Crohn's Disease:

Researchers recently have seen advances in the treatment and etiological investigation of this mysterious inflammatory bowel disease

BY LINDA GARMON

Burrill Crohn remembers the hot summer day Crohn's disease gained worldwide notoriety. That day, says the 95-year-old retired doctor who first described the inflammatory bowel disease that bears his name, then-President Dwight David Eisenhower underwent surgery because of obstruction due to Crohn's disease. Although The New York Times eventually would headline a favorable presidential prognosis — "Eisenhower [Crohn's disease] case 'safest type,' "—the initial news of Eisenhower's operation caused a $3.5 billion drop in the stock market. As Eisenhower's condition improved, Wall Street forgot Crohn's disease and the digestive malady slipped from the national limelight.

Now, however, public awareness of Crohn's disease again is increasing, because incidence of the disease is rising; in fact, Crohn's disease is considered a significant health problem.

The National Foundation for Ileitis (inflammation of the small intestine) and Colitis (inflammation of the large intestine) reports that one of every 3,000 adults in the United States has some form of Crohn's disease. And this figure underestimates the significance of the disease because it fails to take into account the number of diagnosed cases in children. Increased incidence also has been documented in Sweden, Norway and the Netherlands.

Gastroenterologists, doctors who specialize in disorders of the digestive system, particularly notice the increased incidence of Crohn's disease. One such specialist in the Washington area, Stuart Donovitch, says Crohn's disease is "one of the most common diseases" he sees.

The first symptoms of the disease usually are diarrhea, bleeding, weight loss, anemia, fever and pain, Donovitch says. Only about half of his patients require surgery, such as removal of a diseased section of the intestine, but all face "a lifelong disease that has its ups and downs" and, as yet, no cure.

Crohn's disease is a second major category of inflammatory bowel disease; ulcerative colitis is the other. Unlike ulcerative colitis, which usually only affects the inner lining of the colon, Crohn's disease can irritate the deeper layers of the intestinal wall.

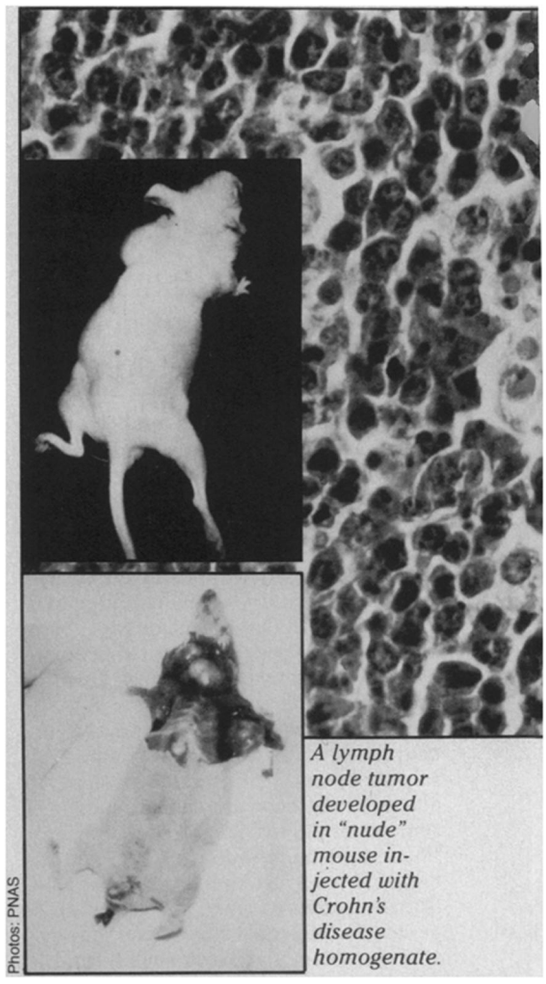
Also, any segment of the intestinal wall — 20 feet of small intestine and 5 feet of large intestine—is vulnerable to attack by the disease. That is why Crohn's is a disease by many other names. When it affects the layers of the small intestine, it is called regional enteritis; when the affliction is in the lower half of the small intestine (the ileum), it is called ileitis. In addition, Crohn's disease can affect the large intestine, or colon, in which case it is referred to as granulomatous (named for the granuloma, or tissue nodules, that form) colitis. When both colon and ileum are involved, the process is called ileocolitis.

In all types of Crohn's disease, masses and fistulae can form. A fistula is an abnormal passageway from the diseased intestinal tissue to another loop of intestine, another internal organ or the skin; it is as if the disease had burrowed a tunnel, connecting tissues that normally remain separated. In addition to developing the intestinal masses and fistulae, some patients also show extra-intestinal manifestations of Crohn's disease — arthritis, inflammation of the eye (iritis), skin lesions and disturbances in liver function.

Finally, since the small intestine is involved in the absorption of food, regional enteritis (Crohn's disease of the small intestine) can cause malnutrition. This is especially a problem in children with the disease, since malnutrition results in growth retardation. To combat growth retardation, doctors traditionally have resorted to Total Parenteral Nutrition (TPN), in which all nutrients are supplied by the intravenous route. Recently, however, Irwin H. Rosenberg of the University of Chicago successfully reversed growth retardation in a group of children (ages 12 to 16 years) with Crohn's disease by means of an "aggressive oral regimen." Rosenberg met with success after testing simple but strict enforcement of oral caloric intake as an alternative to TPN. "The message of this research is simply this: You've got to get these people [Crohn's disease patients] back to ingesting adequate nutrients, or they ain't going to grow," Rosenberg says.

Before patients can respond to oral nutritional therapy, however, their intestinal rage must be calmed. Leading the research on various drugs used for this task is the National Cooperative Crohn's Disease Study (NCCDS). A recently reported NCCDS study, initiated in 1970, involved 1,119 patients and 14 study centers. It was "the largest and most geographically diverse group of Crohn's disease patients ever studied," says John W. Singleton, principal NCCDS investigator at the University of Colorado.

"At the time of initiation of the NCCDS in 1970, there had been a singular lack of progress in the treatment of Crohn's disease," Singleton and colleagues reported. "No [drug] regimen had been subjected to controlled clinical trial to determine efficacy or safety in the treatment of Crohn's disease." A group of investigators met, therefore, to develop a plan to test drugs commonly used in treating the disease, and the NCCDS was born.



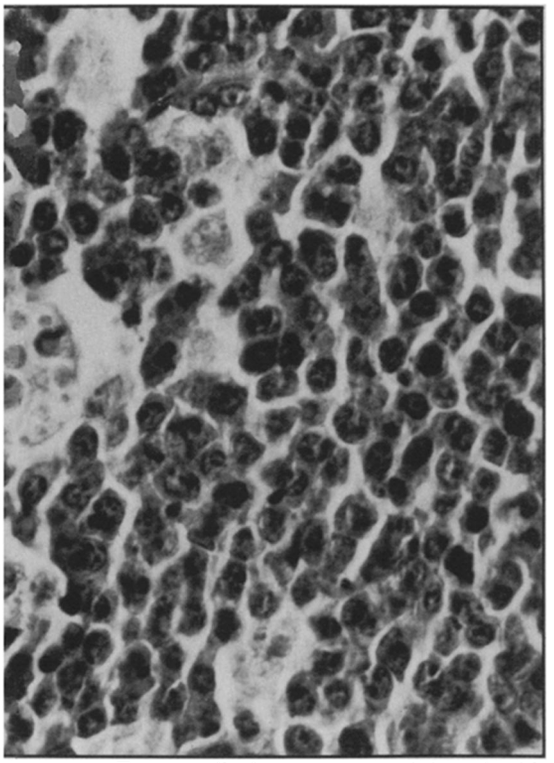
Photos: PNAS

A lymph node tumor developed in "nude" mouse injected with Crohn's disease homogenate.

The NCCDS compared the efficacy of placebo with three drugs — prednisone (a steroid), sulfasalazine (a sulfa derivative) and azathioprine (an immunosuppressant) — and with a drug combination. The results of the study, published in a special supplement to the October 1979 GASTROENTEROLOGY, show that prednisone and sulfasalazine were significantly more effective than placebo in treatment of Crohn's disease. None of the drugs, however, was effective in preventing flare-up of quiescent, or inactive, Crohn's disease.

In a related study, Daniel H. Present and colleagues of the Mount Sinai School of Medicine (of the City University of New York) tested the effectiveness of 6-mercaptopurine (6-MP) in the treatment of Crohn's disease. That drug is a metabolite of azathioprine — the drug the NCCDS found statistically no better than a placebo. Present's results, published in the May 1 NEW ENGLAND JOURNAL OF MEDICINE, indicate that 6-MP "is an effec-

Intestinal Enigma



Tumor cells from a mouse injected with Crohn's disease show excess cytoplasm.

tive and useful agent in the management of Crohn's disease."

In an editorial in the same NEJM issue, Marvin H. Sleisenger of the Veterans Administration Medical Center in San Francisco says that Present's study "challenges the conclusion of the NCCDS with regard to the efficacy of 6-MP (and therefore, of azathioprine) in the treatment of Crohn's disease." Singleton, however, explains that the difference lies not in the conclusions of the two studies, but rather in their study designs — the NCCDS tested azathioprine alone, but Present tested it in combination with steroids or sulfasalazine in most of his patients.

"Many people have tried to make this into a conflict because it's fun and exciting, sells newspapers and drugs and wakes people up at conferences," says Singleton, "but there really is no conflict between our [NCCDS] study and the results of others."

Demographic data collected in the NCCDS confirmed the previously painted picture of the average Crohn's disease patient: The average age of onset is early thirties; the incidence of disease seems to be evenly distributed in both sexes; more than 90 percent are Caucasian.

Interestingly, other studies have shown that the incidence of Crohn's disease is about five to seven times greater among Ashkenazic Jews than among non-Jews in the United States. In Israel, though, the disease is virtually nonexistent.

Far from being epidemiologic, the frequency of the disease in U.S. Jews probably indicates a genetic predisposition to the disease, Singleton explains. But the possibility of a genetic predisposition is more evident in the familial occurrence of the disease: "About 15 to 20 percent of the patients with Crohn's disease will have another family member among their first degree relatives who also has Crohn's disease or ulcerative colitis," he says.

Aside from the observed high incidence of the disease within families—suggesting a genetic factor—little is known about the etiology, or cause, of Crohn's disease. Recently uncovered clues in the etiological mystery, however, suggest that researchers are edging closer to the source of the Crohn's disease problem. Its discovery will close the book on one of the most frustrating stories in medical history.

The story opens with the theory that Crohn's disease is caused by a transmissible agent. About five years ago, three different groups of researchers seemed hot on the trail of such an agent: One group had cultured L-forms of bacteria from diseased tissue; another group had cultured RNA viruses; a third group was able to induce in experimental animals changes pathologically similar to those observed in animals known to have Crohn's disease. Unfortunately, each group soon faced an impasse. Researchers working with the viruses and bacteria involved in Crohn's disease found themselves up against a classic etiological dead end — the difficulty of cultivating "new" agents involved in disease in the batches necessary for lengthy studies. In other cases, results were inconsistent and irreproducible.

So other avenues of etiological investigation were explored. A British investigator, for example, set out to correlate "breakfast habits" with the incidence of Crohn's disease, on the assumption that "food taken on a completely empty stomach is more likely to reach the areas usually affected by the disease." The investigator, whose results appeared in the April 9, 1977, BRITISH MEDICAL JOURNAL, concluded that Crohn's disease patients tended to be "cornflake eaters." The "breakfast and Crohn's disease" theory — refuted almost as soon as it was published — was evidence of the mounting frustration in the fight against Crohn's disease.

Meanwhile, the "transmissible agent theorists" persisted. Although they had reached a deadlock situation — at least in regard to culturing the possible viruses or bacteria involved in Crohn's disease — the research was not without its advances. One researcher, for example, had demonstrated that the incidence of antibodies to double-stranded RNA is significantly higher in Crohn's disease patients and their family members than in control subjects. This observation suggests that the patients and family members have been exposed to an RNA virus.

Whether that RNA virus plays a role in causing Crohn's disease or the disease symptoms is a mystery that Gary Gitnick of the University of California in Los Angeles hopes to solve. Gitnick and colleagues are coordinating the work of six universities to study a "secret agent" isolated from patients with Crohn's disease. The agent, not found in control patients, develops in the cytoplasm of diseased cells and sometimes is present in crystalline-appearing aggregates. "It's a new virus not previously found," says Gitnick, whose collaborative work will be presented at the May American Gastroenterological Association meeting, "and our job is to find out what it's doing there."

Should Gitnick's group discover that its virus is indeed a causative agent, therapeutic and preventive measures more rapidly could develop. Still, the studies remain inconclusive and researchers search for appropriate systems of agent isolation and cultivation.

Kiron Das of Albert Einstein College of Medicine in New York believes his research group has found such a system — nude mice. Nude mice lack the thymus — an organ involved in cell-mediated (as opposed to humoral, or circulating antibody) immunity — so they do not recognize certain foreign materials that may enter their bodies. As a result, these foreign agents can "grow luxuriously and express their processes" in nude mice.

Das and colleagues recently injected lymph node homogenates from patients with Crohn's disease into nude mice. The results, published in the January PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, support Gitnick's viral theory: The homogenate caused lymphoma, or tumor formation, in nude mice.

Although the development of lymphoma signals viral involvement, Das says there is strong evidence to suggest that Crohn's disease also may depend on abnormalities of the immune system. Regardless of the precise etiology, the use of nude mice may present researchers "a handle on a new avenue" of Crohn's disease research. "Whether it will be another five years or ten years before a [causative] agent is isolated is difficult to say," says Das, "but this is a big step."

And "big steps" renew hope for the eventual end to the tragedy of Crohn's disease. "It doesn't kill people," says Donovitch, "but they suffer. They suffer their full three score years and ten." □