Enzyme blocker cools inflammatory reaction

Ulcerative colitis is an inflammatory disease of unknown origin and no known cure. Once diagnosed, its roughly half-million U.S. victims face lifelong recurring bouts — and sometimes bed confinement — with debilitating stomachaches, uncontrollable bloody diarrhea and severe weakness that can last weeks or more at a time. Up to one-third of its sufferers eventually develop such severe symptoms that they must undergo surgery to remove the colon. But preliminary results from human trials indicate that symptomatic relief may be on the way for many people with this and other inflammatory or allergic diseases.

At the American Chemical Society meeting in Boston last week, researchers described engineering a drug to block the action of 5-lipoxygenase (5-LO). The enzyme 5-LO normally plays a key role in initiating the body's breakdown of arachidonic acid — a fatty acid present in all cells — into leukotrienes, potent compounds that stimulate inflammation and allergic responses.

Aspirin and most other nonsteroidal anti-inflammatory drugs work by blocking prostaglandin synthesis by cyclo-oxygenase, another enzyme that can initiate arachidonic acid breakdown. Because leukotrienes are "much more potent inflammatory agents" than prostaglandins, the researchers focused on shutting down production of 5-LO's products, says James Kesterson, who manages the drug's development at Abbott Laboratories in Abbott Park, Ill.

The resulting hydroxy urea compound — for now known simply as 64077 — binds selectively and exclusively to 5-LO's active site, blocking its transformation of arachidonic acid, the Abbott chemists found. They added benzothiophene to make 64077 more oil-soluble so the experimental drug could be taken orally without breaking down before entering the body's cells, where 5-LO triggers leukotriene production.

The drug has already been tested in more than 500 people and is now in controlled clinical trials for ulcerative colitis, asthma, hay fever, psoriasis and rheumatoid arthritis. Preliminary data on 48 participants in the most advanced study — focusing on ulcerative colitis — indicate that 800 milligrams of the drug twice daily provided "significant" symptomatic relief for most treated patients, the researchers report.

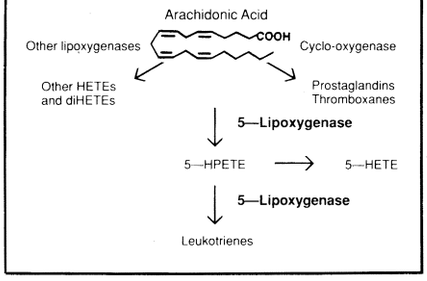
"We put them in remission, so that they felt good and didn't have diarrhea" or other serious symptoms of the disease, Kesterson told SCIENCE NEWS. Whether the drug can halt or cure ulcerative colitis remains unclear. As for side effects, he says, "we haven't seen any," though no one has yet taken the drug for more than a month.

"We believe this compound's going to be put on a fast track [for federal drug approval]," Kesterson says. If so, he adds, it could be available by 1994.

Lonnie R. Empey, who has investigated other 5-LO inhibitors at the University of Alberta in Edmonton, says that to date no one has shown that blocking leukotrienes will prevent or heal inflammatory bowel diseases. "If [Abbott] has, that's really big news," he told SCIENCE NEWS. Empey likens the significance of creating such a drug to "discovering aspirin."

"Currently available therapies for inflammatory bowel disease are not very good," says William F. Stenson, a gastroenterologist at Washington University in St. Louis, who describes the new data as "exciting" and "a big deal." He notes that the steroids usually prescribed in such cases don't always provide symptomatic relief, and even when they do, the drugs can cause osteoporosis, cataracts and high blood pressure. Moreover, "nobody understands how any of these [steroidal] drugs work," he says.

"There's considerable enthusiasm about what [Abbott] has done, . . . not only because it is an improvement in therapy, but also because it's the first [inflammatory bowel] therapy where we're confident about how it works," Stenson says. He adds that such an understanding may provide insight into other ways to combat the disease. — *J. Raloff*



Adapted from Abbott

The arachidonic acid cascade.

CMV and heart disease

Though cytomegalovirus (CMV) can cause flu-like symptoms in infected children and adults, this herpesvirus has prompted concern primarily through its ability to cause birth defects in a developing fetus (SN: 11/19/89, p.327). But a new report suggests another reason to worry about this often asymptomatic infection: "circumstantial" but "increasing" evidence that it can trigger atherosclerosis, a leading cause of death from heart attacks and stroke.

Spurred by evidence that herpesviruses could cause atherosclerosis in birds, Joseph L. Melnick and his colleagues at the Baylor College of Medicine in Houston looked for signs of latent herpes infection in people with coronary artery disease. The team's first report, published in 1983, suggested a possible link. Now, in the April 25 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, they review their follow-ups and other studies involving human tissues or blood, including six published in the past three years. All show a far higher rate of herpes DNA and other signs of herpesvirus infection — especially CMV — in people with advanced atherosclerosis than in people with little or no arterial disease. Because the researchers did not find whole viruses in the atherosclerotic tissue, they suggest "CMV may be an initiating factor" that later vanishes from sites of advanced disease.

Ultimately, they add, confirming CMV's atherogenicity might spur development of a commercial CMV vaccine. □

Manic depression's ex-X

A new analysis of DNA from 14 families with a high rate of manic depression finds no statistical link between the mental disorder and two genetic markers on the X chromosome. Several research teams had previously found the markers — one for color blindness, the other for anemia — among many people in other families with manic depression, and had proposed that as many as one in three manic depressives has a predisposing gene in that region of the X chromosome (SN: 3/28/87, p.199).

The connection between manic depression and the X-chromosome markers is much less frequent than suggested by those studies, reports a team led by Wade H. Berrettini of the National Insitute of Mental Health (NIMH) in Bethesda, Md. An uncommon form of manic depression may be linked to markers on the X chromosome, the NIMH scientists say in the April ARCHIVES OF GENERAL PSYCHIATRY.

Another marker on the X chromosome has also been associated with manic depression (SN: 6/13/87, p.376). But it lies so close to one of the markers used by the NIMH researchers that they excluded its connection to manic depression.

As in prior studies, no fathers and sons in the NIMH families shared a manic depression diagnosis. Some researchers suggest this pattern supports a link between the X chromosome and manic depression. The 23rd pair of human chromosomes contains two X chromosomes for females and one X and one Y for males. The Y is inherited from the father.

The new findings follow a recent report casting doubt on a link between two genetic markers on chromosome 11 and manic depression among Amish families (SN: 11/18/89, p.327). □