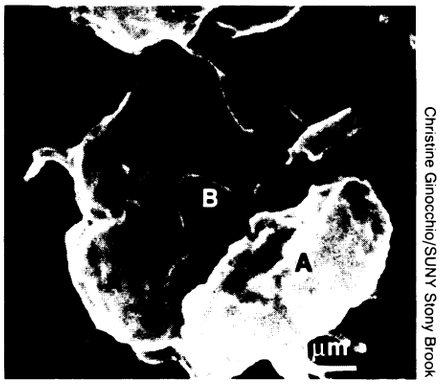
Exposing *Salmonella's* Gutsy Moves

Over thousands of years, bacteria have evolved many ingenious ways to invade the human body. Of all these microorganisms, strains of rod-shaped *Salmonella* have probably intrigued and befuddled scientists the most.

Best known for causing food poisoning and typhoid fever, *Salmonella* bacteria invade the cells that line the intestines. Amazingly, they seem to do this with the unwilling cooperation of the besieged cells. Under an electron microscope, the bacteria can be seen pressing up against an intestinal cell's microvilli—tiny, finger-like structures that stick out of the cell membrane. Soon these microvilli disappear and tiny blisters spring up in their place, engulfing the bacterial invaders. After two hours, the intestinal cell begins to look normal again. But the vanished bacteria are now inside.

Although researchers have watched *Salmonella* subvert intestinal cells for many years, nobody has understood how the microbes do it. But in the June 18 NATURE, scientists from the State University of New York at Stony Brook report finding the first clue: The bacteria use one of the cell's surface receptors to start the process.

In experiments with cultured intestinal cells, microbiologist Jorge E. Galán and his co-workers discovered that *Salmonella typhimurium* binds with receptors for epidermal growth factor (EGF) on the intestinal cell. Once bound, the receptor undergoes a chemical reaction called tyrosine phosphorylation, which sparks a number of changes in the intestinal cell. Eventually, these changes allow the bacteria to enter. When the researchers created a mutant *S. typhimurium* that could latch on to but no longer enter an intestinal cell, they found that the tyrosine phosphorylation reaction didn't occur. But when they added EGF to these mutants, the reaction took place and the mutants invaded the intestinal cell.



Christine Ginocchio/SUNY Stony Brook

In this electron micrograph, a blister (A) on an intestinal cell prepares to engulf a rod-shaped S. typhimurium *bacterium (B).*

How does *S. typhimurium* bind to the receptor for EGF? Galán thinks it may have an EGF look-alike molecule that acts as a passkey. On the other hand, notes microbiologist Daniel A. Portnoy of the University of Pennsylvania in Philadelphia, the EGF receptor is very complex, so the bacteria may use other, more complicated devices to accomplish its goal.

The big question, says Portnoy, is how *Salmonella* manages to coerce intestinal cells into ingesting it. While some body cells, such as white blood cells, regularly engulf and ingest particles from their surroundings, intestinal cells do not, he says.

Galán thinks the answer lies with the cell's internal architecture. Each microvillus contains 20 structures called microfilaments, which function much like the poles supporting a tent. These tiny rods give the microvilli their shape and keep the cell membrane taut.

During tyrosine phosphorylation, however, calcium levels increase inside the intestinal cell. Galán thinks the abundant calcium eventually dissolves the bonds that hold the microfilaments together. As the rods come apart, the cell membrane becomes slack and allows microvilli to swell into the blisters seen during *Salmonella* invasion.

Once scientists discover how these bacteria bind to the EGF receptor, they may be able to develop a vaccine to thwart them, says Portnoy. In the meantime, studies of *Salmonella* should provide insights into cell communication and microbial hijacking. "This area of host-parasite interaction at the molecular level is really very new," Portnoy says.

Moreover, says Galán, "bacteria are becoming a wonderful tool to learn more about fundamental aspects of cell biology." —*M. Stroh*

Breast cancer therapy's leukemia risks

Tamoxifen is not the only postsurgical therapy for breast cancer to pose some risk of fostering new cancers (SN: 4/25/92, p.259). However, few studies have attempted to quantify the long-term risks attributable to such adjuvant therapies. Now a trio of researchers with the National Cancer Institute in Bethesda, Md., have teamed with colleagues from seven other institutions to investigate leukemia risks associated with postsurgical treatments involving radiation, cell-killing drugs or both. Their finding: Such adjuvant therapies can augment a breast cancer patient's otherwise low risk of leukemia substantially—up to 100 times.

The researchers identified 90 apparent leukemias among 82,700 women treated for invasive breast cancer between 1973 and 1985. They compared medical records of each of the 90 with records of two or three other breast cancer patients matched by age, ethnic background, year of diagnosis and years of follow-up.

On average, compared to women receiving no adjuvant therapy, women receiving radiation therapy had a 2.4-fold greater risk of leukemia, and those treated with "alkylating" chemotherapy drugs such as melphalan or cyclophosphamide had a 10-fold greater risk. The risks appear to be dose-dependent, however, report NCI's Rochelle E. Curtis and her coauthors in the June 25 NEW ENGLAND JOURNAL OF MEDICINE.

For instance, high doses of radiation alone (more than 9 grays) were linked with leukemia rates up to 10.4 times those seen in women receiving no adjuvant treatment. Similarly, high doses of melphalan (more than 350 milligrams) appeared to spike the incidence of leukemia to 100 times the rate in women receiving no adjuvant therapy. The new findings also confirm something observed in smaller studies – that melphalan, seldom used anymore in adjuvant therapy, poses roughly 10 times the leukemia risk of cyclophosphamide. Even the low doses of cyclophosphamide typically used today (under 10,000 milligrams) roughly doubled leukemia risks in this study.

Perhaps most important, the researchers conclude, is the apparent synergistic risk of leukemia posed by mixing chemotherapy with high doses of radiotherapy to the bone marrow. This observation raises the possibility that the risks posed by adjuvant therapy may outweigh the advantages in patients over age 60 at low risk of recurrent breast cancer, notes I. Craig Henderson of the University of California, San Francisco, in an accompanying editorial.

In the same issue of the NEW ENGLAND JOURNAL OF MEDICINE, researchers at the University of Texas Health Sciences Center in San Antonio review in detail the factors that signal a low risk of recurrent disease. —*J. Raloff*