# "Modeled Microgravity" Increases Virulence of Common Bacterial Pathogen

*NASA-supported researchers, using technology developed by NASA engineers, have demonstrated that modeled, or simulated, microgravity enhances the disease-causing potential of a strain of* Salmonella *bacteria that is responsible for millions of cases of gastrointestinal illness every year. The researchers have used the same technology to develop improved models of human intestinal tissue for studying how* Salmonella *causes infectious disease. This work is laying the scientific foundations for the development of new drugs and vaccines to treat and prevent* Salmonella *infections.*

Most people know that a weakened immune system increases an individual's vulnerability to infectious disease. What may be less well known is that susceptibility to infection is also influenced by the disease-causing potential of the infectious agent.

"The ability of a microbe to cause disease relies on how virulent the microbe is as well as on the immune status of the host," says NASA-supported investigator Cheryl A. Nickerson, Ph.D., assistant professor of microbiology and immunology at Tulane University Medical Center in New Orleans. A variety of environmental signals, including starvation, pH (acidity), and growth phase, affect the virulence of an organism.

### Effect of Gravity on Microbial Virulence Not Previously Studied

Numerous studies of astronauts have shown that space flight suppresses some aspects of the immune system. Although astronauts are generally very healthy, a weakened immune system—combined with the physical and psychological stress of a space mission—places them at increased risk for infectious disease during flight. "As the duration of human space missions increases, the risk of microbial infection increases," says Nickerson.

The effects of space flight on the immune system are well documented, but no published studies had examined the effect of space flight—or an environment that simulates the lack of gravity during space flight—on the disease-causing potential of microbes. Nickerson and her colleagues set out to address this gap in knowledge by studying the effect of modeled, or simulated, microgravity on the virulence of the bacterium *Salmonella typhimurium*.

This microbe is a leading cause of an estimated two to four million cases of *Salmonella*-induced gastrointestinal illness in the United States annually. Although *S. typhimurium* infection usually resolves without medical intervention in healthy people, it is potentially fatal if untreated in people with weakened immune systems.

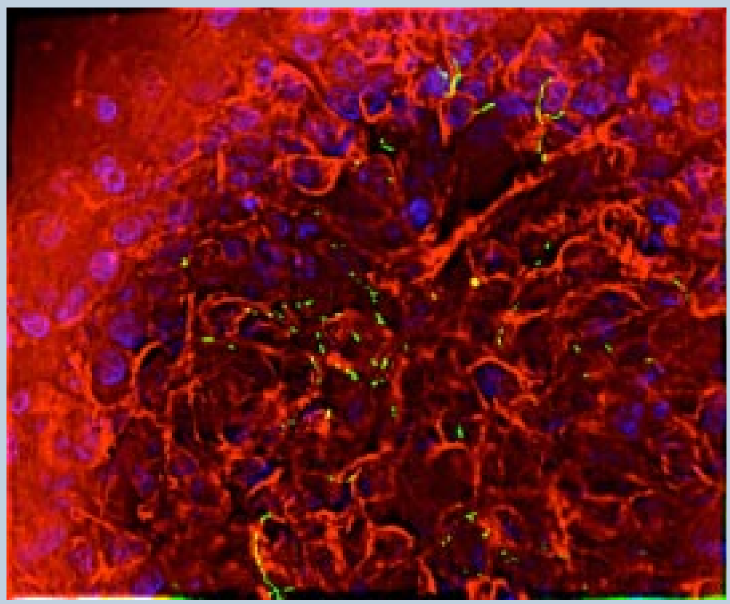

***Image of 3-D human intestinal tissue (stained in red) infected with* Salmonella typhimurium *(stained in green). Staining was done 27 hours after infection. Image obtained through epifluorescent microscopy.***

"Something like food poisoning could disrupt a space mission, at a cost of millions of dollars, or—at worst—threaten crew survival," says Nickerson. Antibiotics—the standard treatment for systemic *Salmonella* infection—might be less effective in space; studies by other researchers suggest that some microbes acquire higher levels of antibiotic resistance in flight.

## Bioreactor—a Device that Simulates Microgravity

Nickerson and her associates performed their experiments using a bioreactor known as a Rotating Wall Vessel (RWV), which simulates aspects of space flight (such as weightlessness) in the laboratory. It simulates microgravity by balancing the force of gravity with equal and opposite forces such as shear, or turbulence. Specifically, as the direction of gravity is randomized across the cell, the shear or turbulence is displaced evenly and thus minimized. The device was developed at the NASA Johnson Space Center in Houston.

***Rotating wall vessel (RWV) bioreactor (Synthecon, Inc., Houston, Texas), which models microgravity.***

Cells of *S. typhimurium* were placed in a culture medium within the bioreactor chamber. When the bioreactor was switched on, causing it to rotate, it maintained the cells in what Nickerson describes as "a suspended state of freefall."

The researchers also cultured *S. typhimurium* under normal gravity conditions. The next step was to infect mice with either the microbes cultured under normal gravity or under modeled microgravity (MMG) in the bioreactor.

## Modeled Microgravity Enhances Virulence

Mice infected with microbes cultured in MMG died an average of three days sooner than the control mice. Additionally, the investigators found larger numbers of the microbes cultured in MMG in the livers and spleens of the experimental mice. These findings indicate that simulated microgravity enhances the virulence of *S. typhimurium*. Thus, gravity or the lack of it may be considered another environmental signal that affects microbial virulence.

Other significant differences in physiology and patterns of gene expression were also observed in the microbes cultured in MMG compared with those cultured in normal gravity. These research results will ultimately provide insights into the molecular basis of *Salmonella* virulence.

## A More Physiologically Relevant Model

In a separate set of experiments, Nickerson and her colleagues used the RWV bioreactor to develop a new cell line that appears to model the physiology of human intestinal tissue more accurately than conventional tissue culture models that have long been used to study how *Salmonella* bacteria behave when they infect the human body.

The researchers cultured three-dimensional human intestinal epithelial cells in the bioreactor, confirmed their physiological relevance as compared to one-dimensional, or monolayer, cultures of the same cells, and then infected the cells with *S. typhimurium*. They found significant differences in the pattern of infection in the three-dimensional cells compared with that seen in the monolayer cultures conventionally used to model human *Salmonella* infection. Many of the differences seen in the three-dimensional cells appeared to more accurately model a *Salmonella* infection in the human body.

"The microbes invaded and killed the three-dimensional cells to a much lesser extent than they were able to invade and kill cells grown as monolayers," explains Nickerson. In response to the microbial invasion, the three-dimensional cells produced higher levels of substances called anti-inflammatory cytokines, which may help limit damage to the epithelial tissue following *Salmonella* infection. These observations are consistent with the self-limiting nature of *Salmonella* infection in most people, according to Nickerson.

"We have built a more physiologically relevant model of human intestinal tissue that will provide us with better insights into how these microbes cause infectious disease as well as how the host responds to the microbe," Nickerson adds. "This information is essential for the development of new drugs and vaccines that will reduce the incidence of *Salmonella* infections not only in space flight but also on Earth."

References


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