Chance reveals deadly rotavirus secret

"Weird," Judith M. Ball mused, peering into the messy cage of mouse number three. The young mouse had diarrhea.

This would have made sense had Ball inoculated the animal with the diarrhea-causing rotavirus. She had not. Instead, she had injected it only with a snippet of the rotavirus protein NSP4. Thought to be harmless, NSP4 turned out to be anything but.

In this way, Ball and her coworkers at Baylor College of Medicine in Houston stumbled upon a specific cause of the rotaviral diarrhea that kills nearly a million infants and children worldwide each year. The agent is a toxin, the first digestive tract poison known to be produced by a virus, the researchers report in the April 5 SCIENCE.

"This is a great example of what drives the passion of scientists," says coworker Mary K. Estes. "You're working on one thing—and you discover something else that's potentially much more important."

Rotavirus, a microscopic, spike-studded globe, is as menacing as it looks. Each year, it strikes 130 million people worldwide, causing diarrhea so severe that 870,000 children die from the disease, mainly in developing countries. Few children in the United States die, but rotavirus sends more than 50,000 of them to the hospital annually, at a cost of $1 billion.

Until now, scientists wondered what gives rotavirus its often lethal punch.

Once inside a cell, the virus pushes into a network of cavities called the endoplasmic reticulum. The virus sheathes itself in the surrounding membrane like a finger poking into a balloon. Just one piece protrudes—NSP4, a 200-peptide protein. When the virus reproduces, NSP4 breaks up the membrane sheath and frees the new viruses. It may also play a role in viral assembly, say Roger I. Glass of the Centers for Disease Control and Prevention in Atlanta and his colleagues in an accompanying commentary.

Estes and her coworkers focused on NSP4, in part because of its unique role in viral reproduction. They injected mice with a synthetic, 22-peptide fragment of the protein in order to generate NSP4-attacking antibodies, which they intended to use to locate the protein in cells. Instead, the injections gave the mice diarrhea. The group quickly realized, Estes says, that the plight of these mice "might be telling us something."

Since then, the researchers have shown that NSP4 afflicts mice in much the same way that rotavirus afflicts mice—and humans. For instance, the young are far more susceptible to diarrhea.

In the experiments, the severity of disease depends on how much NSP4 the team administers. Moreover, only a small region of NSP4 causes illness.

The researchers hypothesize that NSP4 triggers a cascade of biochemical reactions in the intestinal wall that results in chloride secretion into the intestine. This calls forth a gush of water to dilute the chloride. "When you dump water into the gut," says Ball, "that's diarrhea."

The group may also have a lead on prevention or treatment of rotaviral disease. They found they could prevent rotavirus-induced diarrhea simply by giving mice the antibodies to NSP4, Estes says.

"Perhaps NSP4 should be a target for future rotavirus vaccines," Glass and his colleagues suggest.

Several pharmaceutical companies have asked Baylor for permission to develop the NSP4 antibodies for use in vaccines or potential treatments, Estes says, declining to supply any specifics.

A different type of vaccine, formulated by the National Institute of Allergy and Infectious Diseases and soon to be submitted for Food and Drug Administration approval by Wyeth-Ayerst Laboratories of Philadelphia, was tested in 2,000 children. It proved to be 80 percent effective, says NIAID's Albert Z. Kapikian, a developer of the vaccine. — *S. Sternberg*

Finding fault with Midwest seismic maps

In the U.S. heartland, faults seem a thing of the past. Almost all known surface faults in the midcontinent formed hundreds of millions of years ago and have remained quakeless since before the time of the dinosaurs. Now, the discovery of active faults in Missouri may illuminate a seismic threat stretching from Arkansas to Indiana.

The Missouri faults zigzag through the southeastern part of the state at a site called English Hill, say David Hoffman of the Missouri Department of Natural Resources in Rolla and his colleagues. The faults lie north of New Madrid, Mo., which in the winter of 1811–1812 saw the largest series of earthquakes in U.S. history. The scientists reported their findings this week at the annual meeting of the Seismological Society of America in St. Louis.

Although geologists in the 1930s noted the existence of some faults in this area, the age and extent of them remained unclear. Hoffman and his coworkers spent several years looking for the signs of faults—fractured sediment layers—which they identified by drilling in the ground and digging trenches. They found evidence of several quakes within the last 10,000 years. Although they could not determine the timing of these jolts, the scientists estimate that they were fairly large, magnitude 6 or greater.

"The generally accepted standard is that anything active in the last 10,000 years is considered to be an active fault and will be active again," says Hoffman.

The English Hill faults are becoming a tourist attraction for geologists around the central United States, who rarely get a chance to run their hands over active faults. East of the Rocky Mountains, most quake-producing faults are hidden beneath thick sedimentary deposits. "It's quite spectacular," comments Eugene S. Schweig of the U.S. Geological Survey (USGS) in Memphis.

The English Hill faults present potential threats on their own, but an even larger seismic hazard may lie beneath them. At the St. Louis meeting, geophysicists described an enigmatic linear structure running underground for more than 400 kilometers from near Little Rock, Ark., to Vincennes, Ind.

Victoria E. Langenheim and Thomas G. Hildenbrand of the USGS in Menlo Park, Calif., call the feature the Commerce geophysical lineament because it appears most prominently in magnetic and gravity readings taken near Commerce, Mo. They say the lineament could be a major fault zone, an injury left over from when North America almost split apart 600 million years ago.

The discovery of recent quakes at English Hill, above one section of the lineament, has scientists wondering whether other sections may also trigger tremors. "The lineament is an exceptionally long feature," says Hildenbrand, "and anything that is long in earthquake country is scary, because the longer a fault is, the greater magnitude earthquake that could occur on it."

Hildenbrand has a history of finding buried structures. In the 1970s, he identified a geological scar called the Reelfoot rift underlying the Mississippi River valley near New Madrid. Geologists surmise that faults within the rift caused the trio of magnitude 8 shocks that rocked the young United States.

The Commerce lineament runs parallel to the Reelfoot rift, so the newfound structure may have a favorable orientation for producing quakes, suggests Langenheim. At this point, though, scientists know too little about the feature to say whether it represents a threat.

"When geologists and seismologists don't know what a feature is, they usually call it a lineament," says seismologist Arch C. Johnston of the University of Memphis. "Anytime you see that word, it indicates that we've got something there, but we're just not sure what it is."

— *R. Monastersky*