E. Coli: Elusive Enemy of the Gut

Although *E. coli* bacteria have been attacking the human intestinal tract for years, information about their mode of attack as well as methods of diagnosis and treatment are still limited and controversial

BY JOAN AREHART-TRIECHEL

The bacterium *Escherichia coli* (alias *E. coli*) is quite a celebrity these days. In addition to posing as a model one-celled organism for countless cell biology experiments, it is also the vehicle for recombinant DNA research (SN: 5/28/77, p. 340). Less attention, however, has been paid to the unsavory characteristics of *E. coli*. Certain strains can cause human diseases, notably mild to life-threatening diarrhea.

Even though malevolent *E. coli* have been attacking the human gut for years, the science of diagnosing them, understanding their modes of attack, treating them and determining their threat in specific areas of the world is still primitive—and controversial. These facts were brought home at the recent annual meeting of the American Society for Microbiology in New Orleans, at a seminar entitled "*Escherichia coli*—Enteric Pathogen," that was headed by Henry D. Isenberg of the Long Island Jewish/Hillside Medical Center in New Hyde Park, N.Y., and by Albert Balows of the Center for Disease Control in Atlanta. Nonetheless, tempered progress is being made in combatting this widespread public-health problem.

As for the diagnosis of harmful gut *E. coli*, detection techniques since the 1930s have consisted primarily of serotyping. That is, a bacterial culture is isolated from the stool of a diarrhea victim and is placed in the presence of an antiserum that is known to react with an antigen (protein or lipopolysaccharide) present on the surface of a particular enteropathogenic *E. coli* (an *E. coli* that is pathological to the gut). If the antiserum reacts with the culture in question, then there is reason to believe that an *E. coli* enteropathogen might have caused the diarrhea.

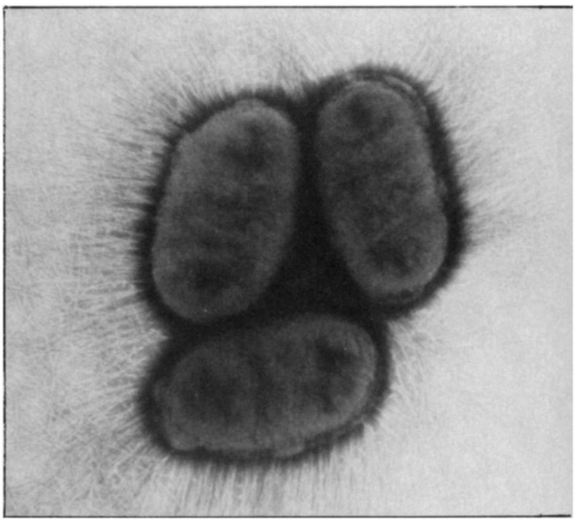
Serotyping has some serious drawbacks, however, as J. J. Farmer III of the CDC points out. For one, there are numerous strains of enteropathogenic *E. coli* containing hundreds of different surface antigens. So while hospital labs tend to run stool cultures from diarrhea patients through a dozen or so different antiserum tests, the tests may not necessarily detect the culprit *E. coli* enteropathogen. Which antisera are most effective in detecting enteropathogens? How many antisera should a lab expose a culture to? These are complex questions, and microbiologists at the CDC are not yet ready to make recommendations on them to hospital labs.

E. coli enteropathogens are confounding for another reason, Farmer continues. In recent years they seem to have mutated so that the culprits of yesterday may not necessarily be identical to the villains of today. The only way to combat *E. coli* trickery of this nature, Farmer says, is to frequently update antisera used in serotyping so that it is more likely to identify current enteropathogens. Bernard Rowe of the Central Public Health Laboratory in London agrees. And even if an *E. coli* enteropathogen is identified by serotyping, it may not necessarily be the cause of a patient's diarrhea, Eugene Gangarosa of the CDC stresses. Enteropathogenic *E. coli* have been found in the guts of healthy persons as well as in the guts of diarrhea victims. Thus the cause of a patient's diarrhea may not be *E. coli* at all, rather another bacterium or even a virus.

Still another limitation with serotyping is that it usually identifies only one kind of harmful *E. coli*—the so-called enteropathogenic *E. coli*. Yet two other kinds of *E. coli* that cause diarrhea have also come to be recognized during the past decade or so. They are known as enterotoxic *E. coli* (*E. coli* toxic to the intestinal tract) and as invasive *E. coli*. Nursery outbreaks of diarrhea, which may range from mild to life-threatening, are usually due to enteropathogenic *E. coli*. Traveler's diarrhea and some outbreaks of childhood diarrhea, which are usually mild, are triggered by enterotoxic *E. coli*. Severe systemic disease that resembles dysentery in its symptomatology results from invasive *E. coli*.

Although toxic *E. coli* are usually not invasive, and invasive *E. coli* are usually not toxic, enteropathogenic *E. coli* may possibly be toxic from time to time. The latter can be recognized by serotyping. For instance, one toxic strain that caused traveler's diarrhea was detected with antisera. However, serotyping will never determine the presence of the usual enterotoxic *E. coli*. And it will certainly not pinpoint the presence of invasive *E. coli*. So what is needed is not only serotyping for enteropathogenic *E. coli* but diagnostic tests for toxic and invasive *E. coli* as well. Fortunately, some progress has been made toward these ends.

A test for invasive *E. coli*, for example, is available to hospital labs and is quite simple. A culture from a patient's stool is placed in the eye of a guinea pig. If it causes disease, invasive *E. coli* are present. According to John C. Feeley of the CDC, diagnostic tests for enterotoxic *E. coli* that are already available to hospital labs or soon to become available include the following: A filtrate of a culture from a patient's stool can be injected into rabbit skin, and if it increases the permeability of small blood vessels in the skin, the culture contains enterotoxic *E. coli*. A stool culture filtrate can be injected into an isolated loop of rabbit bowel, and if excessive fluid accumulates in the bowel, the culture contains enterotoxic *E. coli*. A culture filtrate can be placed in the presence of tissue culture cells from the adrenal gland, and any changes in the cells indicate the presence of enterotoxic *E. coli*. Similarly, a culture filtrate can be put in the presence of a culture of hamster ovary cells, and if the cells change their shape, enterotoxic *E. coli* are present. The CDC has found a good correlation between the latter two tests in detecting traveler's diarrhea among American tourists in Mexico, Feeley says.



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Enterotoxic E. coli *taken from a patient.*

Scientific advances in understanding the action of enterotoxic *E. coli* have likewise been made, according to S. D. Douglas of the University of Minnesota School of Medicine. Like the cholera bacterium, the organism releases toxins that attack epithelial cells in the small intestine. A toxin binds to a target cell, enters it, activates the intracellular messenger cyclic AMP and mobilizes the energy molecule ATP, which in turn leads to a migration of ions and water from the cell. If such migration occurs in hundreds or thousands of intestinal cells, diarrhea results. Still, not much is known about the means by which invasive *E. coli* trigger disease beyond the fact that they do their dirty work in person rather than by sending out toxins to do it for them, and that they attack mucosal cells in the large intestine. And

while enteropathogenic *E. coli* have been recognized for at least half a century, virtually nothing is known about their method of causing disease.

Considering that the diagnosis of diarrhea-causing *E. coli* is often confusing and that the means by which these *E. coli* trigger disease are not altogether understood, it is hardly surprising that treatment for such diarrhea is also limited. True, the primary choice of treatment for all kinds of *E. coli*-caused diarrhea—fluid replacement—has greatly reduced deaths due to it. Yet there is disagreement over the value of giving antibiotics to *E. coli* diarrhea patients. Enterotoxic *E. coli* seem to be somewhat more sensitive to antibiotics than invasive *E. coli.* Also, no drug is currently available to successfully combat the discomfort of traveler's diarrhea, although Bradley Sack of Baltimore City Hospital is looking for such a chemical.

Finally, the epidemiology of *E. coli* diarrhea presents grave difficulties. For instance, it is hard to say how prevalent the disease is either globally or in specific areas of the world, Rowe admits, because most studies have not shown how common *E. coli* diarrhea is compared to that caused by other pathogens. Yet *E. Coli*, especially of the enterotoxic and invasive types, do seem to concentrate in rural areas with poor sanitation, and especially in developing countries, Sack reports. Another question is whether people are more susceptible to *E. coli* diarrhea at certain times of the year. Rowe says that recent studies in Britain suggest that *E. coli* nursery diarrhea seems to be a summer disease, but studies have not been conducted to determine whether enterotoxic and invasive *E. coli* diarrhea are predominant in certain seasons. Still another epidemiological challenge is determining how much of *E. coli* vulnerability is due to differences in host resistance and susceptibility. Little scientific research has been directed toward this question. Should hospital microbiologists routinely screen for nursery outbreaks of *E. coli*, since enteropathogenic *E. coli* are often not a problem, and since it is difficult to estimate what is an excessive number of cases in a particular nursery population? The CDC scientists do not think so. Rowe does; enteropathogenic *E. coli* detected by serotyping still cause disease in Europe.

Regardless of these numerous questions about, and problems with, *E. coli* diarrhea, microbiologists are confident that they will eventually come to grips with them, particularly as more is learned about other diarrhea-causing bacteria and viruses. Quips Rowe: "Now that virologists have gotten cleverer, maybe they can help us more." □