Insight From the Urchin

What a spiky sea creature has shown us about genes, reproduction, and cancer.

Sex, cancer, chromosomes, genes, cell division and development—the spiky, ocean-dwelling sea urchin has been pivotal in helping us understand all these biological basics. The story of the urchin's role in research is one of monumental discoveries, visions of unseen phenomena, and scientists devoting themselves to answering the fundamental questions of life. It's also a lovely illustration of how science progresses over time to expand our understanding of nature, with each successive discovery contributing to the next. All this, from a humble little sea critter that resembles a scrub brush.

A few urchin facts:

• With a potential lifespan of over 200 years, the red sea urchin is the longest-lived animal on earth.

• Sea urchin roe, alled uni, is considered a delicacy in Japan, as are its reproductive organs.

• Urchins' mouths are called Aristotle's lantern, after his description of their star-shaped arrangement of five plate-like teeth.

• Sea urchins may sometimes appear to be inanimate (or dead), but they can actually move repidly across surfaces using their spines.

• Seashell collectors prize the bony sphere, or test, that forms the sea urchin's shape.The test is comprised of five parts, which form a star at their junction on the underside, showing the urchin's relation to the sea star.

Though urchins inhabit ocean waters all around the globe, and their eggs are eaten in many parts of the world, their use in biological experiments began by chance.

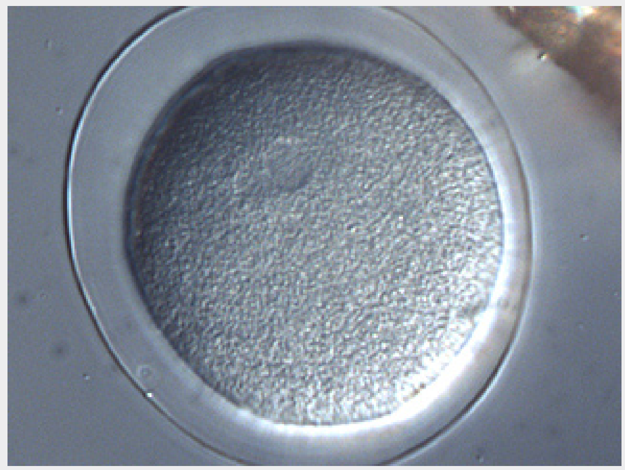
The era of modern biology started in the 1870s, shortly after scientists realized that all organisms are composed of cells. Improvements in microscopes were also letting researchers see new things. At the time, German scientists led the way in biological research. While working at a marine station in Naples, Italy, some German scientists looked to locals for samples to study. They noticed fishermen dining on urchin eggs, and brought the eggs back to their labs.

Under the microscope, scientists found relatively large cells so transparent they could easily see what was happening inside them. That quality, along with the incredible abundance of eggs that can be collected from just one urchin, made this sea creature a lab favorite. And as researchers watched the see-through eggs, they witnessed profound events still of interest to scientists today.

The Aha Moment

When the urchin began its life in science, just 130 years ago, scientists couldn't yet answer the question "where do babies come from?" They knew male sperm needed to enter a female's body—but some thought a tiny human, or homunculus, lived in the sperm, waiting to grow once it was inside a female.

Then, in 1875, German biologist Oskar Hertwig watched as an urchin sperm entered an urchin egg. The sperm nucleus then fused with the egg nucleus, triggering a chain of events that caused the cell to divide. This was it—fertilization. The beginning of a new organism. The aha moment. The long sought-after explanation of sexual reproduction.



The joining of egg and sperm nuclei. Hertwig's view of this in 1875 led him to understand what was then the mystery of sexual reproduction.

The urchin's unique contribution to this revelation was the transparency of its eggs. Hertwig could see the nucleus of the sperm, a darkish circle against the lighter background of the egg cell, grow when it entered the egg and move toward the egg's nucleus. He watched as the two small circles met and slowly became one. Today, researchers still observe this activity, searching for clues to treat certain forms of infertility. In fact, many of the methods used in modern human fertility research can be traced back to early work done using urchins.

Uncovering the Role of Chromosomes

The observations of Hertwig and others made it clear that reproduction involved the donation of a nucleus from both a male and a female. But what did that mean in terms of inheritance? Scientists of the time knew that offspring inherited traits via some substance that carried parental information, and they believed this substance was found in the nucleus. Seeing two nuclei fuse implied that each made a contribution to inheritance. But what specific role did each play?

In 1901, German biologist Theodor Boveri began to answer this question. By that time, Boveri had discovered that mature egg cells have half as many chromosomes—complex coiled structures containing DNA, found inside the nucleus—as did other cells, and that egg and sperm donate equal numbers of chromosomes. Around this same time, Boveri also became familiar with the work of Gregor Mendel, a Belgian monk who, fifty years earlier, had noted patterns of heredity that emerge over generations, but whose findings had gone largely unnoticed.

The fact that urchin eggs divide synchronously is one of the things that makes them so valuable for research.

Boveri performed several ingenious experiments using sea urchin embryos to demonstrate two new points: a fertilized egg must have a specific number of chromosomes to develop normally, and each individual chromosome contributes different qualities.

These findings, combined with what Boveri knew from Mendel about patterns of inheritance, led him to a grand conclusion: chromosomes are the carriers of inheritance. This is something we take for granted today, but just over a century ago, it was a major discovery.

One Becomes Two, Two Becomes Four—and so on

Due in part to Boveri's work, scientists had a better understanding of the mechanisms behind fertilization and inheritance. But as is common in science, these timeless discoveries prompted still more questions. Once an egg cell is fertilized, what makes it start dividing? How does each new cell get the right chromosomes? Again, research on the urchin would lead to more answers.

In order to tackle such questions, researchers must capture chemical "snapshots" at different points during the process of cell division. By comparing these chemical profiles, they can "see" the biochemical changes that occur as a cell divides. But to get large enough amounts of these chemicals to study in the first place, scientists need a lot of embryos going about their business, all doing the same thing at the same time. Urchin embryos, it turns out, divide synchronously in two ways: cells in the same egg tend to divide at the same time, and a group of eggs tend to undergo cell division at the same rate. These synchronies make urchins perfect subjects for studying questions of cell division.

Shortly after World War II, American biologist Daniel Mazia and Japanese biologist Katsuma Dan, took advantage of the urchin's tendency to divide in synchrony to collect a sufficient quantity of cells and isolate the structures that pull sets of chromosomes apart. Identifying these bits and pieces, now known as the mitotic apparatus, was a major accomplishment. Today, researchers still strive to understand the subtleties of how the microtubules and proteins of the apparatus work to assure that new cells have the right complement of chromosomes.

What makes urchins great models for research?

- A developing urchin embryo is somewhat transparent, letting researchers see what's happening.
- Cells in developing embryos divide at the same time, and a group of fertilized eggs also tend to divide synchronously.
- It's easy to obtain and fertilize thousands of urchin eggs at once.
- Having thousands of eggs at once makes it possible to isolate substances that occur only in very small quantities in each urchin.

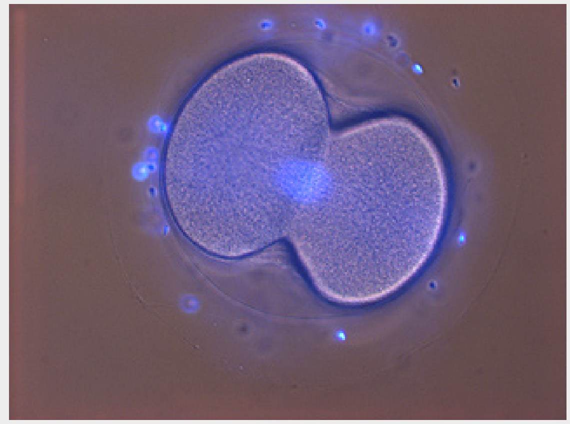
Knowing the Why Behind the How

Once again, solving one of the major mysteries in cell biology raised new questions. What makes cells divide in the first place? How do they know when to "rev up" for mitosis? Solving these mysteries would provide insight into a host of diseases—most notably cancer. And once again, the urchin provided answers.

As late as 1980, the secrets of what controlled cell division remained elusive. Preliminary experiments had pointed toward possible explanations, but it wasn't until 1982 that the real driver of cell division was spotted. That summer, researcher Tim Hunt was experimenting on fertilized urchin eggs, following the rate at which proteins were made in the cells. He noticed that the level of one particular protein built up until a cell began to divide. Then, during division, the protein disappeared, only to build up again until the next round. He dubbed this new protein cyclin and published a paper describing it as the controller of cell division.

At first, Hunt's ideas were met with skepticism, until research by other scientists showed not only that cyclin indeed played a key role in orchestrating cell division, but that similar proteins—cyclins—performed that same function in organisms from yeast cells to human beings. In 2001, Hunt, along with two other researchers who were also studying the cell cycle, received the Nobel Prize, giving the sea urchin some recognition for its hard work over the previous century.

Hold it Right There



One of the hallmarks of cancer is uncontrolled cell division. Researchers can learn mor about how to treat cancer by studying urchin eggs like this one. Its DNA has been damaged, and so the cell fails to divide because it can't replicate its genetic information properly.

It's no surprise that Hunt's work moved from cell cycle control to cancer research. Cancer is caused by a form of uncontrolled cell division, so understanding and regulating the cell cycle holds keys to cancer treatments. The urchin's contribution to our understanding of cancer began with Boveri, who noted abnormal division in cells with irregular chromosomes. Today, researchers employ urchins in the development of chemotherapy drugs that prevent mitosis by interfering with the formation of the mitotic apparatus of the replication of DNA. Again, the urchin is specially qualified: its eggs cells can be fertilized in a sea-water-like bath containing different drugs, and researchers can watch as the cells divide—or try to, but fail.

However, these attack every dividing cell, not just tumor cells, which is why chemotherapy patients lose their hair and go through other physical challenges. Ideally, a drug would interfere with cell division only if there was a problem with DNA replication or regulation of the cycle. Fine-tuning new drugs to target only cancer cells is a key challenge in current cancer research.

Though the urchin has been contributing to biology for over a century, it remains on the cutting edge of research. In recent years, scientists have begun to use urchins to study gene regulatory networks, groups of genes that, working together, control the expression of traits. In fact, the urchin genome (which is relatively close to ours—another advantage of urchin-based research) has recently been sequenced. Urchins may one day help us understand the special properties of stem cells, the secrets to longevity, and how to prevent of skin cancer. So the next time you spot an urchin in an aquarium, or find its eggs glistening atop your sushi, stop a moment to thank this prickly invertebrate for all it's taught us.