

## Why the petri became science's favorite dish

by Scott LaFee

Throughout the history of science, lasting fame and glory have generally been reserved for the men and women with the big ideas: Galileo, Sir Issac Newton, Charles Darwin, Marie Curie, Albert Einstein, Francis Crick and James Watson, to name a few.

Robert Koch arguably belongs on this list. A 19th century German physician, Koch discovered that microscopic organisms caused diseases like tuberculosis, cholera, diphtheria and anthrax.

CULTURAL REVOLUTION - Life becomes art in these bacterial colonies, cultured in petri dishes as part of a collaborative project between Eshel Ben-Jacob, a professor of physics at Tel Aviv University in Israel, and Herbert Levine, co-director of University of California San Diego's Center for Theoretical Biological Physics. CNS Photo courtesy of Eshel Ben-Jacob, Tel Aviv University. But while Koch is highly esteemed among modern-day scientists - the putative father of germ theory, co-founder of modern bacteriology with Louis Pasteur - his name isn't broadly recalled. That distinction belongs to a one-time lab assistant, a fellow named Julius Petri, who invented a dish.

Before 1877, scientists exploring the nature and mechanics of microscopic life had a real problem. Bacteria used for study were typically cultured or grown in bottles or bowls of broth. Koch greatly improved the situation by developing ways to grow microbes in gel, which allowed researchers to separate and investigate individual types of bacteria.

But practical problems remained. It was hard to manipulate bacterial colonies through the small openings of bottles. Worse, there was the issue of contamination. Nothing stayed sterile, pure.

Enter Petri, whose lasting and eponymous contribution to science was the invention of a shallow, cylindrical glass dish with a transparent lid.

"The discovery was the lid," said Moselio Schaecter, a microbiologist and adjunct professor at the University of California, San Diego, and San Diego State University. "The way (many earlier scientists) had worked was with plates stacked with glass rods separating them, the whole thing put under a glass bell. It was about as awkward as could be. You couldn't keep anything from becoming contaminated."

Petri went on to have a generally forgettable career, though he did rise to head of the Museum of Hygiene in Berlin. His dish, in contrast, not only endured, it changed science.

"I don't know where we would be without petri dishes," said Schaecter.

## RESEARCH IN THE ROUND

Petri dishes offer scientists a grand view of an unseen world. Filled with a nutrient gel like agar (a seaweed extract that provides the substrate upon which microorganisms can grow and feed), petri dishes create microbial worlds that are easily viewed, studied and manipulated.

"For a microbiologist, the biggest thing is to have a large surface for your subject and the ability to look down at them with a microscope," said Schaecter.

Inside these tiny created worlds, researchers can rear a billion or more bacteria in search of a single mutant. They can create colonies with different properties, study how they reproduce and grow, how they react to various stimuli. The microbes can be sorted by their abilities, dangers and possibilities.

Koch used Petri's dish to great effect. So, too, have countless other scientists and would-be scientists in labs and classrooms around the world since 1877.

As the dish has changed science, so has science changed the dish. While millions of petri dishes, now made of plastic, are still used each year to conduct the basic culturing of microbial life, researchers have dramatically expanded what they can learn and achieve with the dishes.

At UC San Diego, for example, biochemist Michael Sailor and colleagues last year debuted the "smart petri dish," which is capable of rapidly screening new drugs for toxicity or identifying cells in the early stages of cancer.

A major concern in the development of any new drug is toxicity. Will it do more harm than good? Pharmaceutical companies typically screen the health effects of potential drugs on laboratory animals, usually rats.

"But it's very expensive to screen every potential (drug) candidate on living animals," said Sailor. "So if you can use just a few cells from the liver (which is particularly sensitive to toxins) rather than the entire animal, you can perform many more, thorough tests."

Working with Michael Schwartz, a postdoctoral scholar, Sailor's lab constructed its smart petri dish by first fabricating a crystalline silicon structure pocked by micron-sized wells - each no wider than a human hair - at the bottom of the dish.

Inside the wells, researchers place individual rat liver cells. Such cells are finicky and delicate, but snuggled inside the wells, they grow, connect and behave as if they are part of a normal, functioning liver, Sailor said.

Once established, the cells can be exposed to whatever drug or agent is being tested. Researchers then beam light at the cells, measuring how that light is deflected and reflected.

"The (drug) interaction with the cells affects the way the nanostructure reflects light," said Sailor. "As these cells shrivel up in response to a toxin, they scatter light better, much like fog on a car windshield, allowing us to quickly detect which drugs may have adverse side effects when taken in combination with another."

Besides being more cost-effective than testing on live lab animals, the smart petri dish promises to provide scientists with more directly applicable information and evidence. Drugs don't necessarily behave the same in all species. A drug that is found to be safe in rats may later prove problematic in people. UC San Diego scientists say human liver cells can also be grown in their smart dish, providing the opportunity of direct analysis without actually placing any person at risk.

## SIDE DISHES

You don't have to look far for other examples of cutting-edge science under glass. Or in it. Two cases in point:

- The idea of in vitro meat production - that is, growing beef, chicken and fish in a dish - has been around since at least the 1930s, but only now is it inching closer to reality.

In 2002, NASA scientists took a notable step, creating a small amount of fish in a dish. One researcher later engineered some frog meat, which he reported "tasted like chicken."

More recently and seriously, University of Maryland food scientists published papers exploring two methods of growing meat cells: one on small glass beads to create processed meat products like sausage; the other on

thin membranes to create steaklike products.

Cultured meat offers some significant benefits, advocates say. It could be engineered to be lower in fat and cholesterol. And no actual animals would be harmed in the process. But the debut of cultured meat remains uncertain at best, both in terms of when the products might actually appear on shelves and, of course, how the public would respond.

NASA, incidentally, also has an interest in in vitro meat of a sort. The space agency has commissioned two British researchers to explore the possibilities of growing replacement human tissue for astronauts on future Mars missions.

Colin McGuckin and P. Nicolas Forraz of Kingston University in London were awarded a \$1 million grant to determine the potential of growing new body tissues to replace tissues damaged or turned cancerous by space radiation.

"We plan to use adult stem cells derived from astronauts' blood and to put that in a zero-G-microgravity-simulating bioreactor," McGuckin told Wired News. "Using the right cocktail of stimuli, we can instruct the cells to grow into not only blood, but also the liver or part of the muscles, for example, to regenerate damaged tissue. The long-term goal would be (to be) able to take those bioreactors on a space flight to regenerate tissue for the astronauts."

An ambitious goal, to be sure, but there's time. The earliest potential date for a manned mission to Mars, according to NASA and Bush administration officials, is sometime in 2030.

- Borrowing a technology used to make microchips, researchers have crafted patterned glass surfaces in dishes that encourage live nerve cells to grow, connect and wire themselves to attached electrode arrays.

At the Georgia Institute of Technology, for example, biomedical engineer Steve Potter and colleagues have grown "minibrains" of rat neurons capable of communicating and controlling external computers and robots, in some cases thousands of miles away.

In 2003, Potter linked a dish of wired rat neurons to a computer in Australia. The neurons were then exposed to a photo of a person's face, which was reduced to a pattern of electrical signals and fed to the neurons through the electrodes. The neurons reacted with their own electrical activity, which was communicated to the Australian computer and a robotic arm, which translated the signals into line art.

The two images looked nothing alike - the neurons' work was crude at best - but Potter's larger goal is to expand and deepen the links between brain cells and computer chips, to push forward the beginnings of a "smart machine."

Last year, Potter and colleagues connected cultured rat neurons to computer-simulated animals or "animats." The brain cells received data about the virtual animal's environment, processed that information and ordered corresponding simulated behaviors.

For example, cells have ordered animats to move toward a light or to chase a target. The goal, said Potter, is to better understand how brain cells and networks adapt and respond to stimulation - in other words, how they "learn."

## BEYOND THE DISH

Will science's love affair with the petri dish eventually grow cold? Some researchers suggest the dish is already inching toward obsolescence.

Shugang Zhang at the Massachusetts Institute of Technology's Center for Biomedical Engineering argues that the two-dimensional dishes limit what scientists can learn about - and do with - three-dimensional life.

"The time has come to move on," he said.

Zhang and colleagues have done so, culturing stem cells on tiny three-dimensional scaffolds composed of protein nanofibers, each 5,000 times smaller than a human hair and containing pores up to 20,000 times smaller than the eye of a needle.

Meanwhile, Sailor at UC San Diego is working on a miniaturized version of the smart dish.

"In this case, we take the nanostructured silicon off of the support and break it up into 25-micron particles," he said. "These particles retain many of the sensing properties of the smart petri dish, but they allow us to work in fluid solution rather than on a flat surface."

"We are trying to attach these particles to individual cells. For instance, we are trying to add the particles to a blood serum sample. The goal is for these particles to attach themselves to and fish out cancer cells from a patient sample, to aid in the diagnosis and treatment of various cancers."

Some observers of the biological sciences say it may be possible, perhaps even probable, that the petri dish will ultimately disappear altogether, that computer models will replace live cultures.

Computer modeling has come a long way, agreed Potter at Georgia Tech. "We use it ourselves. But one of the reasons we still use petri dishes is to answer the questions modelers don't know.

"Biology is far too complicated for us to figure out anytime soon. Even the complexity of a single cell is amazing. You look inside and you see superhighways with identifiable things whizzing along from place to place. And that's just one cell. Put 100 billion together in a brain and you get a whole new set of properties and questions."

Potter thinks there's still a place in science's cupboard for the petri dish.

"We'll still be using them to look at cells for many more years, if not centuries."

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