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Lung's Natural Defense Yields New Approach to Cystic Fibrosis

For most of us, breathing in bacteria is not a problem. Our lungs constantly clear out microbes and keep going. For people with cystic fibrosis (CF), everyday bacteria can be deadly. That's because CF sufferers can't fight off microbes that enter the lungs. Now, researchers are beginning to learn why. Hughes investigator Michael J. Welsh at the University of Iowa College of Medicine has shown that CF inhibits a substance that normally controls bacterial infection in the lungs.

First identified as a clinical syndrome in 1938, CF is caused by one or more mutations in a gene that makes the protein CFTR, the cystic fibrosis transmembrane conductance regulator. CFTR is a regulated chloride channel that controls salt and water movement across cells that line the body's surfaces. Without working chloride channels, the body's sweat glands cannot absorb chloride. Salty perspiration and thick, sticky mucus in the airways result.

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— **Michael J. Welsh**

Reporting in the April 19, 1996, issue of *Cell*, Welsh and colleagues showed that cells lining the lung's airways secrete a substance that normally kills inhaled bacteria. This host defense mechanism goes awry in CF patients. People with CF do produce the bactericidal factor. However, the surface fluid in their airways is so salty that it somehow inhibits the factor. When Welsh's team reduced the surface fluid's chloride concentration, the bacteria killing factor began working again.

"Bactericidal activity is a first line of defense in the lung," Welsh said. "We think the first abnormality in cystic fibrosis airways is the disruption of this local host defense mechanism. When it is impaired, aspirated bacteria survive." He suggests that the secretion of more and thicker mucus is a secondary manifestation of CF that results from inflammation, irritation and

immune system activity.

Welsh's research offers a new way to think about CF. Rather than generally study lung mucus, scientists can zero in on the bacteria-killing capability of airway cells. Welsh hopes to identify the factors responsible for killing the bacteria. These factors may resemble defensins, one type of molecule that kills bacteria in other parts of the body.

Eventually, researchers might be able to create a drug that dilutes the saltiness of airway fluid in CF patients. That could restore the factors that normal fight off bacteria in the lungs. In the distant future, researchers would like to replace the faulty gene that causes CF with a healthy version.