Tropical Enteritis: Nutritional Consequences and Connections with the Riddle of Cholera

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ABSTRACT One of the important consequences of the infection–nutrition interaction is mediated by malabsorption associated with chronic inflammation in the intestine, enteritis. Studies made possible after development of the peroral intestinal biopsy technique in the 1950s indicated the wide prevalence of enteropathy, particularly in tropical developing countries with poor levels of sanitation. Some consider this so-called subclinical tropical malabsorption to be the base of an iceberg, whose tip is tropical sprue, a severe form of malabsorption leading to nutritional deficiency that had been reported in colonial expatriates in tropical countries for 200 y. Some of the first demonstrations of the prevalence of tropical enteritis in Asia were made in quest of the pathologic lesion of cholera, and further examination of the water and electrolyte, as well as nutrient, malabsorption in cholera led serendipitously to the discovery of the oral rehydration solution for the treatment of diarrheal disease. J. Nutr. 133: 333S–335S, 2003.

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Since the temporal focus of this symposium on Nutrition and Infection is 1968, the year of publication of the seminal WHO monograph on nutrition and infection by Scrimshaw, Taylor and Gordon (1), this historic analysis of tropical enteritis will take off from that year as prologue and progress. In that year, marred also by the anguish of the Vietnam war, with its own connection to tropical malabsorption (2), and the beginnings of the Biafra famine, John Lindenbaum and his co-workers published an article on jejunitis in Peace Corps volunteers in tropical East Pakistan (3), which will serve us as the first citation for the term “tropical enteritis.” (This historical note is dedicated to the memory of John Lindenbaum, who contributed so much to this topic and so much else in hematology, gastroenterology and medical care.) For a reference to cholera in 1968, let me immodestly cite a paper by Norbert Hirschhorn and this author on the depression of ATPase in cholera and other diarrheal diseases (4). I will return later to the contribution of this paper to our topic of this symposium. Presently, I will describe a more critical association of tropical enteritis and the quest for an understanding of the pathogenesis of cholera, which was missed by our 1968 paper.

First, to tropical jejunitis, its meaning, its nomenclature, its causes and importance. There are at least two schools of thought about tropical enteritis, which before 1968 was referred to as subclinical (tropical) malabsorption (5), and after was often referred to as tropical enteropathy. One school, to which I subscribe, considers tropical enteritis or subclinical malabsorption to be the base of a very large iceberg, of which tropical sprue is the clinical pinnacle. Others would argue that this widespread observation is a mix of entities relating to persistent environmental contamination, recurrent enteric infections and bacterial overgrowth, which is endemic in a great many developing countries and places of defective hygiene, but different from tropical sprue, with its characteristic hematologic presentation with diarrhea, malabsorption, folate and vitamin B12 deficiency and anemia. Intestinal lesions are indistinguishable, with tropical sprue having the more severe mucosal abnormalities, but with considerable overlap with what has been reported as jejunitis or tropical enteropathy. Tropical sprue was the term used by Manson in 1880 as his translation of the Dutch Indische Sprouw (6), while referring to a condition of English expatriates in tropical countries in the empire, similar to what had already been reported in the Dutch West Indies. The history of tropical sprue has been well reviewed by Klipstein and others (6), but its virtual disappearance is no better explained at this time than its etiology. Although many references were made to subclinical malabsorption, as perhaps an early and less severe manifestation of tropical sprue (5), it must be noted that the term “subclinical” is probably faulty, given that many such individuals were...
suffering from clinical symptoms of diarrhea and indeed, when studied, were found to have some malabsorption. The use of subclinical was more justified later when the peroral intestinal biopsy was introduced in the middle of the 20th century and allowed for the observation, as later noted, that the intestinal lesion associated with tropical sprue was also widely present in indigenous populations without the florid symptoms and anemia of tropical sprue. Whatever the proper nomenclature and relationship to tropical sprue, the importance of tropical malabsorption as a factor in the worldwide prevalence of malnutrition was explored and documented in a symposium on the topic of nutrition and malabsorption in 1972 (7).

Sharpening our focus on the intestinal biopsy will lead us to the description of the pathology of tropical enteritis and establish the connection with cholera, which was also endemic in some of the same countries where tropical enteritis would be described in both indigenous and expatriate populations. Although there may be some argument about primacy, the best chronology that I can obtain for small intestinal biopsy for small intestinal biopsy reported by Wood in 1949, Schiner in 1956, Crosby and Krugler in 1957, Flick, Quinton and Ruben in 1960 and Baker and Hughes in 1960. Before these method advances, the pathology of small intestinal diseases based on postmortem specimens was highly unreliable, relating largely to the distortions of postmortem autolysis. Peroral intestinal biopsy provided an opportunity for examining the morphology of the first specimens and changed the course of diagnosis and interpretation of small intestinal disease and of malabsorption in general.

Within this time frame of excitement in the late 1950s and early 1960s, there was also the exciting quest for an understanding of the pathogenesis and, indeed, pathology, of cholera in several centers, not least the Cholera Research Laboratory in Dhaka, East Pakistan, which had been established in 1961. The research director of that laboratory, Robert Gordon, was on loan from the National Institutes of Health, and his fertile mind turned quickly to the promise of the peroral intestinal biopsy as a means of examining the intestinal pathology of cholera. Before that time, the postmortem specimens from deceased cholera patients had been interpreted as showing a total denudation of the intestinal mucosa, which might well have explained the copious loss of fluid into the intestine, characteristic of cholera. Gordon established a collaboration with the U.S. Army laboratory in Thailand, which had available the newly developed Crosby capsule. William Crosby was then at the Walter Reed Army Institute of Research. The Army team, which included William Beisel, a participant in this symposium, performed intestinal biopsies on patients who had recently recovered from acute cholera and the pathology was that of an inflamed intestinal mucosa with blunted villi. Because the intestinal mucosa “was not sloughed off,” as noted by Beisel in his introduction, pathology derived previously from autolyzed postmortem specimens was rejected. A first thought was that the lesion of cholera was acute enteritis with villous distortion and, by physiological extrapolation, malabsorption of water and electrolytes. But wait. What about the controls in the same population in Thailand who had not had cholera? Their biopsies showed the same intestinal lesion. Thus was born, in my view, the description of endemic tropical jejunitis or tropical enteropathy. The biopsy of the cholera patient was no different from the biopsy of those in the indigenous population, and thus we were no closer in 1962 to understanding the pathogenesis of cholera, but we had uncovered the phenomenon of a perhaps widespread jejunitis, which was indeed subclinical (see Fig. 1).

Another more seminal near miss at the Cholera Research Laboratory was referenced earlier with the observation that biopsies from cholera patients were deficient in sodium potassium ATPase (4), a critical enzyme in the intestinal sodium pump, and presumably required intact for the absorption of salt and water. Hirschhorn and Love and others at the Cholera Research Laboratory then tested our hypothesis that cholera patients had a defective sodium pump and water malabsorption by the clever experimental design of perfusing the intestine of actively purging cholera patients with a solution that had not only water and sodium, but also glucose as an additional test of the sodium pump in sodium-dependent glucose transport. A near miss again, given that sugar and salt absorption was intact in the actively purging cholera patients, thus rejecting nearly conclusively our hypothesis that the pathogenetic defect was one of salt and water malabsorption based on a damaged ATPase-dependent sodium pump as the target of the vibrio cholera toxin. However, once again there was an important and this time even earthshaking serendipitous outcome. Those cholera patients who were being perfused with the solution of water, salt and glucose got better! Although the diarrhea did not stop, the hydration improved, and Hirschhorn and colleagues were clever enough to realize that they had an intestinal route for rehydration of cholera patients if the solution was right. Thus was born Oral Rehydration Solution, a simple mix of water, salt and sugar, which was then developed both at the Dhaka lab and at the sister lab in Calcutta, and eventually was expanded to all infectious diarrheal diseases, not only cholera. Millions of lives have since been saved.

Returning to the jejunitis story, we do not need to leave the Cholera Laboratory in Dhaka yet. Gordon and U.S. Army co-workers and others had already established that there was an intestinal lesion in the Thai indigenous population, which we can now say was a histologic description of subclinical tropical malabsorption. John Lindenbaum came to the Cholera Lab in the mid-1960s and engaged in a series of studies that established simply and elegantly that expatriates, in this case Peace Corps volunteers in East Pakistan, developed a jejunitis lesion within a half year of their exposure to the countryside, which was associated with mild malabsorption (3), and from which they would recover when they left the contaminated environment, as he and colleagues showed by studying returning Peace Corps volunteers to the United States (8). In parallel, he and co-workers showed that lesions of the indigenous population, Indians and Pakistanis also disappeared.
when they came to the different environment in New York City (9). Thus, tropical jejunitis was an acquired lesion and it was reversible when the person left the apparently offending environment. At the same time, Tom Sheehy of the U.S. Army was calling attention to enteric disease among U.S. troops in Vietnam, of which tropical jejunitis was a significant component (2). Of special interest was the subsequent observation that tropical enteritis was observed within 3 mo of arrival of Special Forces personnel, who tended to live in the countryside, whereas it was absent in those who ate at the Army mess.

The international distribution and functional and nutritional importance of tropical enteritis was examined in the 1972 symposium held under the auspices of the International Committee of the Food and Nutrition Board of the National Academy of Sciences (7). For our purposes here, suffice it to say that wherever this lesion and/or “subclinical” malabsorption was examined in tropical and developing countries, the prevalence was widespread and the functional impact was significant. Interestingly, low grade malabsorption and enteritis were never embraced by either the nutrition or the development community as major concerns, although both were aware that improved hygiene and sanitation would provide many benefits with respect to both nutrition and infection (10). In the year 2002, a third century after 1968, we may observe that tropical sprue has virtually disappeared from reports, and although we have no good documentation or surveillance of the prevalence of tropical jejunitis or enteropathy, it seems that it, too, is disappearing. To attribute that disappearance to the gradual improvement of hygiene and water quality around the world, such as the use of tube wells in Bangladesh (formerly East Pakistan), is tempting, but that attribution would need to depend on a more precise understanding of the pathobiology of tropical sprue and tropical enteritis than we have ever achieved.

**LITERATURE CITED**