clarify the mechanism that gives rise to superconductivity. Unfortunately, the results of these experiments alone cannot make a definitive statement in this direction. But they do have one intriguing and controversial implication: if the compression in the plane of the film gives rise to an expansion perpendicular to it (the 'Poisson effect') (Fig. 1), that would imply that the superconducting T_c increases with increasing distance between CuO_2 planes. This is contrary to several experimental and theoretical claims[5,6]. But some caution should be exercised with this conclusion, as the Poisson effect does not always occur in thin films. Furthermore, experiments generally find that separating two CuO_2 planes from one another decreases

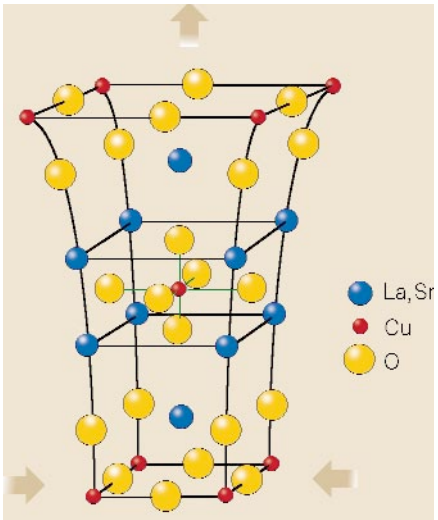

Figure 1 **$La_{1.9}Sr_{0.1}CuO_4$, on a substrate that forces it to distort its usual crystal structure (the actual strain is exaggerated here). This distortion can increase the substance's superconducting transition temperature by a factor of two.**

the transition temperature in the case of yttrium–barium–copper oxides, and T_c is claimed to be independent of distance[5] in BiSCCO, a particular bismuth compound. So the question of what transition temperature a single CuO_2 plane would have is still unsolved.

The present results[1] clearly demonstrate that the application of large uniaxial strain can increase superconducting transition temperature by a substantial factor, and perhaps this technique can be extended to other superconductors and lead to even higher transition temperatures.

Practical devices based on thin films are always grown on properly chosen substrates. Thus a judicious choice of substrates could considerably benefit applications using films that are thin enough to be subject to large epitaxial strains. □

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Immunology

The original sin of killer T cells

Andrew J. McMichael

The phrase 'original antigenic sin' was first used to describe the antibody response to influenza virus. After an initial infection, reinfection (or vaccination) with a new strain of the virus boosted the concentration of antibodies specific for the earlier infecting strain[1,2]. Although these antibodies cross-reacted with the new virus, they had higher affinity for the original infecting strain. This was immediately seen to have big implications for vaccine design — a vaccine based on a new strain of influenza virus might be unable to prime antibodies to the intended virus in people who had already been infected with a related viral strain.

Until now, original antigenic sin has been regarded as largely an antibody phenomenon. But, on page 482 of this issue, Klenerman and Zinkernagel[3] describe original sin in the response of cytotoxic T lymphocytes (CTLs) to lymphocytic choriomeningitis virus (LCMV). Their work was stimulated by studies of people with the human immunodeficiency virus (HIV), who sometimes mount a CTL response to an immunodominant strain of the virus with weak or no response to the other immunogenic variants present[4,5].

The authors attacked the problem *in vivo*. They infected mice with strains of LCMV that were either normal (wild type) or mutated at the immunodominant epitopes recognized by the CTL. For each mutated strain studied, they found that the CTL response was asymmetrical. Mice infected with the wild-type virus showed only a weak cross-reactive specificity when challenged with the mutant strain, reacting mainly to the wild-type virus. The low reactivity of CTLs against the mutant strain was also associated with delayed clearance of this strain by the immune system. In contrast, the CTL responses from mice infected with the mutant virus cross-reacted equally with the mutant and wild-type strains. Thus, the order in which the mice are exposed to different variants of the virus could have a significant effect on the outcome of the infection.

How does this happen? A possible explanation[6] for antibody original antigenic sin emerged when helper T cells were discovered, and it was realized that T cells react with peptide fragments of viral proteins that are often conserved between different strains. So, helper T cells, primed by the original virus and then stimulated by the new infection, might activate memory B cells that are specific for the original virus (although it is not clear why antibodies specific for the new variant are not stimulated too). In the same way, the phenomenon observed by Klenerman and Zinkernagel[3] might reflect the very strong CTL memory response to LCMV infection. Studies[7–9] of acute LCMV infection in mice showed that massive CTL responses occurred, whereby 25–50% of all CD8-positive T cells were virus specific. Even after recovery, 10% of peripheral CD8-positive T cells were specific for the immunodominant LCMV epitopes. A weakly cross-reacting new virus might, therefore, reactivate these plentiful CTL memory cells more readily than the much less abundant naive CTL precursors (Fig. 1). Although this mechanism depends on very high levels of memory CTLs, similar numbers are seen in persistent HIV infection[10], where original antigenic sin may also occur[4,5].

A second possibility is that activated memory CTLs remove enough of the antigen-presenting cells (APCs) to abort the primary CTL response to the new viral epitope. This would be consistent with the delayed clearance of mutant compared with wild-type virus in secondary challenges. The memory CTL could simply kill the APC, although recent results[11–13] indicate another possibility. A type of APC called the dendritic cell must be activated in order to initiate CTL responses. Activation occurs through an interaction between the CD40 ligand on T helper cells and CD40 on the dendritic cells. But if this requirement for activated dendritic cells is less stringent for the memory CTLs, these CTLs could deactivate the dendritic cells, thereby inhibiting new

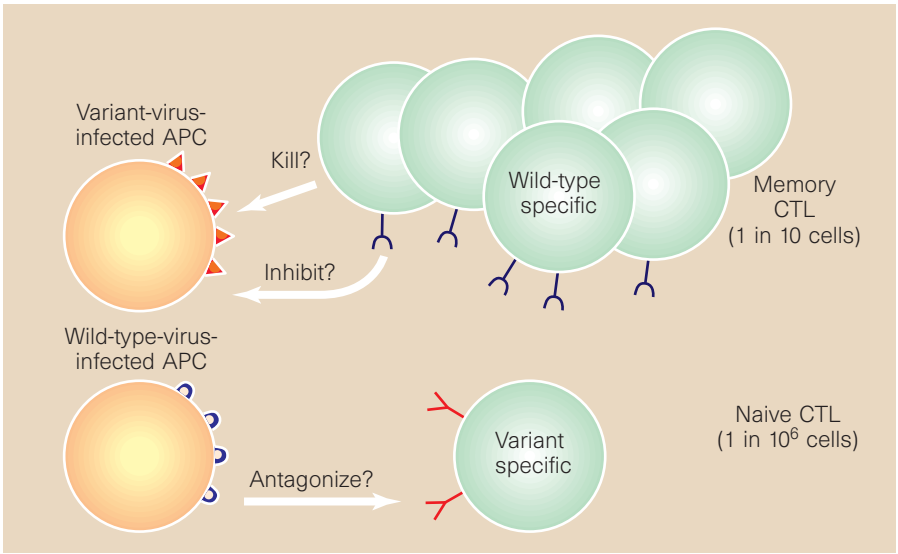

Figure 1 **Original antigenic sin in cytotoxic T lymphocytes (CTLs). Klenerman and Zinkernagel[3] have discovered that the phenomenon of original antigenic sin — whereby infection with a virus boosts the concentration of antibodies against a related strain from a previous infection — also occurs in the response of CTLs. Memory CTLs stimulated by wild-type antigen (blue) are abundant and, although weakly stimulated through their receptors, can kill or inhibit antigen-presenting cells (APCs) presenting the variant virus (red). Persisting APCs that present the wild-type virus may partially activate and antagonize naive T cells specific for the variant virus.**