

The Small Intestine

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Abstract

Clinical investigation of the small bowel at The Mount Sinai Hospital began with David Adlersberg's arrival in 1931. His research interests were in bile acids, cholesterol, carotene, and vitamin A. In 1952, he was given a Nutrition Laboratory and later, a Nutrition Clinic. His vitamin A tolerance test and interest in malabsorption led him to a comprehensive study of sprue, the separation of the tropical and non-tropical forms, and their different etiologies and treatments. Adlersberg's work was complemented by (a) Marshak and Wolf's radiologic examination of the small bowel (especially in sprue and other malabsorption disorders); (b) Gerson's perfusion experiments; and (c) Friedman, Waye and Wolf's motility studies. Lieber and his colleagues explored the deleterious effects of alcohol on the function and structure of the small intestine. Gerson explored the nutrition of patients with Crohn's disease of the small intestine, especially after extensive resection or bypass leading to ascorbic and folic acid deficiencies and hypergastrinemia. **Key Words:** Malabsorption, small intestine, jejunum, ileum, sprue, Crohn's disease, vitamin A, vitamin C, folic acid, alcohol.

The Small Intestine

THE ERA OF small bowel clinical investigation at Mount Sinai Hospital began with Dr. David Adlersberg in the 1940s. Having earlier established a reputation in the study of bile acids and cholesterol, in Vienna, he had the good fortune to be invited to The Mount Sinai Hospital in 1931 as a member of the Chemistry Department. He then extended his research interests to carotene and vitamin A. This led him to develop the use of the vitamin A tolerance test and a continuing interest in malabsorption syndromes. In 1952, The Mount Sinai Hospital established the Nutrition Laboratory under his supervision.

Celiac Sprue

In addition to the Nutrition Laboratory, Adlersberg had established a Nutrition Clinic where he followed a large number of patients with sprue. While non-tropical and tropical sprue had been recognized as clinical entities in the 19th century, their differentiation and the etiology

of celiac sprue were not established until the classic report by Dicke, of the role of gluten, in 1952. However, in 1947, Adlersberg and Schein (1) published an extensive clinical description of a series of forty patients with sprue. This included findings of macrocytic anemia, steatorrhea, flat vitamin A tolerance test, and response to the diet then employed for sprue patients. Twenty-seven patients showed excellent response to a high protein, low fat, monosaccharide diet supplemented by liver extract, B complex and folic acid.

The first definitive description of villous changes in celiac sprue is attributed to Paulley in 1954 from surgical biopsy material. Schein (2), from Mount Sinai's Pathology Department, wrote an accompanying article to the above clinical description, also in 1947, from an autopsy of a patient with sprue. He described clubbing and mushrooming of small intestinal villi, "hitherto undescribed lesions of the intestine." This was clearly one of the first descriptions of an altered villous architecture in non-tropical sprue.

In 1951, Adlersberg and colleagues (3) were one of the first three groups to report on the beneficial effect of cortisone and ACTH in the treatment of sprue. The necessity for gluten restriction in the diet was not yet known so the treated patients were described as having refractory non-tropical sprue. Five of seven patients responded dramatically to steroids. In the early 1950s, this

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was a breakthrough form of therapy, as it still may be in patients resistant to a gluten-free diet.

In 1957, the *Journal of The Mount Sinai Hospital* published an entire issue devoted to sprue. Included was an article that summarized Adlersberg's experience with 94 patients with sprue (4). He was then able to define clinical and laboratory criteria that helped separate non-tropical and tropical sprue. This was the culmination of a long and productive career in the investigation of sprue.

Years later, in 1996, Kahn, Fiel, and Janowitz (5) returned to the subject of sprue with a report of a patient with celiac sprue and several autoimmune entities, including idiopathic thrombocytopenic purpura. In their article, they discussed HLA phenotypes and their possible role in the linkage of immunological conditions.

Tropical Sprue

Tropical sprue, another cause of malabsorption that is distinct from celiac sprue, was the subject of several research reports by Gerson. First, in collaboration with Lindenbaum (6), the small intestines of 68 Indian and Pakistani subjects who had come to New York were studied. Initially, these subjects were found to have functional and structural abnormalities known as sub-clinical tropical enteropathy. By following them sequentially, it was shown that their small bowels improved spontaneously after arrival in the United States. This indicated that environmental factors in South Asia were responsible for tropical enteropathy. Using a jejunal triple lumen perfusion technique, Gerson, Cohen, and Brown (7) were able to demonstrate the relationship between folic acid and hexose malabsorption in sprue. In the report by Meyers, Schweitzer, and Gerson (8), the occasional confusion and overlapping of findings between tropical sprue and pernicious anemia were clarified in a series of illustrative cases.

Radiology

Richard Marshak, best known for his radiologic studies of inflammatory bowel disease, was interested in all aspects of small bowel radiology. One of his interests was sprue. In collaboration with Wolf and Adlersberg (9), he published the first large series of sprue patients in 1954. With his typically critical eye, he described the radiologic characteristics of sprue that distinguished it from other small bowel diseases. He was one of the first to emphasize proximal dilatation as the earliest change. He also complemented Adlers-

berg's work by demonstrating x-ray improvement after steroid therapy.

Marshak published numerous articles on various small intestinal disorders, and became a national and international expert in this area. His weekly radiology conference at The Mount Sinai Hospital was avidly attended by physicians from near and far. His observations were finally recorded in a classic medical text, "Radiology of the Small Intestine" (10), published in 1970.

Motility

The next investigative work concerned small bowel motility. In the 1950s and 1960s, knowledge in this area was limited, in part due to the technical difficulties in studying the small intestine. Motility research was largely confined to the proximal small bowel. Gerald Friedman and Jerome Waye (11) developed a new technique utilizing pressure transducers and a series of three catheters with openings 7 cm apart. These were placed in the gastric antrum, and various levels of the duodenum and proximal jejunum. They began to describe, in several reports, the differentiation of various wave types in the duodenum. In collaboration with B.S. Wolf (12), they correlated pressures with cineradiographs so that pressures could be compared with motility patterns. They appreciated that there were propulsive contractions and mixing contractions. At that time, techniques for measuring the migrating motor complex, especially phase III with its "house-keeping" function, had not yet been developed.

Alcohol

Charles Lieber is best known for his work on alcohol and the liver (13). However, his experimental model of feeding alcohol while maintaining normal nutrition was also utilized to study the effects of alcohol on the small intestine. In 1969, in collaboration with John Lindenbaum (14), he published the first report to show that alcohol inhibited intestinal absorption of vitamin B₁₂ despite the presence of intrinsic factor and pancreatic enzyme. This finding led to a more extended study of small intestinal structure and function. Several articles documented anatomical changes. Emanuel Rubin and colleagues (15) showed electron microscopic changes in mitochondria, endoplasmic reticulum and cytoplasmic degradation, both in jejunum and ileum. Later (16), histologic changes were demonstrated with an increase in crypt-villous ratio, cellular infiltration of the lamina propria, and some erosion of villous tips.

Perlow and Lieber (17) also measured enzyme activity in the brush border of chronic alcoholic men. There appeared to be diminution in sucrase activity and lactase activity, compared with controls. These enzyme levels increased after two weeks of abstinence; there was an increase in both enzymes, suggesting that alcohol was responsible for the findings.

Crohn's Disease

In the 1970s, Gerson published a series of papers related to the effects of Crohn's disease on small intestinal absorption and nutrition. In an effort to correlate ileal disease or resection with absorptive parameters, 68 patients with ileitis were studied (18). Resection of 90 cm of terminal ileum was a major determinant of steatorrhea, while resection of 60 cm uniformly caused vitamin B-12 malabsorption. Jejunal function was well maintained in most patients except those with short bowel syndrome whose absorption parameters were most impaired. This study emphasized the nutritional consequences of intestinal resection, which then was performed more freely than it is today.

One of the consequences of extensive intestinal resection with a resultant short bowel syndrome is gastric acid hypersecretion. In the early 1970s, Straus and Yalow were able to measure serum gastrin levels in a series of patients with short bowel syndrome in whom hypersecretion of gastrin was the probable cause of excess acid (19). It was suggested at that time that some inhibitory factor had been removed in the resected distal small bowel, but this hypothesis has still not been clearly established.

Patients with Crohn's disease often avoid fruits and vegetables because of problems with diarrhea. Because it was known that this dietary restriction may cause folic acid deficiency, Gerson and Fabry studied another vitamin present in the same foods, ascorbic acid (20). Serum and leukocyte ascorbic acid levels were significantly reduced, sometimes in the range seen in scurvy. Dietary histories showed that vitamin C deficiency was correlated with reduced ascorbic acid intake.

Because ascorbic acid is important for collagen formation, tissue ascorbic acid concentration was then measured in surgical ileal specimens from patients with and without fistulae. Both tissue and serum ascorbate levels were significantly lower in patients with fistulae. This study demonstrated that vitamin C deficiency can be a nutritional consequence of Crohn's disease.

Folic Acid Absorption

Another area of active investigation by Gerson and co-workers (21) included the use of a triple lumen tube to perfuse various substances over a 30-cm segment of proximal jejunum. Fluid aspirated from the distal port of the perfusing system could be used to measure accurately the absorption of various solutes, such as folic acid. Adding other substances to the perfusate could be shown to affect folate absorption. Glucose increased the absorption of folic acid, possibly due to solvent drag. Diphenylhydantoin (DPH), on the other hand, when added to the perfusate (22) was shown to inhibit folate absorption, thus explaining the association between DPH and folate deficiency. Folic acid absorption was found to be normal in patients with Crohn's disease (23). Acetazolamide inhibited the absorption of salt and water by the normal human jejunum (24).

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