

DuPont H L, Formal S B, Hornick R B, Snyder M J, Libonati J P, Sheahan D G, LaBrec E H & Kalas J P. Pathogenesis of *Escherichia coli* diarrhea. *N. Engl. J. Med.* 285:1-9, 1971.

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*Escherichia coli* strains were examined for virulence properties. They were shown to cause human disease by two mechanisms: elaboration of a cholera-like enterotoxin and shigella-like intestinal epithelial penetration. [The SCJ® indicates that this paper has been cited in over 355 publications since 1971.]

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The experiments described in this paper were carried out just after I had completed a two-year tour with the Center for Disease Control's Epidemic Intelligence Service, during which I worked at the University of Maryland on the development of enteric microbial vaccines. The timing and place for the study were ideal. Although at that time we did not know the causes of most cases of diarrhea occurring anywhere in the world, we did understand the pathogenic mechanisms of disease produced by *Vibrio cholerae* (enterotoxin production) and *Shigella* strains (invasiveness), and tests were available to detect these virulence properties.

At the University of Maryland, Dick Hornick, Ted Woodward, and Merrill Snyder<sup>1</sup> had developed an extremely productive volunteer program wherein enteric infection was studied in man under controlled conditions. I had previously learned the techniques of intestinal biopsy and sampling of various levels of the small bowel through intubation with triple-lumen polyvinyl intestinal tubing. Simultaneously, Sam Formal and his colleagues<sup>2</sup> worked steadily on studies designed to elucidate the pathogenesis of enteric infection in experi-

mental animals. Essential aspects of the study include the initial isolation of *E. coli* from stools of adults with diarrhea acquired in various regions of the world, the characterization of the organisms' virulence properties in the laboratory, and finally establishing the medical significance of these properties in adult volunteers with experimentally induced infection.

Selection of the proper *E. coli* strains for productive study was the first critical step. The strains from which the selection was made had been sent to Formal at Walter Reed from a variety of sources worldwide. The only available marker of the 15 strains we selected for study was serotype, although all but one (a control strain) had been isolated from cases of human or animal diarrhea. In the tissue-culture and animal models, the strains were divided into three groups: avirulent, enterotoxic, or invasive. The volunteer studies confirmed the pathogenic mechanisms found in the animal assays with one important exception. A porcine pathogen produced copious amounts of enterotoxin in the laboratory assays but showed low pathogenicity for man. We demonstrated the inability of the porcine strain to colonize the upper gut, which we now know is explained by the presence of host species-specific colonization fimbriae on enterotoxigenic *E. coli* (ETEC).

The paper has been cited frequently for four main reasons. First, the studies showed the validity of the available animal models in predicting pathogenicity of human *E. coli* and confirmed two important mechanisms whereby *E. coli* produced diarrhea in humans (enterotoxigenicity and invasiveness). Second, the studies demonstrated the host specificity for ETEC. Third, they offered the information that ETEC needed to colonize the upper intestine before diarrhea was produced. And, fourth, they predicted that these diarrhea-producing *E. coli* would be implicated in the etiology of travelers' diarrhea, a finding since then confirmed.<sup>3</sup>

1. Hornick R B, Greisman S E, Woodward T E, DuPont H L, Dawkins A T & Snyder M J. Typhoid fever: pathogenesis and immunologic control. *N. Engl. J. Med.* 283:686-91; 739-46, 1970. (Cited 240 times.)
2. Formal S B, Baron L S, Kopecko D J, Washington O, Powell C & Life C A. Construction of a potential bivalent vaccine strain: introduction of *Shigella sonnei* form I antigen genes into the gal E *Salmonella typhi* Ty 21a typhoid vaccine strain. *Infect. Immunity* 34:746-50, 1981.
3. Gorbach S L, Kean B H, Evans D G, Evans D J, Jr. & Bessudo D. Travelers' diarrhea and toxigenic *Escherichia coli*. *N. Engl. J. Med.* 292:933-6, 1975. (Cited 210 times.)