REGARDING THE DEFINITION OF TROPICAL SPRUE

The existence of a disorder occurring among the indigenous population of the tropics characterized by diarrhea, weight loss, and manifestations of nutritional deficiencies appears to have been recognized initially in India some 2000 years ago by Caepon, who referred to it as "Grahani Vyadh."

The first description of such a disorder in the medical literature appeared in 1759 in a report from the island of Barbados where it was called "Aphthoides Chronicus" because of the presence of oral lesions. Commencing after 1815, descriptions of an apparently similar disorder originated from other areas of the tropics including India, Southeast Asia, China, Java, and the Philippines. Although the disorder was referred to by a variety of names in these reports, the clinical descriptions were similar in that all recognized gastrointestinal symptoms, glossitis, edema, weight loss, and weakness to be a characteristic part of the condition. Thus, by the time that Manson in China anglicized the Dutch word "sprouw" to sprue to apply to this disorder in 1880, it was generally accepted that the various previously employed terms were actually synonyms for the same condition and, by the turn of the century, the geographic distribution and clinical manifestations of what now is referred to as tropical sprue were well recognized.

Investigations conducted during the first five decades of the present century delimated many of the pathophysiologically aberrations present in tropical sprue. They established the fact that the disorder primarily involves the gastrointestinal tract and that the development of anemia and other nutritional deficiencies are secondary to malabsorption. Morphological abnormalities of villous structure were described as early as 1915, fat and glucose absorption were shown to be impaired, the megaloblastic nature of the anemia was recognized, and reductions in the serum concentrations of various nutrients such as albumin, calcium, and cholesterol were shown to occur. The advent of World War II lent impetus to further work which reemphasized the occasional epidemic nature of tropical sprue and led to the recognition that certain nutritional manifestations of the disease as seen in expatriates in the tropics are related to the duration of illness. Although certain variations from the general pattern were recognized, these were incorporated into subdivisions such as parasprue and, by midcentury, the criterion for the diagnosis of tropical sprue generally was considered to be the presence of the characteristic gastrointestinal manifestations, a megaloblastic anemia, steatorrhea, and other evidence of malabsorption.

The introduction during the past two decades of new techniques has led to a vast increase in our knowledge of tropical sprue. Vitamin assays have defined the pathogenesis of the anemia, peroral biopsy techniques have made intestinal tissue readily available for histological and biochemical evaluation, and the application of isotopic and other techniques have permitted a more precise delineation of the factors responsible for malabsorption of nutrients. This body of information, summarized previously in this journal, and described in detail more recently elsewhere, has made it apparent that our concepts of tropical sprue require further modification, since the application of these techniques has shown that the diag-

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nosis of tropical sprue can no longer be restricted to persons who fulfill the previously defined diagnostic criteria.

The results of recent studies conducted among members of the indigenous population of the tropics, visitors to the tropics, and expatriates who have returned from the tropics to a temperate climate have clearly shown that tropical sprue can be associated with a spectrum of clinical manifestations and laboratory abnormalities, the nature and extent of which are related, in part at least, to the duration of the disease and to the nutritional background of the affected individual.

Although usually present, gastrointestinal symptoms may never occur in some persons with symptomatic tropical sprue, who may present solely because of edema or weakness secondary to anemia.\textsuperscript{12, 14} Glositis, stomatitis, edema, or other manifestations of nutritional deficiencies are not consistently present.\textsuperscript{11, 12}

Megalooblastic anemia has long been considered in Puerto Rico to be a hallmark of tropical sprue and it is probably this historic consideration which accounts for the fact that cases recognized among the indigenous population of that island have been confused mostly with persons with this form of anemia.\textsuperscript{9, 18, 17-19} However, megaloblastic anemia has not been a consistent finding among visitors from temperate zones who have acquired tropical sprue in Puerto Rico\textsuperscript{10} nor among persons from the indigenous population with tropical sprue studied elsewhere in the West Indies\textsuperscript{2, 11} or India.\textsuperscript{1, 12, 19, 22, 23} Studies, conducted among British expatriates who acquired malabsorption in Malaya, have demonstrated clearly that the development of folate and vitamin B\textsubscript{12} deficiency is related to the duration of the disease; nevertheless, in other areas there are patients with long standing illness who still have a normoblastic marrow.\textsuperscript{11, 12, 14}

Since the measurement of the amount of fat excretion in the stools was one of the earliest techniques for the investigation of intestinal function applied to the study of malabsorption, it was natural that this should be considered by some to be a bio-

chemical sine qua non for the diagnosis. It is now apparent, however, that an identical disorder can occur in subjects without steatorrhea but with demonstrable malabsorption of other substances.\textsuperscript{11, 11, 22} Other tests of intestinal absorption using substances such as glucose, xylose, vitamin B\textsubscript{12}, and folic acid also show variable patterns of abnormality in different subjects with tropical sprue.\textsuperscript{1, 12, 24} Therefore, none of these can be used individually as a criterion for defining the disease.

It might have been thought that examination of jejunal biopsy material would be helpful in the diagnosis of tropical sprue; however, in some instances, the appearance of the jejunal mucosa in persons with overt tropical sprue has not differed from that of control subjects from the same region who did not have malabsorption,\textsuperscript{1, 12, 19, 22, 23} and a normal jejunal architecture has been described during the early phase of tropical sprue in some visitors to the tropics.\textsuperscript{25}

Thus, no single clinical manifestation or laboratory abnormality can be construed as diagnostic of tropical sprue in persons who present with symptomatic malabsorption. Treatment with either folic acid or oral antibiotic drugs, or both, results in improvement of the intestinal lesion in many persons who have tropical sprue. However, here again, some individuals have been encountered who do not respond in a characteristic manner. Therapy with folic acid and antimicrobials has not been effective in all persons with tropical sprue treated in the tropics.\textsuperscript{12, 17} The response to prolonged antimicrobial drug therapy appears to be more consistent,\textsuperscript{12, 14, 15, 19, 27} but current information is insufficient to say whether all individuals with tropical sprue experience a uniform response to this form of therapy.

It also is now apparent that morphological abnormalities of the small intestine are not confined to persons in the tropics with symptomatic malabsorption, but that qualitatively identical changes\textsuperscript{28} are often present in members of the indigenous population\textsuperscript{12, 16, 28-32} or visitors to the tropics\textsuperscript{14} who are clinically asymptomatic. The pre-
valence of impaired intestinal function among these individuals is uncertain. The absorption of xylose has been reduced in from one-third to two-thirds of various groups studied in the Caribbean or Asia; the absorption of other nutrients such as fat, folic acid, and vitamin B12, although less extensively investigated, has also been impaired in some instances.

It thus appears that malabsorption in the tropics may be associated with a whole spectrum of clinical and laboratory abnormalities ranging from persons who have overt gastrointestinal symptoms, to those who present solely because of edema or symptoms referable to anemia, to completely asymptomatic individuals who are found to have malabsorption. Whether the intestinal disorder in all of these circumstances represents the result of a single disease process with varying manifestations or whether it is the result of multiple disease processes which produce a uniform intestinal reaction is uncertain and will remain so until the responsible etiological factors are identified.

Most, if not all, of the known causes of intestinal malabsorption found in temperate zones, such as celiac disease, intestinal tuberculosis, anatomical lesions of the intestine, congenital enzyme defects, also occur in the tropics. In addition, certain parasitic infestations which are found either more commonly or exclusively in the tropics, such as giardiasis, strongyloidiasis, and capillariasis, may be responsible for malabsorption. Just as the development of new techniques has shown that the syndrome known in the early decades of this century as nontropical sprue actually includes gluten-induced enteropathy, cystic fibrosis of the pancreas, congenital intestinal enzyme deficiencies, and other disorders, so it would seem likely that the syndrome of tropical sprue may well eventually be delineated into specific disorders. For example, it has been proposed that protein deficiency due to inadequate dietary intake may be responsible for intestinal abnormalities in persons in the tropics. Should this be confirmed, then it would be possible to split off one group, perhaps called “hypoproteinemic enteropathy,” from the syndrome of tropical sprue. An infectious factor appears to be involved in many individuals, such as those who acquire malabsorption shortly after arriving in the tropics or during an epidemic and those who respond to antibiotic therapy; here also, it remains to be determined whether the intestinal lesion in these subjects represents a response to single or multiple infectious agents.

It would seem logical that, until its single or several etiologies are established, tropical sprue should be regarded as a syndrome which occurs among the indigenous population and visitors to certain tropical regions that has variable clinical and laboratory manifestations which are related, in part at least, to the duration of the disorder and to the nutritional reserves of the individual. For the time being, included in this syndrome would be all persons who have malabsorption of two or more unrelated substances for which no etiology can be ascertained.

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