also have the potential to reveal more about cosmology and the very early history of the Universe. The density fluctuations that 'seeded' the Universe are thought to be quantum in origin, created during an early period of accelerated expansion called inflation. This inflationary period should have created a stochastic background of gravitational waves which, as they rippled through the Universe, would also have generated anisotropies and polarization in the CMB. Unfortunately, these anisotropies are too small for DASI to have observed. However, the patterns of polarization produced by density perturbations and by gravity waves are very different (the polarization vectors can only have a curl component if gravitational waves are present). Future polarization experiments could perform a unique test of inflation by identifying this gravity-wave signature. Furthermore, if inflation occurred when the Universe had cooled to an energy scale around 10^{16} GeV, the relic background of gravitational waves would actually be strong enough to be detected by CMB experiments.

The CMB polarization is also expected to contain clues about other periods in the evolution of the Universe. Almost a billion years after the recombination epoch, the first stars and quasars are thought to have started shining. The precise sequence of events in this period, usually referred to as the end of the 'dark ages', is very uncertain. The ultraviolet radiation generated by these early sources re-ionized all the hydrogen in the Universe, providing a fresh opportunity for the CMB to scatter and become polarized — but by the time of reionization, the expansion of the Universe had diluted the density of hydrogen so much that only a few per cent of the CMB photons are thought to have been affected. Even this small fraction is enough to leave behind an observable polarization signal in the CMB. If it could be detected by future experiments, it would provide vital clues as to how and when the dark ages ended.

The detection of polarization by DASI at the level predicted by the cosmological standard model is both a remarkable technical achievement and a wonderful consistency check for the theory. In coming years, as more experiments characterize polarization on different angular scales, cosmologists hope to learn more about a variety of events in the history of the Universe. DASI has launched us on this journey. ■

Matias Zaldarriaga is in the Department of Physics, New York University, 4 Washington Place, New York, New York 10011, USA.
e-mail: mz31@nyu.edu

1. Penzias, A. A. & Wilson, R. W. *Astrophys. J.* **142,** 419–421 (1965).
2. Leitch, E. M. *et al. Nature* **420,** 763–771 (2002).
3. Kovac, J. M. *et al. Nature* **420,** 772–787 (2002).
4. Fixsen, D. J. *et al. Astrophys. J.* **473,** 576–587 (1996).
5. Smoot, G. F. *et al. Astrophys. J.* **396,** L1–L5 (1992).
6. Hu, W. & Dodelson, S. *Annu. Rev. Astron. Astrophys.* **40,** 171–216 (2002).

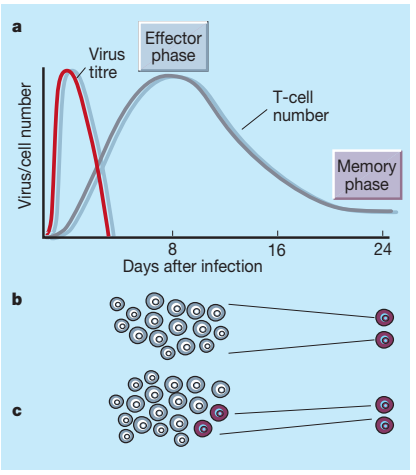

Figure 1 **The T-cell response to a virus that is rapidly cleared from the body.** a, **The number of T lymphocytes that react with viral antigens increases dramatically for 8 days following infection, producing larger numbers of effector lymphocytes that kill infected cells. T-cell numbers decrease after the effector phase, leaving a stable population of memory cells.** b, c, **Models for how memory cells might develop.** b, **A few effector cells might be randomly selected for survival and differentiation into memory cells.** c, **Alternatively, the differentiated precursors of memory cells may already exist at the effector phase. Ahmed and colleagues' finding[1] that a few effector cells gradually convert to long-lived memory cells, even as most effector cells die, supports proposition** b.

Immunology

Remembrance of things past

Michael J. Bevan

Memory T cells help us to fight off infectious microorganisms that we have encountered before. There are two models for the generation of memory cells, and new work provides support for one of them.

Vaccination is the cheapest and most effective means of protecting against certain infectious diseases. Part of this protection comes from a numbers game. In response to disease, the immune system's T lymphocytes are drafted into service: they detect and kill infected cells, and send signals that the corpses need to be removed. But killer T cells that recognize the structures (antigens) characteristic of a given infectious organism are rare in people who have not encountered that pathogen previously. Vaccination can cause the numbers of those T lymphocytes to increase many-fold, and also leads to the formation of a population of long-lived memory T cells, ensuring a rapid response to future infection. A better understanding of this process should aid vaccine development. Writing last week in *Cell*, Ahmed and colleagues[1] proposed that the production of memory killer cells is a gradual process that may take weeks to accomplish, and requires the elimination of antigen from the body.

Killer, or cytotoxic, T lymphocytes are produced from bone-marrow-derived stem cells, which mature into precursor killer cells in the thymus and are then released into the bloodstream and lymph vessels. Each killer T cell carries the CD8 molecule on its surface, and also expresses a receptor that detects foreign antigens. These receptors vary greatly within the cell population, such that perhaps only ten cells in a million have the same antigen specificity.

When 'naive' killer T-cell precursors encounter their cognate antigen — in the form of a pathogen or a vaccine — they multiply rapidly (Fig. 1a). As they do, they acquire the ability to kill antigen-expressing target cells and to secrete cytokine and chemokine proteins that are important in combating infection. They also change their migratory behaviour, allowing them to get out of the blood and lymphoid tissue and into any tissue or organ that may harbour the infection. At the peak of the response, in certain infections, activated killer T cells (effector cells) specific for the pathogen can comprise as much as 50% of the entire CD8-expressing T-cell population.

If the infection is cleared, the number of effector cells declines dramatically, and a stable population of memory T cells is left behind, often making up 1% of the CD8-expressing population. These memory cells are more common than are the naive precursors, and can also respond more quickly following re-exposure to the antigen[2]. The mystery is, how does the immune system 'know' to leave behind an expanded pool of long-lived memory cells? Is it that not all effector cells die when antigen is cleared (and if so, why)? Or do all effector cells in fact die off, with memory cells forming by a separate pathway that splits off early from the path leading to full-blown effectors? Ahmed and co-workers[1] aimed to find out which of these models (Fig. 1b, c) is correct.

The authors started by studying the response of mice to a short-lived (acute) infection with lymphocytic choriomeningitis virus, isolating virus-specific killer

T lymphocytes at 8 days after infection (effector cells) and at later time points as memory cells developed. They probed these cell populations by analysing gene expression and function, searching for clues to when memory cells appear.

They found that the expression profiles of effector and the later, memory cells overlap, suggesting that memory cells derive from effector cells and are not a separate lineage. The results also support the interpretation that memory cells do not exist at the peak of the effector response, but appear gradually over three weeks after the antigen has gone. The results of the functional and expression analyses — carried out at various time points between the peak of the effector stage and over 40 days after the infection was cleared — imply that the properties of effector cells fade gradually as the hallmark properties of memory cells are acquired. This slow conversion occurs even as the number of antigen-specific cells declines.

Ahmed and colleagues[1] also tested the ability of effector and later populations to handle a second encounter with the same pathogen: only the late populations did this effectively. The explanation for the superiority of late memory cells may be provided by the authors' demonstration that only these cells can undergo a second explosive population expansion in response to re-encounter with the antigen. Clearance of the antigen after the first acute infection, resulting in the cessation of signalling from the T-cell antigen receptor, apparently allows a fraction of effector cells to 'reload' to respond to re-infection.

This type of immunological memory, however, probably protects only against acute infections, such as that studied by Ahmed and colleagues, and not against chronic infections by pathogens that find ways to coexist with the immune system. In diseases such as AIDS, tuberculosis and leprosy, the differentiation of this kind of memory population may not be permitted, because antigen is not removed. Control of these infections probably depends instead on the continuous presence of effector cells[3].

Recently, it has become apparent that memory T cells exist in two flavours. First, there are central memory cells that circulate through the lymphoid system just like naive T cells specific for the antigen, but in greater numbers and with a more rapid response rate. And second, there are 'effector' or 'tissue' memory T cells that can leave the blood and access all tissues where they might meet antigen (mucosal tissue, for example), before the pathogen has a chance to disseminate[4]. It remains to be seen whether these memory T cells represent distinct pathways of differentiation from effector cells, or different stages along a single pathway — although another recent report[5] suggests the latter possibility, that effector memory T cells convert into central memory cells. And it is still a mystery as to how a fraction of effector cells 'decides' not to die but to become memory cells. What is clear is that the more we learn about the progression of the immune response, the better able we will be to design strategies for effective vaccination. Judging by the present results[1], it is clear that 'booster shots' for vaccinations should be timed for the period when the first antigen has been cleared, and a stable population of memory cells has developed. ■

Michael J. Bevan is in the Department of Immunology, Howard Hughes Medical Institute, University of Washington, Box 357370, Seattle, Washington 98195-7370, USA.
e-mail: mbevan@u.washington.edu

1. Kaech, S. M., Hemby, S., Kersh, E. & Ahmed, R. *Cell* **111,** 837–851 (2002).
2. Sprent, J. & Surh, C. D. *Curr. Opin. Immunol.* **13,** 248–254 (2001).
3. Zinkernagel, R. *Curr. Opin. Immunol.* **14,** 523–536 (2002).
4. Sallusto, F., Lenig, D., Forster, R., Lipp, M. & Lanzavecchia, A. *Nature* **401,** 708–712 (1999).
5. Wherry, E. J. *et al. Nature Immunol.* (in the press).

Condensed-matter physics

Dense ice in detail

Dennis D. Klug

A substance as simple as water is in fact a rich source of interesting physics. The solid phase contains several amorphous forms of ice, including one with a very dense structure, the details of which have now been revealed.

Ice is famously anomalous — unlike most solids, in its usual form it is less dense than liquid water. In fact, regular ice has so far been found to come in at least 13 different forms. Furthermore, many types of amorphous ice, without the regular molecular structure of normal ice, have been discovered. Writing in *Physical Review Letters*, Finney *et al.*[1] describe the structure of a new, very dense form of ice, whose existence has profound implications for many aspects of research into amorphous ice and other solids, and for our understanding of the phase diagram of water and ice (Fig. 1).

This 'very-high-density amorphous' (VHDA) ice, 40% denser than ordinary ice, was originally discovered by Loerting *et al.*[2] when they modified the conventional recipe for preparing high-density amorphous ice, commonly denoted HDA. The HDA form does not have the hexagonal crystal structure of ordinary ice, and is nearly 30% denser: each water molecule is surrounded by roughly five nearest-neighbour water molecules, whereas in hexagonal ice each molecule has exactly four nearest neighbours.

The preparation of HDA was first reported in 1984 by Mishima *et al.*[3], by a method called pressure-induced amorphization: samples of crystalline hexagonal ice are pressurized at low temperatures (usually 77 K) and, at a pressure of about 1 gigapascal (GPa), a very sharp transformation occurs as the ice takes on the HDA form. The HDA ice can be brought back to ambient pressure as long as the temperature remains low. But if it is warmed to about 120 K at ambient pressure, it transforms into low-density amorphous (LDA) ice, releasing a fair amount of heat[4]. A series of amorphous-ice forms with densities between that of HDA and LDA have since been characterized[5]. When Loerting *et al.* modified the Mishima recipe and heated HDA up to about 160 K, maintaining the pressure at 1.15 GPa, they noticed that the ice became even denser — VHDA had formed.

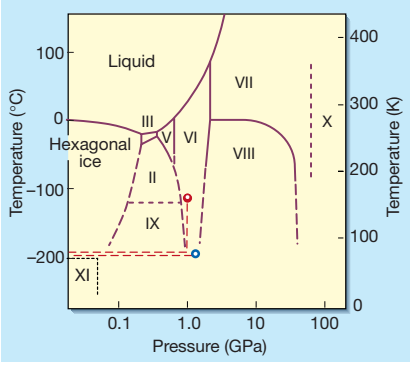

Figure 1 **The phase diagram of ice. The temperature and pressure regimes associated with most of the 13 known crystalline phases are indicated here. When hexagonal ice at 77 K is subject to increasing pressure, so-called amorphous ice forms: at 1 GPa (blue circle), high-density amorphous ice forms; if the temperature is then raised, very-high-density amorphous ice forms (red circle).**

Why is VHDA important? The original discoveries of HDA and LDA led to the suggestion that HDA and LDA were related to supercooled forms of liquid water. The idea was based mainly on the observation that HDA was formed at high pressure close to the extrapolation of the curve that describes how the melting point of hexagonal ice changes with pressure. The melting curve of ice has a negative slope and ice in fact melts at –20 °C under a pressure of 0.2 GPa, so this was a reasonable initial suggestion. There has been speculation that, as HDA and LDA exist, there may be two forms of liquid water at low temperatures. A well-defined boundary between these phases could mean that there is a second critical point, for transitions