small pore diameter (2 nm; 'closed' state). Other agents that affect closure of VDAC include synthetic polyanions, cellular constituents such as NADH, and the so-called VDAC modulator[6]. Shimizu *et al.* now add Bcl-x$_L$, Bax and Bak to this list.

The authors reconstituted VDAC in liposomes, and show that Bcl-x$_L$ stimulates closure of the channel, whereas Bax and Bak facilitate its opening. Moreover, they show that Bax and Bak allow cytochrome *c* to pass through VDAC. This is surprising, because the diameter of VDAC is normally too small to allow cytochrome *c* to pass. Shimizu *et al.* propose that, after VDAC interacts with Bax and Bak, its conformation changes. This allows VDAC — possibly in combination with Bax or Bak — to form a megachannel that is permeable to cytochrome *c* (Fig. 1a). The authors illustrated the requirement for VDAC using mitochondria purified from VDAC-deficient yeast mutants. When they added human Bax to these mitochondria, there was no release of cytochrome *c*. But by complementing the mutant mitochondria with human VDAC, they restored the ability of Bax to induce an efflux of cytochrome *c*.

In fact, VDAC is not the only protein required for the function of Bax in yeast — the ANT (ref. 7) and the F$_0$F$_1$-ATPase proton pump[8] are also needed. Moreover, Bax can interact with the ANT, and Bax does not cause death in ANT-deficient yeast mutants[7]. Shimizu *et al.* claim that the ANT is not needed for release of cytochrome *c* through VDAC. But perhaps, under some circumstances, the ANT, through binding to Bax, may facilitate opening of VDAC. Such a picture would fit with the PTP opening model (Fig. 1b).

Another function of VDAC, in concert with the ANT, is ATP/ADP exchange — that is, it allows ATP to move out of the mitochondria and ADP to move in. In its closed conformation VDAC is impermeable to ATP[6], and, earlier this year, Vander Heiden *et al.*[9] reported that an early event in apoptosis (before cytochrome *c* release) is a defect in mitochondrial ATP/ADP exchange. So perhaps, during apoptosis, the ANT or VDAC (or both) fails to transport adenine nucleotides. In cells rescued by overexpression of Bcl-x$_L$, however, ADP/ATP exchange is stimulated to sustain coupled respiration[9]. In light of Shimizu and colleagues' results we can exclude the possibility that VDAC is responsible for this increase. Instead, it seems that Bcl-x$_L$ closes VDAC, but that it maintains ADP/ATP exchange through a VDAC-independent mechanism.

Members of the Bcl-2 family are multifunctional — control of cytochrome *c* release is only part of their activity. They are found in other intracellular membranes, such as the endoplasmic reticulum and nuclear membranes, raising questions about whether they might control transport of molecules across other membranes. Their mitochondrial activity may, however, be prevalent only in cells where the mitochondria are likely to be crucial to cell death. This may be the case in neurons, where, because of their mobility, mitochondria are ideal sensors of death signals that impinge on widely spaced regions such as the cell body, neurites and synapses. But wherever it may act, the arrival of VDAC into the apoptosis arena pinpoints this protein as a potential therapeutic target for preventing mitochondrial dysfunction in acute pathologies associated with apoptosis. ☐

Jean-Claude Martinou is at the Serono Pharmaceutical Research Institute, 14 chemin des Aulx, CH-1228 Plan-les-Ouates, Geneva, Switzerland.
e-mail: jean-claude.martinou@serono.com

1. Shimizu, S., Narita, M. & Tsujimoto, Y. *Nature* **399,** 483–487 (1999).
2. Kroemer, G., Zamzami, N. & Susin, S. A. *Immunol. Today* **18,** 44–51 (1997).
3. Green, D. R. & Reed, J. C. *Science* **281,** 1309–1312 (1998).
4. Kelekar, A. & Thompson, C. B. *Trends Cell Biol.* **8,** 324–330 (1998).
5. Mannella, C. A. *J. Struct. Biol.* **121,** 207–218 (1998).
6. Colombini, M., Blachly-Dyson, E. & Forte, M. in *Ion Channels* (ed. Narahashi, T.) 169–202 (Plenum, New York, 1996).
7. Marzo, I. *et al. Science* **281,** 2027–2031 (1998).
8. Matsuyama, S., Xu, Q., Velours, J. & Reed, J. C. *Mol. Cell.* **1,** 327–336 (1998).
9. Vander Heiden, M. G., Chandel, N. S., Schumacker, P. T. & Thompson, C. B. *Mol. Cell* **3,** 159–167 (1999).

Climate change

Cornucopia of ice core results

Bernhard Stauffer

Natural archives of Earth's past climate take several forms — sea and lake sediments, tree rings, peat bogs and glacier ice — all of which are used in reconstructing climate history. But the records locked up in the large polar ice sheets are especially valuable. Cores of this ice not only allow reconstruction of changes in local temperature and precipitation, but also provide information about volcanic activity, storminess, solar activity and atmospheric composition.

Such records have already taken us back 150,000 years, a period covering about two glacial–interglacial cycles. Petit *et al.* (page 429 of this issue[1]) now extend the most important records to four climatic cycles — that is, to about 420,000 years BP (before present). This extension has been made possible because, last year, ice-core drilling at Vostok station in Antarctica reached a record depth of 3,623 m. Most notably, analysis of the core allows investigation of whether transitions from glacial epochs to interglacials, and back again, always follow the same pattern or whether a variety of mechanisms is involved.

Over the past few years, ice cores from polar regions (Box 1) have delivered a variety of unexpected results. It is because of ice-core data that we know that large variations in climate were accompanied by naturally caused changes in the atmospheric concentrations of CO$_2$ and CH$_4$ — the most important greenhouse gases. Cores from Greenland provided the first evidence for fast and drastic climate changes during the last glacial epoch, including the transition to the present interglacial (the Holocene, the past 10,000 years) in the Northern Hemisphere. The records covering this transition, both from Greenland and from Antarctica, inspired various proposals as to the mechanisms causing or amplifying the temperature increase. With the extra data[1], these proposals can now be tested further.

The four transitions from glacial to warm epochs, covered by the new Vostok records, started at about 335,000 years, 245,000 years, 135,000 years and 18,000 years BP. From this one would infer a roughly 100,000-year periodicity, and time-series analyses of the records indeed show a large, 100,000-year contribution to periodicity, along with another at 41,000-year intervals. This supports the idea that changes of the orbital parameters of the Earth (eccentricity, obliquity and precession of axis) cause variations in the intensity and distribution of solar radiation, which in turn trigger natural climate changes.

Of special interest is the interplay between greenhouse gases and climate. All four transitions from cold to warm climatic epochs have been accompanied by an increase in atmospheric CO$_2$ from about 180 to 280–300 p.p.m.v. (parts per million by volume; present concentration is 365 p.p.m.v.), and in atmospheric CH$_4$ from 320–350 p.p.b.v. to 650–770 p.p.b.v. (parts per billion by volume; present concentration 1,700 p.p.b.v.). Petit *et al.*[1] report that, within the uncertainties in the record, the increases in Antarctic temperature, CO$_2$ and CH$_4$ were in phase during all four transitions.

By contrast, based on measurements on the same core, Fischer *et al.*[2] have claimed that for the last three terminations there was a time lag of 500 to 1,000 years between the temperature increase and the CO$_2$ increase. The question of lags and leads in climate change is obviously a highly important one. But identifying a 500–1,000-year time lag is taking the current data and state of knowledge to its limits. Uncertainties stem not only from the limited sampling frequency but also from the problem of assigning dates to the air-containing bubbles in the core[3] (air becomes enclosed in bubbles only at about

Box 1: Ice cores south and north

There are ice-drilling projects in both Antarctica and Greenland. Conditions are harsh, and stuck drills are an ever-present problem.

At Vostok, in Antarctica (pictured), the Soviets started deep drilling in 1980. A depth of 2,202 m was reached in 1985, when it became impossible to continue. A second hole had been started in 1984, and it reached a final depth of 2,546 m in 1990. In 1989, the project became a Russian–French–US endeavour, and the following year a third hole was started; it reached 2,500 m depth in 1992 (age of the ice at the bottom being about

200,000 years BP) and finally 3,623 m in 1998.

In central Greenland, the European GRIP core drilling reached bedrock in July 1992 at 3,028 m depth; likewise the US GISP-2 drilling in July 1993 (3,053 m depth). The undisturbed part of both cores covers the past 105,000 years. A deep drilling at North-GRIP will extend the age scale to cover at least the last interglacial (135,000 years).

Other projects in Antarctica are being run by various national and international groups. In 1996 at Dome Fuji (East Antarctica) the Japanese reached 2,503 m; in January 1999, the US project on the West Antarctic ice sheet hit bedrock at 1,004 m. The European Project for Ice Core Drilling in Antarctica (EPICA) is at work at Dome Concordia (East Antarctica, present depth 786 m) and a second drilling will start shortly in Dronning Maud Land. **B.S.**

100 m below the snow surface, and so air and ice at the same level are of different ages).

Even if there does indeed turn out to be a time lag, CO$_2$ can still be an important amplifier for the temperature increase during the glacial–interglacial transition, which itself lasts several thousand years. However, whether amplification by greenhouse gases was responsible for 50% of the temperature increase, as Petit *et al.* speculate, also remains a hypothesis for the moment. Other amplification factors are relative humidity (water vapour is a greenhouse gas), surface albedo (changing ice cover and vegetation) and planetary albedo (changing cloud cover).

The causes and mechanisms of CO$_2$ increase at the beginning of the four transitions are also open to debate. From the Vostok results for the last two transitions, Broecker and Henderson[4] concluded that the Southern Ocean is likely to be the main agent in regulating atmospheric CO$_2$. Similarities between CO$_2$ concentration and Antarctic temperature for the previous two transitions, as well as other parts of the record, add further support to the idea that the Southern Ocean does indeed have a key role. But although there are plenty of ideas about mechanisms linking events in the ocean to those in the atmosphere (changes in CO$_2$ solubility, phytoplankton productivity, iron fertilization and so on), there is no clear evidence to support any of them.

The Greenland ice cores revealed that fast and drastic temperature changes in the Northern Hemisphere are almost synchronous with fluctuations in CH$_4$ (ref. 5). Those fluctuations are caused by variations in the extent and activity of sources (mainly wetlands in the tropics and in northern mean latitudes) which depend on temperature and precipitation rates. Petit *et al.* speculate that the CH$_4$ jumps in the first three transitions had the same cause as the most recent one, where the evolution of Greenland temperature is known (the sharp temperature increase preceding the start of intense ice melting in the Northern Hemisphere). A highly simplified course of events for all four transitions would then be as follows: first, changing orbital parameters initiated the end of the glacial epoch; second, an increase in greenhouse gases then amplified the weak orbital signal; third, in the second half of the transition, warming was further amplified by decreasing albedo caused by melting of the large ice sheets in the Northern Hemisphere.

Analyses of polar ice cores have added immensely to our knowledge of the mechanisms that govern global climate change. Not least, the results of these analyses provide tests for climate models intended to predict possible future responses to increasing concentrations of greenhouse gases. The results, however, are not easily come by — ice-core drillings in polar regions (Box 1) are long and difficult projects, with many pitfalls. The paper by Petit *et al.*[1] is further demonstration that the perseverance of all those involved in drilling projects — scientists, technicians and funding agencies — has ample rewards. ☐

Bernhard Stauffer is at the Physics Institute, Climate and Environmental Physics, University of Bern, Sidlerstrasse 5, CH-3012 Bern, Switzerland.
e-mail: stauffer@climate.unibe.ch

1. Petit, J. R. *et al. Nature* **399,** 429–436 (1999).
2. Fischer, H., Wahlen, M., Smith, J., Mastroianni, D. & Deck, B. *Science* **283,** 1712–1714 (1999).
3. Schwander, J. *et al. J. Geophys. Res.* **102,** 19483–19494 (1997).
4. Broecker, W. S. & Henderson, G. M. *Paleoceanography* **13,** 352–364 (1998).
5. Chappellaz, J. *et al. Nature* **366,** 443–445 (1993).

Retroviruses

Closing the joint

John M. Coffin and Naomi Rosenberg

We are starting to understand much about how retroviruses integrate their DNA into host genomes. We know, for example, how the viral integrase carries out initial events in the process. But retrovirologists have tended to ignore the subsequent reactions, preferring to pass the buck onto 'cellular repair systems'. A report by Daniel *et al.*[1] in *Science* may now shed the first ray of light on these systems. They have found that a cellular damage-sensing system is implicated in completing retroviral integration.

Retroviruses integrate their DNA into that of the host as part of their replication cycle[2] — a feature that sets them apart from all other agents that infect multicellular organisms. A structure called the preintegration complex is formed from proteins of the incoming virus particle. Within this structure, viral DNA is produced from its RNA genome by the action of reverse transcriptase, leaving a double-stranded DNA molecule with flush ends. Integrase, probably acting with a cellular DNA-binding protein[3], then associates with the ends of the newly made DNA, and carries out two reactions at each end (Fig. 1, overleaf).

The first of these reactions is 3′ cleavage. Two bases are removed from the 3′ end of each strand, leaving a hydroxyl group. In the second (strand-transfer) reaction, the integrase catalyses a direct attack by that hydroxyl group on the target cellular DNA. These two reactions occur 4–6 bases apart, so, although each strand of the viral DNA is joined to its target, there is a 4–6-base gap as well as a two-base mismatch at each end. The reactions carried out by isolated preintegration complexes stop at this point, indicating that cellular repair systems are needed to finish the job. Clearly, if left unrepaired, the gaps would cause serious damage — the checkpoint systems of the