

mophilic Archaea? The explanation is three-fold and lies in the intense interest in the biochemistry of these unusual organisms, in the possibility that they represent the earliest forms of life, and in the biotechnological potential of their genes and gene products.

*Thermoplasma acidophilum* has one of the smallest of the archaeal genomes to have been sequenced so far. Even so, the speed at which Ruepp *et al.*<sup>1</sup> sequenced the genome was remarkable. The full sequence of over 1.5 million base pairs was obtained from only 7,855 sequencing reactions — an effective yield of 199 base pairs per reaction, compared with the 66 base pairs per reaction for the slightly larger genome of the hyperthermophilic bacterium *Thermotoga maritima*<sup>11</sup>. The keys to this efficiency were the use of sequencing vectors containing very large DNA inserts; an extended-sequencing method referred to as 'primer walking'; and a policy of stopping the sequencing of an insert when the primer walking encountered a stretch of DNA whose sequence was already known.

So, what can we learn from this genome? The most startling observation is the high proportion of genes that seem to have been acquired from other species. For example, 17% of all identified 'open reading frames' (the parts of genes that encode proteins) have relatives in the not-yet-completely sequenced genome of the archaeon *Sulfolobus solfataricus*.

There may be several reasons why *T. acidophilum* has such an extraordinary ability to acquire external genes. First, environmental proximity is clearly important. Microorganisms of the genus *Sulfolobus* might be the most common archaeal species in the habitat occupied by *T. acidophilum*. In addition, a further 17% of the open-reading frames of *T. acidophilum* are 'bacteria-like'. So it might also have acquired some of its genes from bacteria such as *Alicyclobacillus*, *Thiobacillus* or *Sulfobacillus*, the habitats of which overlap with that of *Thermoplasma*. Second, the absence of a conventional, protective cell wall could be particularly significant: a cell wall is a major barrier to the entry of large molecules into a cell. Finally, the *T. acidophilum* genome might not be protected by a restriction/modification system, a set of enzymes designed to recognize and destroy foreign DNA. The organism has no 'restriction endonuclease' activity, although its genome might encode a DNA methyltransferase, normally part of a restriction/modification system, and restriction endonuclease genes have little sequence similarity and cannot be recognized in a gene sequence.

Interestingly, the *Sulfolobus*-like genes in the *T. acidophilum* genome are clustered into several (at least five) discrete regions. Ruepp *et al.* conclude that only a few gene-transfer events occurred, each involving movements of large chunks of genetic sequence. But the

transfer of smaller gene fragments between species tends to be more common, raising the question of why this seems not to have happened for *T. acidophilum*.

One issue can be almost settled by the details of this new genome sequence: whether *T. acidophilum* is an ancestor of eukaryotic cells. Ruepp *et al.* compared *T. acidophilum* genes with those in bacterial and eukaryotic databases. The results show that, if anything, the *T. acidophilum* genes are more similar to bacterial genes than to eukaryotic ones. Key 'marker' genes found in eukaryotes (such as genes encoding subunits of the nuclear pore complex) are not found in the *T. acidophilum* genome.

Finally, on a different note, the completion of another genome sequence reminds us how much we still do not know about gene function as a whole. Of the predicted 1,509 open reading frames in the *T. acidophilum* genome, 29% are akin only to 'hypothetical' open reading frames in other genomes, and 16% have no relatives elsewhere. This means that, as yet, we do not know what 45% of the protein-coding regions in the *T. acidophilum* genome do. That is a lot of genes. These percentages are typical for newly sequenced genomes. But the results serve as a reminder of the need both for more advanced data-mining techniques (which would increase our ability to pick out similar sequences from different genomes and to identify putative functions) and for the continuation of more classical molecular and functional research. ■

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### Corrections

In the News & Views article "Global change: Plankton cooled a greenhouse" by Birger Schmitz (*Nature* **407**, 143–144; 2000), the period of 'superwarm' conditions at the Palaeocene/Eocene boundary should have been cited as lasting about 60,000 (not 150,000) years. Proof corrections made to the paper concerned (by S. Bains *et al.* **407**, 171–174; 2000) were not passed on to the News & Views author.

In Jim Gillon's "Earth systems: Feedback on Gaia" (*Nature* **406**, 685–686; 2000) a huge expansion of vegetation was cited as having taken place 550 million years ago. The generally accepted date for that expansion is around 400 million years ago.

### Daedalus

## Talking to animals

Last week Daedalus presented his mobile 'Ultraphone' for silent speech. The user whispers or mouths his message silently. His voiced tone is replaced by an inaudible ultrasonic tone launched into his mouth. His tongue and palate modulate this into inaudible ultrasonic speech. A heterodyne circuit downshifts it back to an audio signal, which is transmitted.

Daedalus now has a biological use for the technique. Many animals — cats, dogs, bats, rats and many insects — communicate partly or mainly in the ultrasonic band, above human hearing. Instruments can downshift their voices into the audio band, as the Ultraphone does. But the Ultraphone also performs the converse operation. It upshifts the human voice into a range much more significant to animal ears.

So DREADCO animal keepers are now speaking to their charges on an adapted Ultraphone. Its intense ultrasonic beam lets them 'speak' loudly and clearly in this waveband. Its wideband microphone and heterodyne circuit downshifts the animals' ultrasonic responses back into the audio for human recognition. The ultrasonic frequency of the 'Animal Ultraphone' can be adjusted to the band in which the conversation seems to flow most freely.

Laboratory rats are the first subjects. These bright and companionable rodents can be tamed quite well by normal means. An added vocal channel should bring them even closer to human understanding. The DREADCO staff are trying to imitate their language, and give them ultrasonic 'names' that they can recognize. Bats, those ultrasonic experts, may also respond to the Ultraphone; insects are probably too dim.

But the main impact of the Animal Ultraphone will be on domestic cats. These intelligent pets are famous for their aloof independence. They notoriously refuse to learn (or at any rate to obey) even the simplest commands. To them, human speech is probably a low vague mumbling. But talked to in the right ultrasonic band, even the most suspicious cat should become alert and responsive. It might even reply in tones that, downshifted to mellow audio by the Animal Ultraphone, appeal to the human ear.

Feline-human relations will be transformed. Bonded at last by mutually appreciated vocal expression, cats and cat-lovers will bestow far more warmth and company upon each other, bringing a new and welcome closeness to a long-standing association. And the true intelligence of these friends of Man may at last become apparent.

David Jones

Global change

# Plankton cooled a greenhouse

Birger Schmitz

*et al.*<sup>1</sup>, along with Bellocchio *et al.*<sup>4</sup>, now show that the expression of BNPI in cell lines leads to specific, ATP-dependent uptake of glutamate into vesicles. Does this mean that this protein is what makes a neuron glutamatergic? Takamori *et al.*<sup>1</sup> go on to show that the expression of BNPI in a cell line that can be stimulated by the excitatory neurotransmitter acetylcholine results in the release of packets of glutamate from the cells. Finally, they convincingly show that neurons that normally release the neurotransmitter GABA can be persuaded to release glutamate instead by the artificial expression of BNPI.

So it seems that the vesicular glutamate transporter BNPI may be the best marker by which to define a glutamatergic neuron. But in some ways, all that these groups<sup>1,4</sup> have done is identify another vesicle-bound neurotransmitter transporter. What makes the work much more exciting is that we may now have a way of specifically controlling neurotransmission within glutamatergic neuronal circuits. A wide range of neurological diseases are characterized by the aberrant regulation of glutamate. These include acute stroke (brain injury resulting from a sudden loss of blood or oxygen to the brain), as well as more chronic neurodegenerative disorders such as Huntington's disease and amyotrophic lateral sclerosis. Both vesicular<sup>5</sup> and transmembrane<sup>6</sup> glutamate transporters have been implicated in these diseases.

The past decade has seen an enormous effort by pharmaceutical firms to develop potent 'anti-glutamate' agents as neuroprotective compounds. But many of these have been either ineffective or too toxic. The new results afford us the opportunity to control the release of glutamate by manipulating its loading into vesicles. But some questions remain unanswered. For example, BNPI was identified as a phosphate transporter. Can it function as such *in vivo* and, if so, which is its main role — to uptake glutamate or to transport phosphate? In addition, BNPI is not found in all of the known neuronal pathways along which glutamate travels, so other types of vesicular glutamate transporter may exist. If so, we may one day be able to develop drugs that are specific to these different types, allowing us precise control of the glutamatergic neuronal circuitry. ■

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Scientists who can perform laboratory experiments are lucky — a megalomaniac climatologist can only dream of putting an Earth-like planet in a giant test tube, pumping billions of tonnes of CO<sub>2</sub> into its atmosphere, and registering the effects on life and climate. Fortunately, there are other approaches. At the Palaeocene/Eocene (P/E) boundary 55 million years ago, nature appears to have done the greenhouse experiment for us. Bains *et al.*<sup>1</sup> (page 171 of this issue) now report that they have identified a rather unexpected response of the oceanic biosphere to dramatically high concentrations of atmospheric CO<sub>2</sub>, and temperatures, at this boundary — one that can account for a subsequent reduction in atmospheric CO<sub>2</sub> and cooling.

In the early Palaeogene, 65 to 41 million years ago — a period that includes the Palaeocene and the first half of the Eocene — the Earth was generally much warmer than today. The polar regions were free of continental ice sheets, alligators and turtles thrived on Ellesmere Island at 75° N, and palm trees grew as far north as Kamchatka. For a period of about 60,000 years, 'super-warm' conditions developed at what is known as the P/E thermal maximum. Oxygen isotopic (<sup>18</sup>O/<sup>16</sup>O) analyses of shells from

marine microorganisms called foraminifera show that surface-water temperatures off the coast of Antarctica rose from about 13 °C to 20 °C (ref. 2). Subtropical regions also became warmer; but the higher the latitude, the greater was the effect<sup>3,4</sup>. The warming coincides with some of the most dramatic biotic changes since the mass extinctions at the Cretaceous/Tertiary boundary, 65 million years ago. Deep-sea, bottom-dwelling foraminifera suffered major extinctions, while terrestrial mammals and different oceanic plankton groups underwent considerable diversification.

Events at the P/E boundary coincide with a large decline in the <sup>13</sup>C/<sup>12</sup>C ratio of the carbon dissolved in the ocean<sup>2–4</sup>. The decline happened rapidly, within a few tens of thousands of years. It is recorded in the shells of both planktonic and deep-sea, bottom-living foraminifera, as well as in the teeth of land mammals, indicating that the entire ocean-atmosphere carbon reservoir altered in composition.

How could such a big change have happened so quickly? Several years ago, Dickens *et al.*<sup>5</sup> provided a plausible explanation. Under normal temperature conditions, enormous amounts of carbon are stored in ocean sediments as gas hydrates — solid

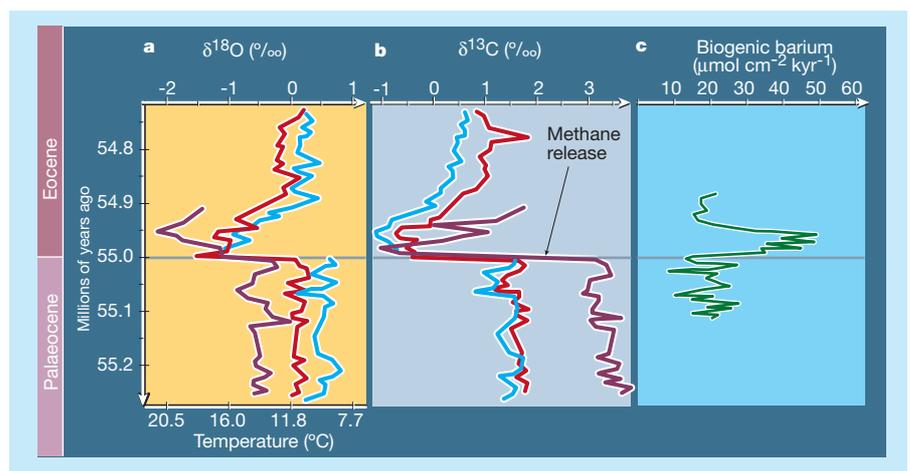


Figure 1 Events at the Palaeocene/Eocene (P/E) boundary, 55 million years ago, inferred from data from an ocean-sediment core drilled in the Weddell Sea, off Antarctica. a, b, Changes in the <sup>18</sup>O/<sup>16</sup>O and <sup>13</sup>C/<sup>12</sup>C isotopic composition of foraminiferal shells<sup>2</sup> (given as δ<sup>18</sup>O and δ<sup>13</sup>C values in parts per thousand), which provide information about temperature and the source of the carbon, respectively. The implication of the δ<sup>13</sup>C record is that there was a massive methane release at the P/E boundary. The isotope data come from foraminifera that lived at three different depths, and show that large changes in temperature and carbon-isotope composition occurred throughout the water column — *Nuttalides truempyi* (blue) lived on the sea floor, at a depth of about 2,000 m; *Acarinina praepentacamerata* (purple) and *Subbotina* spp. (red) were both planktonic, but shallow- and deep-dwelling respectively. c, As described by Bains *et al.*<sup>1</sup>, the biogenic barite record implies that productivity in surface waters increased substantially at and beyond the P/E boundary. They invoke the drawdown of carbon from the atmosphere to explain the return to cooler conditions.

crystals of water and methane. If the ocean warms, these gas hydrates may become destabilized, releasing methane gas which becomes oxidized to CO<sub>2</sub>. The methane is enriched in the light <sup>12</sup>C relative to <sup>13</sup>C, showing that it was originally formed by bacteria which fractionate isotopes during their metabolism. Dickens *et al.* calculated that a release of 1,500 × 10<sup>9</sup> tonnes of methane could account for the large change in carbon isotope ratios at the P/E boundary. On a millennial scale, this would imply a rate of greenhouse-gas emission comparable to current anthropogenic levels.

So what happens if 1,500 gigatonnes of methane are released to the ocean-atmosphere system? Regional differences in temperature are the main driving force for winds and ocean circulation. Palaeoclimate modellers have therefore generally assumed that, with preferential warming at high latitudes, an 'equable' Earth would develop during the P/E thermal maximum. Oceanic circulation would become more sluggish, fewer nutrients would reach the sunlit surface zone, and plankton productivity and photosynthesis would fall.

But some data point to an opposite conclusion. It seems that certain species of plankton characteristic of high-productivity regions flourished all over the world at the P/E boundary<sup>6</sup>. And in rock sections in the Middle East, formed from sediments that were originally under sea, a large peak in biogenic barite (a mineral of barium sulphate) at the P/E boundary indicates a dramatic increase in biological productivity<sup>7</sup>. Biogenic barite has proved a reliable proxy for surface-water biological productivity in the open oceans of the past<sup>7,8</sup>.

The paper by Bains *et al.*<sup>1</sup> not only provides new evidence that oceanic productivity did indeed increase, but also provides a feasible mechanism for how an episode of greenhouse warming may end. They show that in two widely separated ocean drilling cores — one from off Antarctica, the other from the western North Atlantic — the distribution of biogenic barite is a mirror image of the <sup>13</sup>C/<sup>12</sup>C and <sup>18</sup>O/<sup>16</sup>O curves across the P/E thermal maximum (Fig. 1). This implies that biological productivity increased as methane was released and temperature increased (though there is a chicken-and-egg problem here); and productivity decreased as climatic conditions returned to normal. Bains *et al.* propose that higher productivity and the resulting sequestering of excess carbon in the oceans, through photosynthesis, was the feedback mechanism required to bring levels of atmospheric CO<sub>2</sub> and temperatures back to normal.

Proponents of the Gaia theory, which says that the biosphere regulates climate<sup>9</sup>, will love this interpretation. But carbon is not a productivity-limiting nutrient, and Bains *et al.* say there was probably a secondary

feedback between high levels of CO<sub>2</sub> and productivity, or that the relationship is just coincidental. They speculate that greater humidity in a greenhouse world, and consequent increased runoff of water from land, or volcanic fallout (or both), fertilized the oceans' surface waters.

Can we rely on the barite proxy for productivity? I believe we can. There is firm evidence that barite crystals have accumulated in sediments under high-productivity areas in recent times, and that this signal is retained in sediments as old as the early Palaeogene<sup>7,8</sup>. Bains *et al.* show that there are unaltered barite crystals in the P/E sediments they analysed.

However, there is still no consensus as to how the crystals form in the ocean. According to one school of thought, the barite precipitates in decaying organic matter settling through the water column; another holds that the crystals form in living organisms. Various single-celled organisms precipitate microscopic crystals of barite in their bodies, possibly as statoliths for orienting themselves in the gravitational field, but no organism has been clearly linked to the abundant crystals under high-productivity regions<sup>10</sup>.

There are also other puzzles. The idea of a huge release of methane at the P/E boundary is popular mainly because, so far at least, it is the only realistic explanation

for the observed large and rapid decline in the oceanic <sup>13</sup>C/<sup>12</sup>C ratio. But two proxy reconstructions of CO<sub>2</sub> concentrations during the P/E thermal maximum have failed to find evidence for substantially increased concentrations<sup>4,11</sup>. As usual, we need to know more. Is there something wrong with the proxy estimates of atmospheric CO<sub>2</sub> concentrations in the past, or is there another explanation for the decline in <sup>13</sup>C/<sup>12</sup>C at the P/E boundary? And is ocean productivity increasing in our incipient greenhouse world? The paper by Bains *et al.* will trigger much new work on these questions. ■

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Cell biology

## The specifics of membrane fusion

Suzie J. Scales, Jason B. Bock and Richard H. Scheller

The ability to maintain a diverse set of intracellular compartments, with distinct complements of proteins, is a defining feature of eukaryotic cells. Substances can be transported from one membrane-encased compartment to another, but the compartments maintain their unique identities. Transport occurs in membrane-bounded containers called vesicles, and several protein families have evolved to mediate the budding of a vesicle from the donor compartment, and its transport to and fusion with the target organelle. One of the last steps in the fusion process is overseen by a set of proteins called SNAREs. These have been suggested to be the core machinery that mediates the fusing of two membranes, as well as ensuring that vesicles deliver their cargo to the right compartment<sup>1,2</sup>. Writing on pages 153, 194 and 198 of this issue<sup>3–5</sup>, Rothman and colleagues conclude — with some caveats — that SNAREs are indeed important in defining the specificity of vesicle targeting.

SNAREs contain structural features

called α-helices or coils. During membrane fusion, four α-helices from SNAREs found on the vesicle and target membranes come together to form a stable, four-helix bundle or coiled-coil<sup>6</sup> (Fig. 1a). The formation of SNARE complexes is essential for membrane fusion, so a tremendous amount of research has been dedicated to understanding how these complexes form, and what they do. Rothman and colleagues earlier developed an *in vitro* assay that measures the fusion of liposomes — artificial spheres surrounded by a lipid membrane — reconstituted with neuronal SNARE proteins<sup>7</sup>. This system is ideal for assessing the role of SNAREs in isolation. It has been used to show that, when present on liposomes representing the vesicle and the target, SNAREs — in the absence of other factors — can induce membrane fusion<sup>7</sup>.

As well as being involved in driving membrane fusion, SNARE proteins have been implicated in ensuring the accuracy of vesicle trafficking. There appear to be enough SNAREs, differently localized throughout

isocitrate lyase mutant) offer a new tool with which to investigate these issues. Although much remains to be learned about latent *M. tuberculosis* infection, the identification of late-stage mutants represents a milestone in our efforts to demystify mycobacterial latency. ■

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## Earth systems

# Feedback on Gaia

Jim Gillon

Until a few years ago, self-respecting scientists best avoided making any reference to the Gaia hypothesis — as one delegate fondly recalled at a meeting held in June\*, he was once warned that publishing an article with the word ‘Gaia’ in the title could severely damage, if not ruin, a scientific career. Not surprisingly, dissenters still remain, given some of the quasi-religious interpretations of Gaia, such as the notion of the Earth as a living organism. With a name that is Greek for ‘Earth goddess’, maybe this was inevitable. But such conferences show that James Lovelock’s theory<sup>1</sup> of the biotic regulation of Earth has now emerged with some respectability following close scrutiny by the biogeochemical community.

The classic Gaia hypothesis holds that, by introducing feedbacks on climate in particular, life on Earth can regulate and stabilize its environment, possibly indirectly but possibly for its own benefit. One such mechanism proposed by Lovelock<sup>2,3</sup> is the global thermostat stemming from marine algae that produce dimethyl sulphide, a volatile cloud-seeding chemical. The thinking here is that warmer temperatures lead to greater algal growth and release of dimethyl sulphide into the atmosphere; this stimulates cloud formation, increasing the reflection of radiation back into space and cooling the planet. Some estimates<sup>4</sup> suggest that in today’s world such cooling might be as much as 4 °C.

In a vastly different early Earth — during the Archaean, the time before 3,000 million years ago — other climate-policing organisms may have been operating. One suggestion at the meeting (J. Kasting, Penn State Univ.) was that, during the Archaean, when the Sun was 30% dimmer and the Earth much cooler, methane-generating bacteria might

have been responsible for warming the planet to a more hospitable temperature as methane, a strong greenhouse gas, accumulated in the atmosphere. At higher concentrations, however, methane molecules can polymerize and form reflective clouds, in effect creating a global photochemical smog that provides a cooling mechanism to stabilize the climate. Similar processes may have occurred, or may still be occurring, in other methane-rich atmospheres — such as that thought to exist early in the history of Mars, or on Saturn’s moon Titan (the Solar System’s best candidate as an extraterrestrial home for life).

Among the main opponents of Gaia theory are evolutionary biologists, some of whom contend that selection of environment-

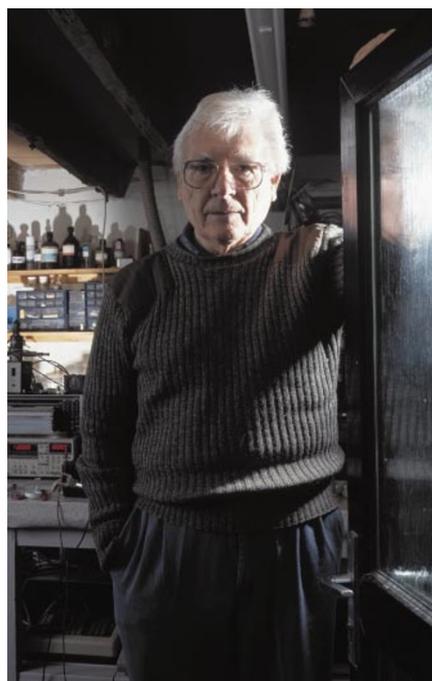
altering traits within organisms is not possible in a darwinian context. Natural selection works at the level of the individual, so how can inherently ‘selfish’ organisms have evolved to change global environment for the common good? One way around this dilemma may come from population biology (D. Williamson, Univ. Liverpool). Self-regulation of populations does not have to be selected for, but is just an emergent property of all individuals trying to maximize their own fitness. Whether this holds for feedbacks on the global scale remains to be seen.

Another criticism of Gaia, voiced frequently at the meeting, centres on the fact that life on Earth has undergone several episodes of near-total extinction — for example, during the periods of almost complete glaciation as a ‘snowball Earth’. This is not the kind of extreme event you would expect from a self-regulating system. Nor indeed are other drastic atmospheric and climatic changes that have followed several of life’s metabolic innovations. One example is the advent of oxygen-generating photosynthesis, which threatened the existence of all anaerobic organisms. Another is the arrival of woody plant tissues, which allowed the huge expansion of vegetation 550 million years ago but induced CO<sub>2</sub>-starvation conditions as mineral weathering of rock, stimulated by the action of plant roots, absorbed large quantities of CO<sub>2</sub>.

When being swamped by case examples and thought experiments both for and against Gaia, it is impossible to discern a clear-cut consensus. Even so, a point of broad agreement at the meeting was that life can produce feedbacks — usually negative feedbacks — that stabilize the environment and result in long periods of stability. Conversely, the advent of new biochemical processes could, for example, have temporarily introduced positive feedbacks and so have created large phase shifts in the Earth’s conditions. Modelling studies on the interaction between vegetation and climate (E. Eltahir, Mass. Inst. Technol.) show that such two-state systems can exist, with a threshold delimiting recovery to a previous state (stabilizing) or entry into a new phase (destabilizing).

These findings would seem to contradict traditional Gaia theory, with its emphasis on planetary homeostasis. Nonetheless, some delegates argued that global destabilization could be ultimately favourable and so still of a Gaian nature. For instance, although it was detrimental to most anaerobic organisms at the time, the large-scale production of oxygen through photosynthesis could have repackaged the energy that life exploits into a more abundant and ‘user-friendly’ form, allowing the subsequent explosion of aerobic organisms to take place (T. Lenton, Univ. Edinburgh).

In the final analysis, judgement on Gaia



James Lovelock: father of the Gaia hypothesis.

\*Second Chapman Conference on the Gaia Hypothesis, University of Valencia, Valencia, Spain, 19–23 June 2000.

theory hangs on the answer to the question: "What have the Gaiaans ever given us?". One response, raised in the summing up (L. Kump, Penn State Univ.), is that an appreciation of Gaia theory has shifted thinking in Earth systems away from cataloguing the fluxes and pools of the Earth's major elements, and towards identifying control systems and feedbacks. Moreover, we have a reminder that there is no harm in taking ideas that were once regarded sceptically and following them through with rigorous

analysis. From these considerations alone, it seems that the general scientific environment has now become hospitable enough for the Gaia hypothesis to last into the future. But how it might evolve is anyone's guess. ■

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(that existing more than 24 hours after the training), but not short-term memory<sup>2</sup>.

Knowing all this, Nader *et al.* trained rats in pavlovian fear conditioning, and tested them 24 hours later with the conditioned stimulus but without the unconditioned stimulus (test 1). The rats froze at the sound of the tone. At this point, when the long-term memory trace was expected to be already insensitive to anisomycin, Nader *et al.* injected the antibiotic into the amygdala. A day later, the authors tested the rats again with just the conditioned stimulus (test 2). Surprisingly, these rats showed a marked decrease in the time spent freezing in response to the tone. The same results were obtained even if test 1 took place 14 days after training, making it even more unlikely that the inhibition of protein synthesis in test 1 impaired a late phase of consolidation initiated by the original training. Omitting the conditioned stimulus before administering anisomycin in test 1 left memory intact. So the memory probably had to be retrieved for anisomycin to have its effect. The anisomycin was effective only if administered within a few hours after memory reactivation.

So it seems that fear-associated memories become temporarily labile on retrieval. Why should the brain invest so much energy in the original consolidation and then risk losing the trace by interference each time it is used? One can come up with teleological explanations — for example, that the brain prefers plasticity at the expense of stability — or mechanistic ones, suggesting in-built constraints on the synaptic machinery. But there is still much to do before we can jump to any sweeping conclusions about the cellular biology of memory retrieval. Some unanswered questions relate specifically to this experiment. Did tests 1 and 2 indeed tap the same memory trace? Did anisomycin abolish the original trace, or merely leave it dormant, waiting to be exposed by some smart behavioural protocol? Which cellular mechanisms are perturbed by anisomycin after retrieval, and are they identical to those that produce the original consolidation?

More generally, might these results apply to different types of memory? Previous studies hinted that pavlovian fear conditioning may not be unique in being shaky on retrieval<sup>9,10</sup>. But even if just a few types of memory must reconsolidate after use, the implications of the results of Nader *et al.*<sup>2</sup> are remarkable. Consider, for example, the prospect of intentionally recalling the memory of a traumatic experience and then selectively erasing it. What such a possibility would mean for psychoanalysts on the one hand, and poets on the other, is quite a different matter. ■

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Neurobiology

## The shaky trace

Yadin Dudai

Penelope would have been sad indeed had she realized that each time she was reminded of her beloved Odysseus — away from home for so many years after the Trojan war<sup>1</sup> — she could entirely lose her precious memory of him. Fortunately this was also unknown to her pushy suitors. But now Nader and colleagues, writing on page 722 of this issue<sup>2</sup>, have made it public. Recollection, they claim, is a dangerous matter: whenever we bring a memory to mind, it may turn shaky and slip into oblivion.

Most memories, like humans and wines, do not mature instantly. Instead they are gradually stabilized in a process referred to as consolidation<sup>3,4</sup>. Newly formed memory traces are sensitive to a variety of brain injuries and drugs, but after they have been consolidated they become more resistant to these treatments. Consolidation takes place at many levels of organization and complexity in the brain, and its overall kinetics depends on the type of memory involved. We know most about what happens in individual nerve cells and synapses — the points of communication between neurons — once they have been recruited to consolidate a memory.

The current textbook version, in a nutshell, goes like this. Training modifies proteins at synapses in the neuronal circuit that acquires the new memory. This alters synaptic efficacy and thus the encoding of information in that circuit. But protein molecules survive only for periods of minutes to weeks, whereas many memories are destined to live longer. It seems that at least part of the immunity of memory to this molecular turnover is achieved by training-induced modulation of gene expression in the modified neurons. The new gene products promote long-lasting remodelling of the activated synapses, in a process that involves crosstalk between the synapses and neuronal cell bodies<sup>5</sup>. It takes a few hours for the new pattern of gene expression and the synaptic change to be consolidated. During this time,

the process can be halted by inhibitors of protein synthesis<sup>5–7</sup>.

This textbook version might tempt one to believe that, for every memorized item, consolidation starts and ends just once. But this view would be naive. Experimental psychologists told us long ago that memory traces are reconstructed with use, and that retrieving a memory involves mingling the representations of the past with the percepts of the present<sup>8</sup>. The study by Nader *et al.*<sup>2</sup> echoes earlier reports that a consolidated memory can apparently be induced to vanish, provided that the memory is activated shortly before the use of the treatment leading to amnesia<sup>9,10</sup>. The problem with these early studies was that, because the treatments were applied to the whole brain or even the whole body, and because little was known about the relevant neuronal circuits, the researchers could not target cellular mechanisms in identified memory traces. This has now changed.

Nader *et al.* took advantage of 'auditory fear conditioning' in rats. This works as follows. The rat hears a tone (the conditioned stimulus) in conjunction with a mild foot-shock (the unconditioned stimulus). The electric shock elicits fear (an unconditioned response). After one training session, the tone elicits fear responses, such as freezing, even in the absence of shock (a conditioned response). For readers who are not well versed in the emotional life of rats but do recall the story of Pavlov and his salivating dogs, suffice it to note that the situations are basically similar: both the dogs in Petrograd and the rats in Manhattan had to learn to associate conditioned and unconditioned stimuli. The protocol is therefore aptly dubbed 'pavlovian fear conditioning'. The neuronal circuit underlying pavlovian fear conditioning includes the lateral and basal nuclei of the amygdala. Inhibiting protein synthesis in this brain region immediately after fear conditioning, by infusing the antibiotic anisomycin into this region, blocks long-term fear memory