MEDICAL RESEARCH

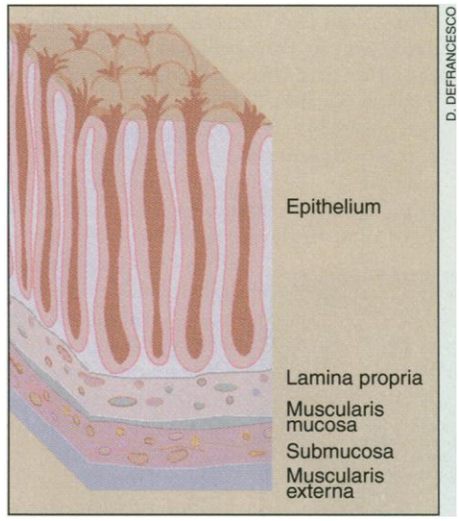
Surprising New Target Found For Anti-Ulcer Drugs

For almost 20 years, physicians have known that ulcers can be treated effectively with drugs that counter the production of acid by the stomach lining. Indeed, that knowledge has made Tagamet and Zantac, both of which help ulcers heal by preventing the acid secretion induced in the stomach by histamine, two of this country's best-selling drugs. But if National Institutes of Health (NIH) researchers Éva Mezey and Miklós Palkovits are right, anti-ulcer drugs such as Zantac and Tagamet do not work quite the way everyone thinks—a suggestion that may turn the world of ulcer research upside down.

Anti-ulcer drugs suppress acid production by preventing histamine from binding to the receptors through which it exerts its effects on stomach cells. Almost from the moment of their discovery in the early 1970s, researchers naturally assumed that the receptors targeted by the drugs were on parietal cells, the acid-secreting cells in the stomach's epithelial lining. And the case appeared clinched when researchers detected the receptors on parietal cells isolated from the stomach and grown in lab cultures. But now come neuroendocrinologists Mezey and Palkovits with a report on page 1662 of this issue of *Science* in which they contend that anti-ulcer drugs may not act exclusively on parietal cells after all. They suggest instead that a target of the drugs may be immune cells lying just below their acid-secreting neighbors.

To say that this has dumbfounded the ulcer community is an understatement. "Holy mackerel! That really is a surprise," exclaimed gastroneurologist T. Edward Bynum of the Harvard Digestive Disease Center, when first informed of the result. "I'm amazed if it's true. It doesn't fit with anything I know about the system. We would have to postulate a whole new mechanism for the drugs," responded Richard Galbraith, an ulcer specialist at Rockefeller University Medical Center. Galbraith cautions, however, that other researchers will have to replicate the finding before it becomes accepted. Moreover, the therapeutic implications are unclear. The discovery may help researchers better understand ulcer formation and even lead to new drugs way down the road, but ulcer therapy is already effective: 80% to 90% of cases are cured within weeks, and even better drugs are in the pipeline.

Mezey and Palkovits did not set out to shock anyone. They simply wanted to find out what cells in the stomach hold receptors for the neurotransmitter acetylcholine, one of several substances in addition to histamine that affect acid production by the stomach, says Mezey. Like histamine, these other substances, which include the hormone gastrin and the neurotransmitter dopamine also have to bind to specific receptors to exert their effects. But, recalls Mezey, "we didn't see any [acetylcholine receptors] on the acid-secreting cells. We saw them on the immune cells."



Under cover. Anti-ulcer drugs may work through immune cells in the lamina propria.

Spurred on by that revelation, the two researchers decided to look at the whole range of receptors for compounds that affect acid secretion. They used a technique called in situ hybridization histochemistry, in which investigators can determine which cells are making a particular protein, such as a receptor, by looking for the messenger RNA (mRNA) that directs the protein synthesis. This is done with radioisotope-labeled single strands of DNA that complement stretches of the receptor mRNA and thus "stick" if they encounter one another. Mezey and Palkovits used such probes to scan for mRNAs for histamine, dopamine, gastrin, and acetylcholine receptors in sections of rat stomachs and duodenums. There were more surprises in store: "We didn't see anything in the acid-secreting cells at all," says Mezey. Instead, just as they found with acetylcholine, the radiolabeled cells were concentrated in the lamina propria, a network of connective tissue containing nerves, blood vessels, and immune cells that lies beneath the epithelium.

The NIH team's next step was to identify which cells in the lamina propria express the receptor mRNAs, a task that called for a combination of in situ hybridization histochemistry and staining with antibodies that could distinguish the various types of cells from one another. Two types of immune cells, macrophages and antibody-producing plasmocytes, revealed themselves in these experiments. "I'm sure macrophages are major players. They seem to make all the receptors," comments Mezey.

But what role these immune cells play is still up in the air, she admits, although a few clues have emerged. For instance, Mezey and Palkovits noticed that the number of immune cells in the area around an ulcer increases dramatically when ulcers are induced in rats by stress or drugs. Moreover, says Mezey, the immune cells lie very close to epithelial cells and may even be attached to them, suggesting they may be in direct communication. The two researchers will next try to determine how the immune cells might affect the acid secretion of parietal cells.

Another obvious question is how ulcer researchers could have been wrong for so long about the target cells of the anti-ulcer drugs. One explanation suggested by Mezey and Palkovits is that the cultured cells used to examine how the drugs work contain only 60% to 95% parietal cells. The remaining cells, they suggest, may have included immune cells from the lamina propria. "Everything they found could have worked through those [contaminant] cells," says Mezey. Still, she cautions that while their work shows that immune cells must now be seen as potential sites of anti-ulcer drug action, it does not rule out the possibility that parietal cells also have the various receptors since the researchers assayed for the mRNAs, not the receptor proteins themselves.

But even if the NIH researchers are right, some ulcer specialists believe the therapeutic implications of their work may be limited since the coming generation of anti-ulcer treatments is not receptor-based. Some focus, for example, on directly preventing acid release by parietal cells or on using growth factors and cell protective agents to strengthen the stomach's protective lining.

Mezey and Palkovits, however, aren't ready to dismiss the possibility that their finding may have therapeutic implications, although Mezey concedes that "it needs a lot of research before we can hope for anything." But one hope Mezey does express is that their work may extend beyond ulcers to other illnesses of the gastrointestinal tract, such as Crohn's disease, an autoimmune disorder that does not respond nearly as well to treatment as ulcers do. The first step, however, will be for other ulcer researchers to either confirm or refute the NIH duo's work. Even Mezey says, "I would really like to know the truth."

–John Travis