the cell lines were derived, and these, too, had the mutations, although normal cells from the same patients did not. And since the paper was written, Vogelstein says, the researchers have screened dozens of primary tumors from HNPCC tumors, and "nearly all have the same mutations."

Even that impressive evidence doesn't necessarily prove that the mutation contributes to the cancer development. "You have to be careful about ascribing a role [to a mutation], since so many genes are mutated in cancer cells," Vogelstein cautions. But the researchers have evidence that the mutation in the RII gene is more than just an innocent bystander. When the Brattain-Markowitz-Willson team transferred a good copy of the gene into a line of colon cancer cells that lack it and normally form fast-growing tumors when injected into nude mice, they found that the cells lost their tumor-forming capacity. "This demonstrates that there really is a biological consequence of the mutation," Brattain says.

Researchers who study TGF-β are thrilled by these results. NCI's Roberts notes that while there was ample reason to suspect that a receptor defect might be involved in tumor cells' loss of responsiveness to TGF-β, "this really nails it down" for a human cancer. Another TGF-β pioneer, Harold Moses of Vanderbilt University School of Medicine in Nashville, Tennessee, agrees: "This is the first demonstration of a mechanism for the loss of the growth inhibitory response, and to tie it in with the repair defects is particularly interesting."

In addition to providing a possible solution to the problem of what causes loss of response to TGF-β, these results suggest, says Minna, that the RII gene may be a critical kind of gene called a tumor suppressor, whose loss or inactivation may lead to cancer. He points out that the gene maps to an area on chromosome 3 that is thought to contain a tumor suppressor because it is deleted in several cancers. His own team, he says, is exploring whether loss or inactivation of the gene might contribute to development of small-cell lung cancer. Indeed, he says, "several components within the pathway [by which TGF-β inhibits growth] could be tumor suppressors."

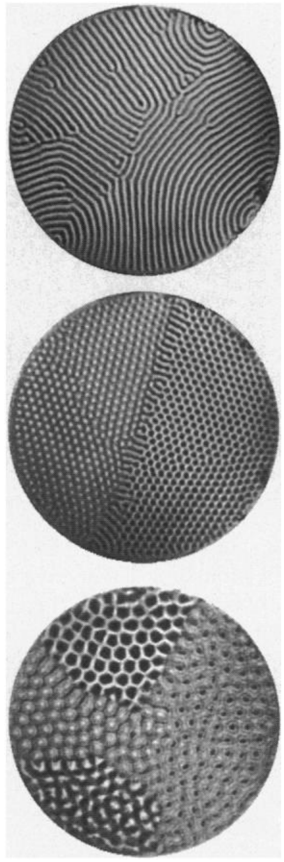
On the clinical front, Markowitz and Willson want to explore whether it is possible to detect HNPCC colon and ovarian cancers by screening for cells that carry the RII mutation in blood or stool. And beyond that lies the goal of using gene replacement therapy to treat cancers that have lost their responsiveness to TGF-β by putting in a good copy of the RII gene. That's a long way off, but the new work at least opens up the possibility of doing what the cell's mechanic should have been doing all the time.

–Jean Marx

PHYSICS

Grown-Up Physicists Play Serious Games in the Sandbox

An old adage holds that all problems in physics are either trivial or insoluble. Those categories can actually be near neighbors. Take the bouncing, flowing, mixing, oscillating, avalanching substances called granular materials—of which sand is the most familiar. "Sand," says University of Chicago physicist Heinrich Jaeger, "we associate with something terribly simple. Something whose behavior we can obviously predict. But if we look more closely," says Jaeger, who recently helped organize a conference on granular materials,* "we are faced with an unbelievable complexity of outcomes."



SOURCE: UMBANHOWAR *ET AL.*/UNIV. OF TEXAS, AUSTIN

All shook up. A layer of particles shifts from one surface pattern to another as the vibration amplitude changes.

That mix of simplicity and complexity won't come as a surprise to industrial engineers, who have struggled for decades with fertilizers that plug hoppers and pharmaceuticals that won't stay mixed as they form pills, to cite just two examples. Granular materials are polymorphous: They can resemble solids, liquids, or gases, depending on the situation, and engineers have learned the hard way that a weird amalgam of known and unknown physical laws governs their behavior. But physicists have been latecomers to the sandbox. "A few years ago you used to be a laughingstock if you were working on sand," says Anita Mehta of the University of Birmingham in the United Kingdom.

Now, she says, "it has become rather trendy." The complex behavior of sand and other granules has enchanted physicists by giving them a model of other difficult areas of physics. "The sandpile is a metaphor for a lot of systems in physics that we have been struggling with for a long time," says Jaeger. As speakers at the conference showed, granular materials can mimic the roiling convection cells that form in fluids, undergo "phase transitions" analogous to those of solids changing from one crystal structure to another, and form bizarre, fingerlike clumps through processes that may mimic structure formation in the early universe. And these phenomena are yielding new insights for the industrial engineers who have traditionally struggled with granular media on their own.

Like an avalanche triggered by a single pebble tumbling down a slope, much of the recent surge of interest in granular materials began with the 1987 publication of a paper by Per Bak, Chao Tang, and Kurt Wiesenfeld, then at Brookhaven National Laboratory. The paper laid out a notion these researchers dubbed "self-organized criticality." They proposed that under the pressure of outside stimuli, a system of many complicated, interacting parts—anything from a sandpile to the stock market—will organize into a precarious state, far from stability, that is prone to unpredictable fluctuations. In the case of a sandpile, the theory predicts that as sand is added to the pile, it will slough off not in regular, catastrophic avalanches but in an unpredictable series of small and large ones.

Whether nature really behaves this way is still a matter of debate. But by getting physicists to take a serious look at sand, the proposal opened up the field. At the University of Chicago, for example, a group that includes Jaeger, Sidney Nagel, and Chu-Heng Liu (now at the Exxon Research and Engineering Company in Annandale, New Jersey) started by looking for self-organized criticality in sandpiles. They failed to see it, says Jaeger, "but got intrigued by all of the other things that happen in sandpiles" and other granular aggregations. Among them was the "Brazil nut phenomenon"—the puzzling tendency of the largest granules in a container to rise to the top when it is shaken.

Two years ago Jaeger and Nagel, along with Chicago colleagues James Knight and Edward Ehrichs, studied the phenomenon by filling a cylindrical container with glass beads, some of them dyed black to serve as

* Dynamics of Granular Materials: Understanding and Control, May 11–13 at the University of Chicago. Organizers: Heinrich Jaeger, Elizabeth Grossman, Sidney Nagel, and Yunson Du.

OTTINO *ET AL.*/NORTHWESTERN UNIV.

The right spin. Experiments in odd-shaped containers show that granules mix in a series of avalanches.

tracers. When they vibrated the container, they saw the beads circulate in a convection pattern similar to those seen in fluids heated from below: The beads flowed down near the walls and up in the center of the container. "Differential friction" at the wall may be responsible, the researchers think: Whenever the vibrating wall lifts a collection of particles, they "fluff up," and as they drop, the wall's grip on them—its upward frictional push—is weaker than the downward tug they experienced on the way up. The result is a net downward shove. To everyone's surprise, the researchers found that the flow probably accounts for the Brazil nut phenomenon: The largest granules don't fit into the thin convective zones at the walls that would otherwise pull them down; as a result, they become trapped at the top.

The dead zone. More recently, with colleagues in the University of Chicago's department of radiology, the group explored the details of the flow by applying magnetic resonance imaging (MRI) to a container of poppy seeds, whose oil makes them visible to MRI (*Science*, 17 March, p. 1632). MRI, first applied to granular media by researchers at The Lovelace Institute in Albuquerque, New Mexico, allowed the Chicago group to clock the convection currents—and yielded an insight that may have industrial benefits. At the conference, Knight reported that MRI scans revealed an exponential slowing of the convection currents with depth—the first quantitative study of what engineers call the "dead zone" near the bottom of a container, where particles resist diffusing when they are shaken up. Such data could help engineers design containers with the right wall friction and shape to expand the dead zone, reducing unwanted sorting of pharmaceutical and ceramic powders, cement, and even flour.

While the Chicago group occupied itself with the innards of granular systems, other researchers probed the mysteries of their surfaces. At the University of Texas, Austin, Paul Umbanhowar, Harry Swinney, and Francisco Melo of the University of Santiago in Chile vibrated a thin layer of tiny bronze spheres in circular dishes. When the team illuminated the dishes from the side with strobe lights synchronized with the vibrations, they saw stripes, squares, hexagons, and other patterns that changed from one to another at sharply defined shaking frequencies and strengths (see illustration on p. 1277). The transformations to complex structures are reminiscent of the "symmetry breaking" seen when, say, an amorphous liquid freezes to a crystalline solid, says Melo—but are "much richer" than standard phase transitions, which are limited by such constraints as conservation of energy. He and his colleagues think they have their hands on a system that can yield fresh insight into the equations that govern symmetry breaking, but they are still struggling to understand it.

In Melo's work, theory is lagging somewhat behind practice. But in some areas of granule work, theory is opening new paths. One group found that a simple theory could help them understand a very practical problem: mixing in spinning containers. In the mixing of granules, says Julio M. Ottino of Northwestern University's chemical engineering department, one member of the group, "lots of things do not have an analogy with how fluids mix." For example, in contrast to most fluids, which mix smoothly throughout a spinning container, a granular material often mixes mostly around the container's edges, where the grains can tumble freely, leaving an immiscible "core" at the center.

The Northwestern group, which also includes Troy Shinbrot, Guy Metcalfe, and Joseph McCarthy, approached the problem by assuming that mixing in a rotating drum takes place in a series of avalanches. When the drum is stationary, the grains tend to form a horizontal surface; when the drum begins turning, the surface gradually steepens until it slumps in an avalanche. The group assumed that each avalanche cuts a pielike wedge of material from the top of this slope and deposits it downslope—thoroughly mixing the grains in the wedge along the way.

These simple assumptions, says Shinbrot, turn out to "work surprisingly well," as the Northwestern group found when they packed different-colored batches of grains into a drum, spun it, and watched the mixing process. The simple avalanche picture successfully predicts the efficiency of mixing not only in cylindrical drums but also in irregularly shaped containers (see illustration) whose behavior would be far too complex to calculate in more elaborate models of mixing.

Order from randomness? Those insights could help engineers in the pharmaceutical industry and elsewhere design better mixers. But some of the most striking theoretical results presented at the conference have implications extending all the way to an underpinning of physics—its picture of how collections of randomly colliding particles behave. If no long-range force is acting on the particles, classical statistical mechanics predicts that they will remain randomly distributed no matter how long they knock about. But when Sean McNamara and William Young of the Scripps Institution of Oceanography at the University of California, San Diego, used a computer to simulate particles colliding in two dimensions, they were startled to see structures spontaneously take shape.

Work in one dimension had already shown that when collections of inelastic particles—those that lose energy in collisions—start with random initial positions and velocities, groups of three or more particles tend to clump together. These "collapses" can occur when two particles are moving toward each other and a third is caught between them, where it acts as a cushion, dissipating the energy of the converging particles by rattling back and forth between them. That way, the particles don't rebound but remain "stuck" together.

But Young and most other physicists had thought that collapse was a "pathology" of one dimension. He recalls that he bet McNamara "a million dollars" they would see no such phenomenon in their 2D simulations—and lost, when they identified fingerlike structures within which particles were colliding rapidly. The structures moved as a unit within larger, amorphous clumps. (McNamara graciously accepted a used textbook in lieu of cash.)

Exactly why the structures take shape remains mysterious. But the fingers "are extremely reminiscent of the structure astronomers find in sky surveys," says the University of Chicago's Jaeger. He raises the possibility that the giant walls and filaments of galaxies seen in the distant universe might not have formed solely by gravitational interactions, as theorists often assume. Instead, they might have emerged from random processes, as dust, star clusters, and galaxies collided early in cosmic history.

Linking a sandpile, even a theoretical one, with the early universe requires climbing out on "a very thin, long limb," says Jaeger. But if sandpiles can help explain the origin of cosmological structure, it's a limb that could quickly get crowded.

–James Glanz