Both methods made the cells sensitive to drug-induced apoptosis (Fig. 1b, c). Conversely, manipulation of the malignant cell line through another adhesion system (with β1-integrin antibodies) caused a partial reversion to normal glandular structures, which then were resistant to apoptosis (Fig. 1a, b). Additional experiments showed that cell growth did not affect their sensitivity to cell death.

A key mechanism appeared to be the binding of a specific cell-adhesion receptor, α6β4-integrin, which is present on the epithelial-cell surface, to the basement-membrane protein laminin (Fig. 1e). Mutated receptors with abnormal anchorage to the basement membrane did not protect against apoptosis. Interestingly, however, cells were even protected by minimal basement-membrane-type contacts induced by small beads coated with anti-α6β4 antibodies (Fig. 1f). This finding is important, because it implies that protection occurs at the level of the individual cell: as long as cells can initiate normal α6β4-integrin interactions to achieve molecular polarity, they do not need to be organized into glandular structures in order to resist apoptosis. But what links integrin-mediated adhesion to protection from apoptosis? In further experiments, Weaver *et al.*[2] showed that the key signal was NF-κB, a well-known regulator of gene expression, thereby linking integrin binding to gene regulation (Fig. 1d).

These findings might help to explain some puzzling observations. For instance, tumour cells growing in monolayer culture are quite susceptible to chemotherapeutic drugs, but become resistant when grown as cell clusters or spheroids suspended in medium[4]. Given the results of Weaver *et al.*, it would be expected that the cells should be resistant to such drugs if they form organized three-dimensional structures. Moreover, a laminin peptide that promotes the formation of three-dimensional structures by salivary epithelial cells can also promote experimental metastasis, perhaps because of its effects on epithelial organization[5,6].

A critical question is whether the findings of this new study are directly relevant to human cancers. Is there a direct correlation between the susceptibility of human tumours to chemotherapeutic apoptosis and the absence of α6β4-integrin-dependent polarity? If there is, a potentially valuable approach would be to consider α6β4-integrin-mediated adhesions as new targets for chemotherapy.

Viewed more broadly, these findings underscore the importance of tissue organization and the three-dimensional relationships of cells. Previous studies established that epithelial-cell polarity is essential for maintaining normal function[7]. Indeed, work with the epithelial-cell model system has shown that three-dimensional organization affects the regulation of cell growth and tumorigenicity[8,9]. Conversely, the fibroblastic cells found in connective tissue are normally surrounded by a matrix, rather than polarized towards a basement membrane. Placing fibroblasts in cell culture induces an artificial polarity towards the culture substrate, and returning the cells to a three-dimensional matrix promotes a morphology more like that seen *in vivo*, and stimulates migration and proliferation[10].

These studies with epithelial and fibroblastic cells carry both a warning and a promise. Experiments in which cells are cultured on the commonly used flat surfaces, in which normal three-dimensional relationships with the extracellular matrix and other cells are distorted, may produce mistaken conclusions. Analysing cell interactions in more natural three-dimensional settings, as in Weaver and colleagues' study[2], promises to provide a view that is closer to what actually happens in living organisms. Such approaches may also provide a new dimension to cancer treatment, by going beyond the intrinsic genetic, growth and migratory characteristics of cells, and focusing on their microenvironment and organization. ■

Kenneth M. Yamada and Katherine Clark are at the National Institute of Dental and Craniofacial Research, National Institutes of Health, 30 Convent Drive, Bethesda, Maryland 20892-4370, USA.
e-mails: kenneth.yamada@nih.gov
katherine.clark@nih.gov

1. Johnstone, R. W., Ruefli, A. A. & Lowe, S. W. *Cell* **108,** 153–164 (2002).
2. Weaver, V. M. *et al. Cancer Cell* **2,** 205–216 (2002).
3. Frisch, S. M. & Screaton, R. A. *Curr. Opin. Cell Biol.* **13,** 555–562 (2001).
4. Durand, R. E. & Olive, P. L. *Methods Cell Biol.* **64,** 211–233 (2001).
5. Hoffman, M. P. *et al. J. Biol. Chem.* **273,** 28633–28641 (1998).
6. Yoshida, Y. *et al. Int. J. Oncol.* **18,** 913–921 (2001).
7. Roskelley, C. D., Srebrow, A. & Bissell, M. J. *Curr. Opin. Cell Biol.* **7,** 736–747 (1995).
8. Weaver, V. M. *et al. J. Cell Biol.* **137,** 231–245 (1997).
9. Wang, F. *et al. Proc. Natl Acad. Sci. USA* **95,** 14821–14826 (1998).
10. Cukierman, E., Pankov, R., Stevens, D. R. & Yamada, K. M. *Science* **294,** 1708–1712 (2001).

Planetary science

Earth's lunar attic

Clark R. Chapman

Rocks blasted long ago from the surface of Earth and other planets may be preserved on the Moon. Although hard to identify, they could hold a unique record of the chemical history of the planets and even evidence of life.

Two decades ago, it was realized that a few unusual meteorites in our museums are actually pieces of Mars[1]. Isotopic ratios derived from gas trapped inside the rocks indicate their provenance. Meteorites that originated on the Moon were soon recognized, and one that might be from Mercury[2]. Calculations of the interplanetary transport[3] of material support the possibility that such rocks are being carried to the Earth, and of course there has been speculation that ancient transport of earthly rocks to Mars, lofted by giant cratering impacts, may have 'seeded' life on that planet — or the other way round.

The chances of finding meteorites from Venus on Earth are poor, partly because of the rarity of impacts large enough to eject material out of the planet's very thick atmosphere. But long ago, the inner Solar System was a much more violent place, and the venusian atmosphere might have been thinner, allowing meteorites to escape. Writing in *Icarus*, Armstrong, Wells and Gonzalez[4] suggest that the Moon may be a repository for precious, ancient meteorites from other planets, including Venus, Mars and the Earth itself.

Armstrong *et al.*[4] argue that rocks delivered from other planets to the Moon are specially blessed. For the past 3.8 billion years, the lunar surface has been tranquil compared with the pervasive geological and geochemical evolution of planets such as the Earth, Venus and Mars. As a result, venusian meteorites delivered to the Moon aeons ago (long before the global volcanism on Venus that largely ended half a billion years ago) might remain and could give insight into the history of Venus during epochs for which evidence in the planet itself has been obliterated.

The paper's charming title, "Rummaging through Earth's attic for remains of ancient life", reveals its theme. The authors propose that, very roughly, 20,000 kg of mainly ancient terrestrial rocks may remain in a typical 10×10 km^2 region on the Moon; around 200 kg are expected from Mars, and just 1–30 kg from Venus. But these exotic rocks can't simply be scooped up. Most would be buried hundreds of metres deep in 'megaregolith' — the massive lunar crustal materials that were blasted around the surface when the Moon's huge impact basins, several hundreds of kilometres in diameter, formed.

It is thought that a quarter of the Moon's several dozen impact basins formed during the short 50-million-year interval between 3.9 and 3.85 billion years ago — termed the Late Heavy Bombardment (LHB)[5]. The remaining three-quarters are even older, and a controversial number of basins, since obliterated, formed earlier still. In most LHB scenarios, the Earth and other terrestrial planets were bombarded by asteroids long

THE CLEMENTINE PROJECT

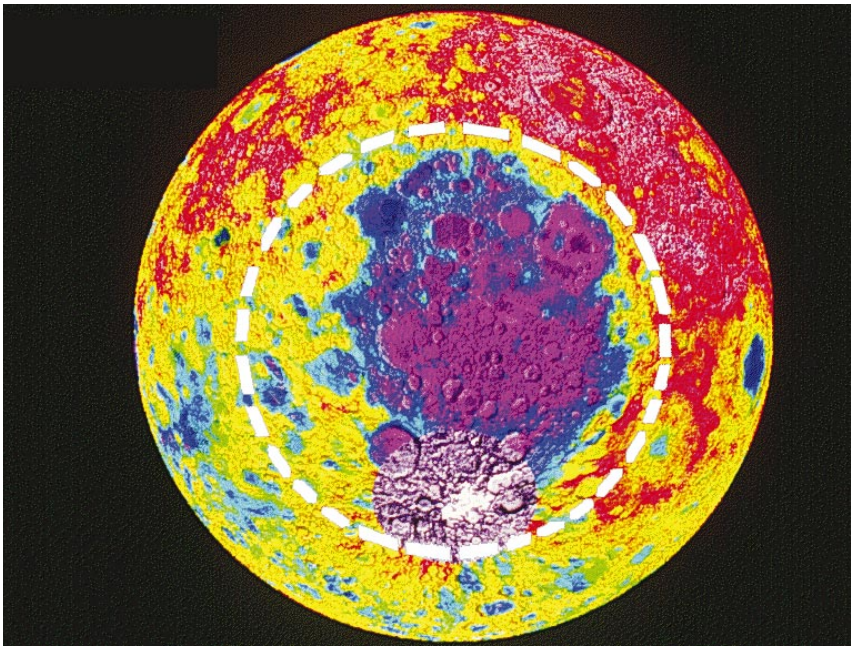

Figure 1 **The South Pole–Aitken Basin. This false-colour mosaic of images from the Clementine mission shows the huge impact crater on the far side of the Moon, more than 2,000 kilometres in diameter. The scarring of the Moon records a heavy bombardment by asteroids and comets during the early history of the Solar System. Armstrong *et al.*[4] suggest that rocks from other planets preserved on the lunar surface would document the chemical history of the Earth and Venus, as well as other planets, during that epoch.**

after the Solar System formed (hence the term 'Late'); outer Solar System bodies such as Jupiter's moons were also conceivably bombarded[6]. On Earth, the 100-plus basin-forming impacts would have made for a hellish time indeed, just as life was struggling to gain a foothold on our planet, and possibly on others[7]. Rocks blasted into space from these impacts would dominate the terrestrial 'contamination' of the Moon.

Armstrong *et al.*[4] estimate that around 7 parts per million of lunar surface materials are of terrestrial origin — in which case there might already be a few grams sprinkled among samples brought back from the Moon. Whether from existing samples or from some future mission to hunt for extra-lunar planetary samples on the Moon, how could such needles in the haystack of lunar soils be recognized? How could every grain be efficiently sampled for a signature of terrestrial or venusian origin?

On the Moon, would these rare rocks even be accessible? We might similarly ask how representative are the lunar samples we already have, and how solid is their evidence for the LHB. Whether returned by astronauts, Soviet robotic missions or even as lunar meteorites, all come from the immediate surface of the well-churned lunar soil (regolith), or from the uppermost few metres. What movement and processing have they been subject to and how certain can we be about which giant impact basin (let alone which planet) they might be from?

Dating the LHB relies on the validity of geological inferences that associate certain rocks with often distant impact basins[8]. Moreover, the spike in impact rates associated with the LHB is actually defined by the rarity of basin-forming impacts before then (inferred from the virtual absence of impact melt-rocks older than 4 billion years[9]). If regolith processes preferentially bury or destroy such older melt-rocks, so that they can't be collected at the surface, then we could be misled. Similar processes might make collecting extra-lunar meteorites even more difficult than it already seems.

Would extra-lunar meteorites even preserve the vital evidence we seek? After all, they must have been blasted off the Earth or Venus in catastrophic explosions, somehow penetrating thick atmospheres, before slamming into the lunar surface at a speed of several kilometres per second. Obviously, such violent delivery might disturb or destroy the valuable biological or chemical information about primordial epochs that we seek.

Understanding the LHB and assessing the practicalities of searching for extra-lunar rocks depend on understanding how impact cratering forms and modifies both the Moon's surface regolith and deeper megaregolith. Armstrong *et al.*[4] rely on rather simple parametrizations of these processes. But renewed theoretical modelling of regolith processes is under way in several research groups.

The most exciting prospect for under-

100 YEARS AGO

Is there not room for some provisional hypothesis which shall include both Galton's and Mendel's ideas, which are not necessarily antagonistic, but may turn out to be as simultaneously true as the laws of Boyle and Charles, so that the final results may be of the nature of a product or resultant? I mean that instead of drawing a hard-and-fast line between "recessive" and "dominant" characters we may suppose that these differ like heat and cold, in degree but not in kind. … To take an instance. Last year (1901) I carefully hybridised two varieties of the sweet pea, using lens, paint brush and muslin nets. One variety used was "Gorgeous," of a salmon-orange colour. … The other variety was a new cream white, Eckford's "Mrs Kenyon," novelty of 1901. ... None of the flowers of the offspring have been cream-coloured; the seeds borne on "Mrs Kenyon" by pollen from "Gorgeous" have all yielded purple flowers unlike either immediate parents, but probably taking their colour from the known remote purple ancestor of our sweet peas. Of seeds borne on "Gorgeous" by pollen from "Mrs Kenyon," eight plants yielded flowers like "Gorgeous" but ten of the plants yielded purple flowers. Here the dominant purple appears to be due to the previous long ancestry; the salmon variety of ten years' standing has several representatives, but not one single cream flower stands for the 1901 novelty.
From *Nature* 23 October 1902.

50 YEARS AGO

During the past two years, simple mud-walled, thatch-roofed huts fitted with exit window traps and occupied by volunteer Africans have been sprayed with various formulations of the three insecticides, DDT, BHC and dieldrin, and the effect on the *Anopheles gambiae*, *A. funestus* and culicine mosquitoes entering them observed. Daily mortalities among the mosquitoes were determined by counting the dead individuals on the floors of the huts, and counting those dying later (within 12 hr. of capture) which were caught alive inside the huts in the morning and in the window traps during the night. … In the later experiments a hut was also treated with the new insecticide, dieldrin. This was applied in the form of a wettable powder at a calculated dosage of 50 mgm. dieldrin per square foot… . Results showed this insecticide to be the most efficient of those tested.
From *Nature* 25 October 1952.

standing basin formation and regolith processes is to fly a sample-return mission to the far side of the Moon, near its largest impact crater, the South Pole–Aitken Basin (Fig. 1). Such a mission was given high priority this summer by the US National Research Council's planetary decadal survey[10]. Of course, it is doubtful that a first, moderate-cost mission could locate and return extra-lunar meteorites, given their rarity, but it would be a step towards that goal.

Although Armstrong *et al.*[4] believe that their theoretical calculations are conservative, they could still be too optimistic about the prevalence of extra-lunar materials on the Moon. Such samples must exist, however, in whatever tiny amounts, and set a marvellous challenge as analytical and sampling techniques improve during future decades. ■

Clark R. Chapman is in the Space Studies Department, Southwest Research Institute, Suite 400, 1050 Walnut Street, Boulder, Colorado 80302, USA.
e-mail: cchapman@boulder.swri.edu

1. Bogard, D. D. & Johnson, P. *Science* **221,** 651–654 (1983).
2. Palme, H. *Science* **296,** 271–273 (2002).
3. Gladman, B. J., Burns, J. A., Duncan, M., Lee, P. & Levison, H. F. *Science* **271,** 1387–1392 (1996).
4. Armstrong, J. C., Wells, L. E. & Gonzalez, G. *Icarus* **160,** 183–196 (2002); Preprint astro-ph/0207316, http://arXiv.org
5. Hartmann, W. K., Ryder, G., Dones, L. & Grinspoon, D. in *Origin of the Earth and Moon* (eds Canup, R. M. & Righter, K.) 493–512 (Univ. Arizona Press, Tucson, 2000).
6. Levison, H. F. *et al. Icarus* **151,** 286–306 (2001).
7. Maher, K. A. & Stevenson, D. J. *Nature* **331,** 612–614 (1988).
8. Wilhelms, D. E. *The Geologic History of the Moon* US Geol. Surv. Prof. Pap. 1348 (1987).
9. Ryder, G. *J. Geophys. Res.* **107** (2002) (doi: 10.1029/2001JE001583).
10. National Research Council *New Frontiers in the Solar System: An Integrated Exploration Strategy* (2002); www.nationalacademies.org/ssb/newfrontiersfront.html

Ageing

The old worm turns more slowly

Thomas B. L. Kirkwood and Caleb E. Finch

Detailed studies of cellular changes in ageing nematode worms show that they, like humans, suffer progressive muscle deterioration. Randomness of cell damage is another shared hallmark of the ageing process.

When the nematode worm *Caenorhabditis elegans* was first considered as a model for the study of ageing some 20 years ago, few foresaw how valuable it would prove to be. The past decade, in particular, has seen an explosion of work on the genetics of lifespan in this species. Building on pioneering work by Tom Johnson[1] and others, more than 50 mutations that extend lifespan have now been described, and the metabolic pathways regulated by these genes are being unravelled[2]. Some of these genes regulate a key developmental switch, which directs young worms that find themselves in poor environments to adopt a long-lived stress-resistant form (the dauer larva). Other genes control core processes, such as the overall rate of metabolism. These are exactly the kinds of processes predicted to be important for longevity by the evolutionary theories of ageing, in particular the 'disposable soma' theory, which suggests that competition for metabolic resources between processes such as growth, reproduction and cellular maintenance lies at the heart of the ageing process[3].

But despite its value in studying the genetics of longevity, a major limitation to the use of *C. elegans* as a model of ageing has been the scarcity of data on the pathology of aged worms. We knew how long worms lived, but not how they died. This situation is radically changed by Herndon *et al.*[4], writing on page 808 of this issue, who give a detailed description of the cellular changes that occur with ageing in wild-type and long-lived mutant worms.

The adult worm contains just 959 somatic cells (that is, cells not involved in reproduction) and each cell can be identified in terms of its function. Using a combination of fluorescence and electron-microscopic techniques, Herndon *et al.* have characterized the major cellular changes that accompany ageing in a number of important cell types. Intriguingly, they found that worms are perhaps not so very different from humans, at least in the sense that an important aspect of their decline into senescence is the progressive deterioration of muscle, known as sarcopenia. By contrast, the worm nervous system appears remarkably well preserved. If old worms wriggle less, it is not, it seems, because they have forgotten how to do so.

A dramatic feature of the changes described in the aged worms is the seemingly random nature of the large variations between individuals; in other words, the changes appear to be highly stochastic. This is all the more remarkable in an organism that, in so many other respects, is under strict genetic authority. Nematode strains have exceptional genetic uniformity (arising from the fact that they are self-fertilizing hermaphrodites), they are cultured in highly uniform environmental conditions and they have a developmental process of almost clockwork precision. We know, of course, that in humans one of the hallmarks of the ageing process is an increase in variability. Indeed, it has been said of humans that we are all born copies but die originals. This variability in human populations can readily be attributed to the uniqueness of our individual combinations of nature and nurture, but such an explanation does not work for worms.

In fact, variability in worm ageing has been staring us in the face, but has only recently been noticed[5]. The conventional way to plot data on longevity in worms, as in other organisms, is as a survival curve, where the percentage still alive is plotted against age. If we plot exactly the same data in another way, showing instead the statistical distribution of age at death, we see at once the extraordinary variation in lifespan between individual worms, despite the uniformity of their nature and nurture (Fig. 1). The range of lifespan for a given strain is wide and not so very different, in terms of standard deviation expressed as a percentage of the mean, from that of outbred, free-living humans.

Where does this variability in worm ageing come from? Not, seemingly, from their nature or nurture. The answer may be that,

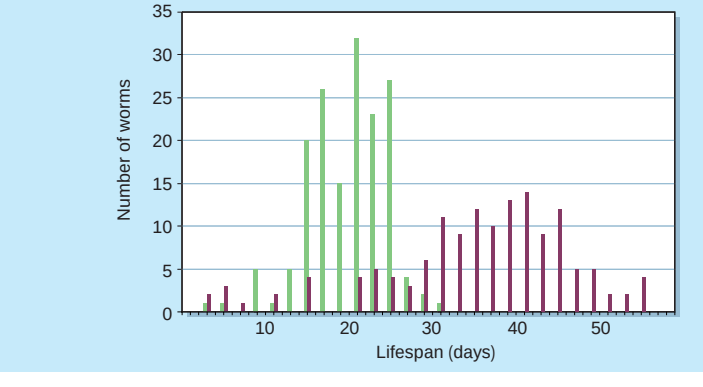

Figure 1 **Lifespan distributions for individual *Caenorhabditis elegans* nematodes in isogenic populations of wild-type (green) and long-lived *age-1* (purple) strains. Although the distributions have different mean values, the spread of both (compared to the mean value) is similarly broad. The range of lifespans in nematodes is indicative of the randomness of the ageing process, which Herndon *et al.*[4] have now investigated at the cellular level (data provided by T. E. Johnson[1]).**