

Ofek I, Mirelman D & Sharon N. Adherence of *Escherichia coli* to human mucosal cells mediated by mannose receptors. *Nature* 265:623-5, 1977.

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This paper demonstrates that *Escherichia coli* binds to epithelial cells by a mannose-specific lectin present on the bacterial surface and points out the importance of lectin-carbohydrate interactions in the initiation of infection. [The *SCI*® indicates that this paper has been cited in over 330 publications.]

## Bacterial Lectins Latch on to Cell Sugars

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Although I have been working on bacteria since the 1950s, focusing mainly on their cell walls, I first learned about bacterial adherence from Itzhak Ofek, when he came to my laboratory in 1975. This was after he had completed his postdoctoral research in the laboratory of Ed Beachey (at the Veterans Administration Hospital, Memphis, Tennessee) on the adherence of streptococci to animal cells. Ofek wanted to apply knowledge gained in my laboratory on carbohydrates and lectins<sup>1</sup> to the investigation of the above problem. Since David Mirelman, a long-time colleague of mine, was working on *Escherichia coli*, we convinced Ofek to study the mechanism of adherence of this organism.

At the time little attention was paid to the results of the pioneering studies in the 1950s of J.P. Duguid in Aberdeen and C.C. Brinton, Jr., in Pittsburg, that the adhesive and hemagglutinating activities of many strains of *E. coli* are inhibited by mannose. The idea that sugar specific adhesion to host cells might be a prerequisite for bacterial colonization and infection was not considered at all. In retrospect, this is all the more surprising since it was already well known that initiation of infection by influenza virus requires its attachment to a sugar (sialic acid) on cells.

Ofek chose to work with epithelial cells, which he routinely scraped from his own mouth. We showed

that *E. coli* adheres readily to these cells and that this adherence is inhibited specifically by mannose and methyl  $\alpha$ -mannoside. Binding was also inhibited by precoating the epithelial cells with concanavalin A, which is specific for mannose, but not by lectins specific for other sugars, and was completely abolished by mild treatment with periodate. Extraction of the cells afforded a lectin-like constituent specific for mannose, but no data on its identity with the bacterial fimbriae were presented.

A manuscript describing our studies (submitted for publication to *Science* early in 1976) was rejected mainly because, according to the reviewer, there was little new in it. After some hesitation, we submitted the paper for publication in *Nature*, where it even provoked a comment in "News and Views" (p. 584 of the same issue).

The relevance of our findings to bacterial infection was proven in a subsequent study carried out in collaboration with Moshe Aronson and his colleagues from Tel Aviv University.<sup>2</sup> Infection of mice bladders with a strain of mannose specific *E. coli* was markedly diminished by presuspension of the organisms in a solution of methyl  $\alpha$ -mannoside. Our findings were confirmed in other laboratories, but no way has yet been found to apply inhibitors of adherence for the prevention of infection in humans.

Ofek moved in 1976 to Hadassah Medical School in Jerusalem and then to the University of Tennessee, where he spent a sabbatical working on bacterial adherence with Beachey, and subsequently to Tel Aviv University Medical School, where he served as chairman of the Department of Human Microbiology (1985-1987). We continue to collaborate closely in studies of bacterial adherence, now a very active area. Two of our recent publications deal with lectinophagocytosis,<sup>3</sup> a phenomenon first observed by us more than 10 years ago,<sup>4</sup> and with the inhibitory effect of cranberry juice (used for treatment of urinary tract infections) on the adherence of *E. coli* to eukaryotic cells.<sup>5</sup> Mirelman, still in our department, continued to be interested in adherence, discovered surface lectins on *Entameba histolytica* and recently edited a comprehensive treatise on microbial lectins.<sup>6</sup>

I believe our paper is frequently cited because it proposed a molecular basis for bacterial adherence and thus stimulated much research on this phenomenon. It appeared at a time when both lectin-carbohydrate and host-pathogen interactions were attracting increasing interest. In addition, it serves as an excellent example of the role of lectins in nature, namely, in cell-cell recognition.

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