cat cloning on a "case-by-case basis" by the end of the year, according to spokesperson Ben Carlson.

For now, at least, pet cloning is mainly of interest to sentimental animal lovers and not to serious dog and cat people. Currently, says Michael Brim, spokesperson for the Cat Fanciers' Association in Manasquan, New Jersey, a clone "wouldn't be registrable with us as a pedigreed cat" because of its irregular parentage. Cloning, says Brim, "would basically jump over all the genetic rules of breeding" and take all the sport out of cat fancying. Besides, the whole idea is to breed animals to approach a perfect ideal, so a clone would be a ready-made has-been.

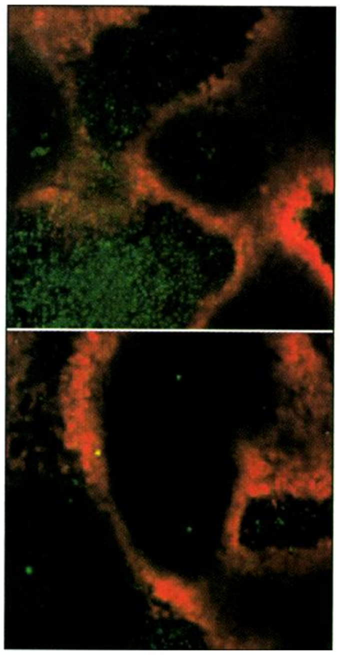
–CONSTANCE HOLDEN

CANCER RESEARCH

Obstacle for Promising Cancer Therapy

Cancer cells are wily. Drug therapies may temporarily halt tumor growth, but all too often the agents lose their effectiveness as the cells' genetic versatility allows them to become resistant. Researchers hoped that so-called antiangiogenesis therapies, which are aimed at preventing the growth of the new blood vessels needed to nourish tumors rather than at the tumors themselves, might circumvent this problem. But recent work suggests that tumors may be able to get around angiogenesis inhibitors, too.

The latest example comes from Joanne Yu, Robert Kerbel, and their colleagues at Sunnybrook and Women's College Health Sciences Centre in Toronto. They report on page 1526 that tumors in which the *p53* tumor suppressor gene has been inactivated—which happens in about 50% of human cancers—are much less responsive to angiogenesis inhibitors than comparable tumors in which the gene is still functional. Researchers already knew that cancer cells can counteract the inhibitors by pouring out more of the factors that promote new blood vessel growth. But loss of the *p53* gene apparently renders tumor cells better able to survive in the low-oxygen conditions present in tumors deprived of an ample blood supply.



Holding their breath. Cells without *p53* (*bottom*) withstand hypoxic conditions in tumors better than do those with the gene (*top*), whose death throes are indicated by green staining.

James Pluda—who has just left the National Cancer Institute, where he oversaw antiangiogenesis trials, for MedImmune Inc. in Gaithersburg, Maryland—describes the Kerbel team's experiments as "a very nice piece of work," one that will help researchers decipher results from clinical trials of angiogenesis inhibitors. Already, some 40 agents are being tested worldwide against a wide range of cancers. Neither Pluda nor others expect the new results to preclude development of the inhibitors. But, Pluda notes, the findings "give us something to look at if patients whose cancers initially respond then progress."

Some 12 years ago, Kerbel proposed that therapies based on inhibiting new blood vessel growth might not be prone to the resistance problem. But hints to the contrary have appeared in the literature, particularly when angiogenesis inhibitors are given alone. Two years ago, for example, Kerbel and his colleagues found that treating human tumors growing in mice with single antiangiogenesis drugs caused them to shrink—but after a month or two they began growing again. Kerbel wanted to know, he recalls, "why were we getting these relapses?"

A clue came last year when his team found that cells within a single tumor vary in their ability to withstand the low-oxygen (hypoxic) conditions that angiogenesis inhibitors create. Because work by other investigators had shown that *p53* loss makes cells more resistant to hypoxia, Kerbel, Yu, and their colleagues decided to test whether that genetic change could account for the reduced susceptibility to angiogenesis inhibitors.

They obtained two lines of human colon cancer cells from Bert Vogelstein's group at Johns Hopkins University School of Medicine in Baltimore, Maryland; the lines were identical except that in one, the *p53* gene had been inactivated. The Sunnybrook workers then transplanted either the unaltered cells or the $p53^{-/-}$ cells into mice. The tumors produced by the unaltered cells "responded quite nicely" to a combination of two antiangiogenic drugs, Kerbel says. But those produced by the $p53^{-/-}$ cells took longer to shrink, and the response was shorter lived, even though the therapy had shown long-lasting effectiveness in previous animal tests.

When the researchers then implanted equal mixtures of $p53^{+/+}$ and $p53^{-/-}$ cells in single mice, the proportion of $p53^{+/+}$ cells decreased dramatically after treatment with the angiogenesis inhibitors. This result also suggests that in natural tumors, which usually consist of genetically diverse cell mixtures, antiangiogenesis therapy might select for the growth of $p53^{-/-}$ cells.

As the Sunnybrook team suspected, the $p53^{-/-}$ cells survived better because they are more tolerant of hypoxia. In mixed tumors, the $p53^{+/+}$ cells tend to cluster around the oxygen-giving blood vessels, and those in the more hypoxic regions succumb to the cellular suicide known as apoptosis. In contrast, very few $p53^{-/-}$ cells died of apoptosis even in low-oxygen regions.

Although Kerbel concedes that the new results are a "bit of a downer," he maintains that "they don't negate the idea of exploiting antiangiogenesis therapy." Indeed, as angiogenesis pioneer Judah Folkman of Children's Hospital Boston points out, although tumors may be able to reduce their reliance on the vascular supply, "this paper should not be misinterpreted to mean that tumors can grow under completely [oxygen-free] conditions." This might be achieved by combining angiogenesis inhibitors with other drugs that destroy existing blood vessels.

Folkman and Kerbel outline additional strategies that might get around the problem of tumor resistance to antiangiogenesis therapy, such as upping the dose of the inhibitors or giving them with drugs that specifically target hypoxic cells. The trick to defeating cancer, this work shows once again, will be to outmaneuver the enemy.

–JEAN MARX

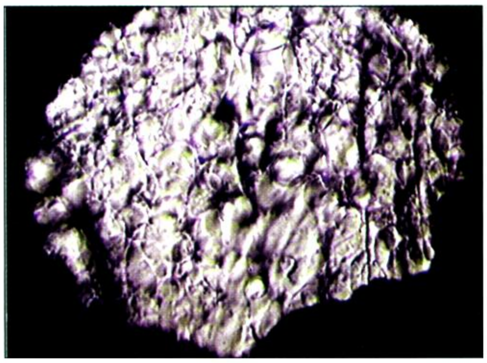
MICROBIOLOGY

Weight of the World On Microbes' Shoulders

Bacteria withstand stress far more gracefully than the rest of us. Sizzle them to above 110°C, freeze them to below –10°, douse them with salt or acid—and, if they had eyelashes, they'd barely bat any. Now a study takes stressful conditions to a new extreme, crushing microbes beneath the equivalent of a 160-kilometer column of water—and showing that, voilà, they survive. To some microbiologists this suggests that similar organisms might survive the high-pressure environments of other celestial bodies, like Jupiter's moon Europa.

To engineer this pressure, geochemist Anurag Sharma, microbiologist James Scott, and their colleagues at the Carnegie Institution of Washington in Washington, D.C., took a 50-year-old tool used by physicists and applied it to microbe physiology for the first time. The high-pressure device, called a diamond anvil cell, is created by

CREDIT: J. YU ET AL.



Superbugs. Microbes carve liquid veins (purple) in ice, where they survive under extraordinarily high pressure.

placing two chiseled diamonds on the ends of opposing cylinders and screwing them together. The Carnegie group layered a film of water and bacteria between the diamonds and began cranking. On page 1514, they report that molecular spectroscopy inside the anvil revealed metabolic activity in the two common bacterial species used, the gut microbe *Escherichia coli* and *Shewanella oneidensis*, which breaks down metals. Under 1.6 gigapascals, roughly 1% of the bacteria lived to tell the tale.

The findings "could expand the habitable zone to areas of great pressure," says John Baross, a professor of oceanography and astrobiology at the University of Washington, Seattle.

Studying microbes under high pressure is technically tricky, but in this case the clarity of diamonds allowed Sharma's team to gaze through the gems with a microscope. To monitor the bacteria's behavior, the group added a dye to the solution. The dye turns clear in cells capable of breaking down an organic compound called formate. By melding observations of the dye with spectroscopy data that revealed peaks and valleys indicative of formate metabolism, the team could determine how many bacteria survived. Test microbes killed with heat before being squished, in contrast, failed to signal life.

The pressure was so great that the solution turned into a form of room-temperature ice known as ice-VI. Of roughly 1 million bacteria, 10,000 remained viable after 30 hours, consuming formate and creating liquid pockets within the once-solid ice. When the researchers turned their diamond anvil upside down, the bacteria hung upside down as well—suggesting that their tails were functional enough for the microbes to cling to a surface or swim.

But whether motility and metabolism are enough to qualify the bacteria as viable is contentious. "My measure of a live cell would be one that can grow and divide," says Art Yayanos, an oceanographer at the Scripps Institution of Oceanography in La Jolla, California. Although Scott points out that the bacteria elongated and displayed characteristics suggestive of early cell division, he agrees that his group has not determined whether the bugs can divide. "I'm certain that what we're seeing is survival," he says. "But I don't know if the cells … will be able to replicate."

Bacteria don't often encounter squeezed-together diamonds, but plenty of people would like to know whether similar creatures live in other extraordinarily high-pressure environments. It's hard to tell how the new results might translate to life on Earth or elsewhere, however. The rate of bacterial survival was low in this study, says microbiologist Derek Lovley of the University of Massachusetts, Amherst, who wonders if many microbes could endure long term. Baross would like to test how microbes that are adapted to extreme environments—unlike *E. coli*—would fare.

In addition, high pressure is normally accompanied by extremes in temperature—generally hot, but on certain icy planets, very cold—and these high-pressure survivors were kept at a comfortable room temperature. Still, by bumping microbe hardiness to a new level, the study expands the range of the search for extraterrestrial life. "When people think about setting up missions to look for life, they tend to think about looking for it on the surface," says Scott. "You might want to look underneath."

–JENNIFER COUZIN

MASS EXTINCTIONS

No 'Darkness at Noon' To Do In the Dinosaurs?

Try as they might, geologists have yet to find clear signs that any day in the past half-billion years was as bad as that one 65 million years ago, when a mountain-size asteroid or comet slammed into the Yucatán Peninsula. Life suffered mightily, the dinosaurs disappeared, and mammals seized the day. The immediate cause of death has long been listed as starvation after the 100-million-megaton impact threw up a sun-shrouding pall of dust. Even a lesser impact's dust could threaten civilization, some warned.

Now, a geologist is questioning whether that ancient impact produced that much dust after all; perhaps the "darkness at noon" dust scenario was more like a dim winter's day in Seattle. The impact still gets the blame, but other killing mechanisms—an obscuring acid haze, global fires and smoke, or a combination of mechanisms—may have done the dirty work. The finding, if it stands up, might help explain the seeming absence of other impact crises and reduce, at least marginally, the potential hazard to civilization if another massive body were to strike.

The challenge to the dust scenario comes from the latest attempt to estimate the amount of the smallest bits of debris from the impact. To cut off photosynthesis and starve the dinosaurs, copious amounts of submicrometer particles would have to have floated in the atmosphere for months. But this fine dust can't be measured directly in the 3-millimeter-thick, global layer of impact debris because it would have weathered away to clay.

Geologist Kevin Pope of Geo Eco Arc Research in Aquasco, Maryland, scoured the literature for reports of the size and abundance of larger, more rugged bits of impact debris—typically quartz grains averaging 50 micrometers in size—found in the global layer, which consists mostly of relatively large spherules condensed from the plume of vapor that rose from the impact. From these measurements, Pope tried to understand the dispersal of the dust cloud.

In the February issue of *Geology*, Pope reports that the size of this larger debris dropped off sharply with increasing distance from the impact, as if it had fallen from wind-blown debris clouds rather than being blasted around the globe by the impact. Indeed, when Pope modeled debris dispersal by winds alone, the modeled drop-off in both size and mass of debris grains resembled that seen in the global layer, but only if the total amount of debris produced by the impact was relatively small.

In addition, assuming that the impact debris had a distribution of particle sizes similar to that of volcanic ash, Pope concludes that less than 1% of the debris consisted of submicrometer particles. Therefore, the dust in the global layer "is two to three orders of magnitude less than that needed to shut down photosynthesis," he writes.

Beginning of the dinosaurs' end. Global fires triggered by the impact rather than obscuring dust may have done in the great beasts.

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