

The Puerto Rico Journal of Public Health and Tropical Medicine (1925-1949): Coverage of Tropical Sprue

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Our current understanding of tropical sprue is that it is a malabsorption syndrome that responds to treatment with folic acid and a broad spectra antibiotic. This realization came only after countless years of research by legions of investigators. Twenty-seven individual studies on various aspects of tropical sprue were published in the *Puerto Rico Journal of Public Health and Tropical Medicine* from 1925 to 1949. This article summarizes significant findings, presented chronologically, and speculates on the direction of future investigations into tropical sprue. [*PR Health Sci J* 2023;42(2):91-101]

Key words: Sprue, Tropical sprue, School of Tropical Medicine, Malabsorption syndromes, Bailey K. Ashford

IN REMEMBRANCE

“This article is dedicated to **Angel Roman Franco**, MD, friend and colleague, who enriched the lives of us who knew him. He is greatly missed.”

This is a mystery story. Indeed, tropical sprue (TS) was an enigma throughout the term of the *Puerto Rican Journal of Public Health and Tropical Medicine (PRJPHTM)*– 1925 to 1949. All the literary elements are present: the case (agonizing deaths due to wasting), a list of suspects (characterization of the culprit), guesses as to the identity of the culprit (theories), the detectives (scientific investigators), and the crime lab (tests and techniques). Like any mystery story, the solution should be found on the last page, but the end of 1949 produced no definitive answer. In fact, even today it is not completely understood, although significant advances have been made. The basic problem of the early investigators was the lack of technology. The real breakthroughs were the development of specific anti-biotics, the isolation and purification of folic acid and vitamin B12, the lack of which had a causative role and the use of endoscopy, all of which were promulgated post -1950. To their credit, scientists formulated structured studies to resolve conditions associated with sprue and laid the groundwork for future advancement. At the turn of the 20th Century, opinion as to the cause was divided with some favoring an infective agent and others favoring the lack of a dietary factor (a toxic factor having been ruled out). However, by the early 1930’s there was almost universal agreement that sprue was a deficiency-associated condition. Nevertheless, by the mid-1940’s the thought was directed back to sprue’s being a nutritional imbalance superimposed on bacterial infection. The following article will document some of the struggles and advances made toward attaining a greater knowledge of TS.

The principal source material appears in Table 1. In the former are listed 27 sprue-related articles which appeared in

Table 1. Sprue-related articles in the Puerto Rican Journal of Public Health and Tropical Medicine, 1925-1949.

Ref#	Vol	Pages	Year	Author(s)	Topic
1.	III	150-161	1927	C Weiss	Review
2.	IV	78-80	1928	BK Ashford	Liver extract
3.	IV	81-83	1928	R West	Liver therapy
4.	IV	212-218	1928	O Costa	Mandry Immunology
5.	IV	219-220	1928	R West	Liver extract
6.	IV	333-343	1929	C Weiss, D Wilkes	Weiss Epidemiology
7.	V	167-175	1929	BK Ashford	Classification
8.	V	263-267	1930	BM Kesten, J Suarez	Skin sensitivity
9.	V	268-277	1930	BK Ashford, EW Lord	Case report
10.	VI	209-216	1930	LG Hernández	Pancreatic juice
11.	VI	310-320	1931	BK Ashford	Monilia
12.	VII	11-22	1931	BK Ashford	Case report
13.	VII	145-161	1931	J Suarez	Hematology
14.	VII	167-201	1931	BK Ashford, JA Pons	Case reports
15.	VII	247-250	1931	BK Ashford	Hematology
16.	VIII	31-33	1932	BK Ashford	Monilia
17.	VIII	419-420	1933	RA Toro	Monilia
18.	XIII	427-459	1937	FM Hanes	Bibliography
19.	XIII	503-521	1938	A Rodríguez Ollerós	Stomach
20.	XIV	157-175	1938	RM Suarez	Case reports
21.	XV	89-100	1939	R Rodríguez Molina	Hematology
22.	XVII	124-128	1941	RS Díaz Y Rivera	Clinical studies Prothrombin
23.	XVII	135-149	1942	R Rodríguez Molina	Case reports
24.	XVII	401-406	1942	RS Díaz Rivera, RM Suarez F Hernández Morales	Clinical studies Histamine
25.	XVIII	314-330	1943	R Rodríguez Molina	Review
26.	XX	257-267	1944	F Hernández Morales	Clinical studies
27.	XXI	79-80	1945	C Kreiss Pratt	Clinical studies Diagnostic aid

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the *PRJPHTM* [Volumes I through IV of the Journal were called *Puerto Rico Review of Public Health and Tropical Medicine*] from 1925 through 1949 and are listed in chronological order showing authors and subject matter. There are 7 articles from the 1920's, 14 from the 1930's and 6 from the 1940's. Two are written in Spanish and the remaining 25 in English. The subject matter includes: 1 bibliography, 1 epidemiology article, 1 immunological article, 1 classification article, 2 reviews, 3 Monilia-related articles, 3 responses to liver extract, 3 organ-related articles (pancreas, stomach, skin), 3 hematologic articles including pernicious anemia, also known as Addison's disease, 4 method articles and 5 case reports. There are 18 authors. All the authors are cited as members of the Puerto Rico School of Tropical Medicine (PRSTM) except for the bibliographer. Predominant was Bailey K. Ashford, whose name appears in almost one third (8/27) of the total publications.

Ashford was a scientist of international renown, and his opinions were highly respected. By the time he reported Puerto Rico's first case of TS in 1907 (28) he was already a national hero having pinpointed a hookworm as the cause of widespread anemia as well as establishing the Anemia Commission which improved living conditions for thousands of islanders. Affiliation with Columbia University was acknowledged in the first 17 articles after which the *PRJPHTM* operated on its own. A brief synopsis of each author's involvement with TS is given in the Appendix. Whenever possible, information included in these 27 articles will be cited preferentially over the same information published elsewhere such as the definition and signs of TS which had been described in hundreds of prior articles.

General notes

Empire expansion, especially in Britain which usurped nations in "tropical" environments (India, Nigeria, Kenya et. al.) and the US, which added the Philippines, Cuba and Puerto Rico as spoils of the Spanish-American war also acquired a passel of endemic diseases which necessitated a greater emphasis on "tropical medicine." For readers interested in the history of tropical medicine in Puerto Rico, attention is directed to the newly published compendium on this topic authored by Mayo Santiago, Rabionet and Roman Franco (29).

Except for the *British Medical Journal*, few scientific studies of tropical medicine were published before 1900. The new Century heralded the advent of specialty journals. The most prominent in Britain were *the Journal of Tropical Medicine* (1898), *the Annals of Tropical Medicine and Parasitology* (1907) and *Transactions of the Royal Society of Tropical Medicine and Hygiene* (1907). In the US, there were the *American Journal of Tropical Medicine and Hygiene* (1903) and the *Journal of Parasitology* (1914) (30). These early journals had societal, school and government sponsorship but the majority had personal sponsorship which consisted of leading scientists providing financial backing and serving as editors (30). The *PRJPHTM* originated as an official bulletin of the Puerto Rico

Health Department and progressed through a series of stages to being a fully bilingual scientific journal. This progression and a detailed presentation of the first journals of tropic medicine have been given by Mayo Santana (31). Consequently, with even more journals added to the list, authors in the early 20th Century would have had no difficulty in finding a journal receptive to their particular interest. Until after World War II, articles were published at the discretion of the editors. Some dates of the initiation for modern peer review are *Nature* in 1973 and *Lancet* in 1977. Articles in the *PRJPHTM* would not have been peer reviewed.

An analogy

The coverage of TS, beginning in 1925, is like starting to read our mystery story at chapter 3. Unlike the journal, sprue did not commence in 1925. The modus operandi presented in this article is to follow the progress in the elucidation of TS from "what was known in 1925" and document year-by-year advances until 1949 when the *PRJPHTM* ceased publication. "What was known in 1925" is presented in chapters 1 and 2.

Chapter 1 (Knowledge of TS prior to 1900)

History of Tropical sprue

Five of the 27 articles provide a brief history of the disease (1,6,18,20,23). The following information was gleaned from these 5 reports. The derivation of sprue was from the Dutch word *sprouw* [Etymologically the word comes from its meaning as metal flow in a runoff in the molding process.]. Reports of a sprue-like illness appear in ancient writings. An illness resembling TS was described in the Indian medical literature between 1600 and 1300 B.C. A possible case of sprue was documented during the reign of Nero in the 2nd Century A.D. Spanish chronicles about the conquest of America contained several accounts, including one in Puerto Rico of a disease resembling sprue. William Hillary (1759) first described the disease in Barbados (B.W.I.) and Sir Patrick Manson (1880) described TS in East Asia as well as including a chapter on TS in his seminal reference work "*Tropical Diseases*" (32). At this same time French clinicians identified a disease they named "Cochin-China diarrhea," which was actually TS.

Description

This treatise begins with a description of the syndrome which quotes Carnegie Brown's 1907 comprehensive review of sprue (33). A general description of a sprue patient is given in the fourth paragraph.

"The usual course of sprue may, broadly speaking, be divided into three periods or phases, each of which has its own characteristic manifestations. They are, first, the prodromal stage — of variable duration, but extending, not infrequently, to five years—during which the lesions are mainly limited to the mouth, tongue, fauces and oesophagus; secondly, the period of gastric and intestinal invasion, of shorter duration, but lasting usually from six months to two years, the chief symptoms of

which are dyspepsia, with a preliminary bilious flux, followed later by characteristic and pathognomonic diarrhea, with marked diminution in the size of the liver ; and thirdly, the period of marasmic toxæmia.”

Brown goes on to write:

“Morbid changes in sprue are those distinctive of a chronic progressive subacute inflammation of definite type, followed by degenerative and destructive changes in the tissues which are chiefly affected, and limited, during the earlier stages of the disorder, to the mouth and pharynx. The inflammation invades in turn, the œsophagus, stomach, and intestines, and its progress is marked by characteristic lesions in all of them.”

And writes, as well, the following:

“Degeneration of the epithelial cells, and the consequent irritable and unsettled condition of the alimentary canal, are necessarily attended by a failure of nutrition, and also by a definite type of anæmia. There is abundant evidence that sprue is more than a mere arrest of nutrition; it is, beyond this, a striking instance of perversion of the absorptive function.”

A more colorful description is from Ashford (28) who writes:

“Imagine a rosy-cheeked, athletic American girl, fresh from one of our great universities. She weighs 135 pounds, is 66 inches tall, and can win set after set of tennis from you. She has come down to teach school for a couple of years in order to learn Spanish. One day she is missing from her classroom. What has happened is that she has had a furious diarrhea following a cake party the night before. But she doesn’t get well. The diarrhea settles down to a steady flux with evil odor movements and a tremendous amount of gas. She gives up tennis and prefers to go home and lie down. A couple of months pass by, and you are shocked to find that she weighs 105 pounds, her rosy cheeks are gone replaced by a sallow, yellow wax-like color. She is suffering from a fiery red, raw tongue, a complete loss of appetite and bloating from intestinal gas. Her nerves are shattered, she is sleepless, and her muscles are sore and aching. She disappears for a couple of months. She is crawling about a mere shadow of her former self. Her weight has descended to 80 pounds, her skin is dark and become pigmented. She informs that now she has a serious anemia with only one-fourth of normal blood values. Before long, she goes North and is not heard of again.”

Classification

There is one article focusing on the classification of TS (7), although the criteria are often mentioned as cited in the next section. Being able to distinguish a specific disease from a multitude of diseases with related symptoms will rely on the diagnostic

criteria developed only after years of careful study. Prior to identifying these criteria, TS cases were often mistaken for malaria, wasting diseases such as dysentery, syphilis, tuberculosis, pernicious anemia and celiac disease, and even being the result of an ill-balanced diet (34). In addition, it was theorized, only to be disproven, that TS was a transmittable disease (23).

Diagnostic description

Twelve of the 27 articles mention diagnostic criteria (1,4,6,7,9,12,14,20,21,23,25). These criteria apply to TS no matter the era. Figure 1, showing the symptoms and signs of sprue is taken from Rodriguez Molina (23). Currently, the D-xylose absorption test is useful in the diagnosis of TS (35).

Methodology

Methods that were used prior to 1900 and still being used by 1925 are described in the book by Brown (33). In those days most chemical and biological assays involved many steps, over a lengthy time period. To illustrate this point, an example is the procedure for the determination of serum calcium (36). Today, a basic metabolic panel can provide a value (along with 7 other important metabolites) within 1 hour. Chemists of the 1920’s had no auto-analyzers, so reliance was put on manual accuracy. In this case, blood samples were collected from TS patients and control “volunteers” all of whom were recruits from the 65th Infantry regiment, US Army (an odd choice but less curious when you recall that one of the article’s authors was a lieutenant colonel). Two mL of boiled water and 1 mL of a 4% ammonium oxalate solution are added to 2 mL serum and allowed to stand for 30 minutes to 1 hour, at that point samples are centrifuged at 2000 rpm for 10 minutes. The supernatant is poured off and the inverted tube is placed on filter paper to dry for 5 minutes.

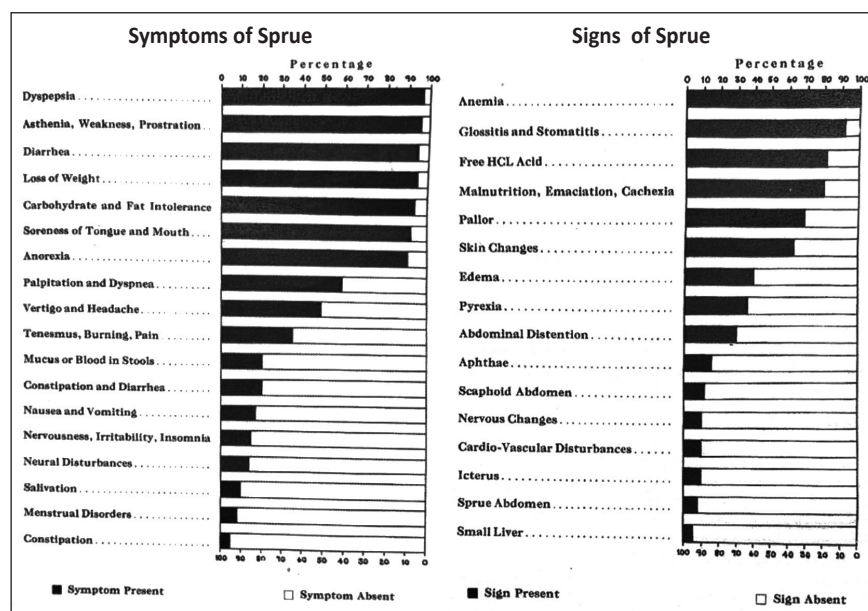


Figure 1. Relative frequency of symptoms and signs of Tropical sprue (23).

The precipitate is washed with 3 mL of dilute ammonia water. The resulting suspension is centrifuged and drained, as before and 2 mL of normal sulfuric acid are added to the precipitate. The tube and its contents are now placed in a water-bath at boiling temperature and the sulfuric acid is titrated with a 0.01 N potassium permanganate solution. The verification of the titration method for blood calcium was a gravimetric measure.

Some tests were markedly accurate such as blood counts, but many were hampered by the lack of specificity and unreliable standards. Figure 2 shows the “state of the art” for the visualization of damage to the small intestine of a TS patient in 1900 and of a TS patient taken in 2006 (33, 37). Modern technology is able to depict the increased caliber and thickening of the mucosal folds. An endoscopic evaluation can show changes in the duodenum and jejunum involving absent duodenal folds and the presence of scalloped folds and mucosal fissures (38).

Case reports

Case reports appear in 5 of the 27 principal articles (9, 12, 14, 20, 23). They are also included in this section because the basic case report of modern medicine, consisting of patient history, the results of any laboratory tests ordered, a diagnosis, the treatment and outcome write-ups remains relatively unchanged. Still, within these parameters differences between now and then are most apparent in the following: 1. the manner in which volunteer patients were selected- Ashford’s use of 78 healthy inmates from the Boy’s Charity School of San Juan as controls for a mycology study of TS was not regarded as irregular (39); 2. the improvement of laboratory tests and treatments which became evident with advances in endoscopy and dietary composition and 3. outcome write-ups were often more subjective, based on whether the patient “felt better or not.” If clinical tests matched established norms, the case was credited as a success although previous problems might resurface at a later date which was common in TS. In all, several thousand patients with varying degrees of TS were reported in the *PRJPHTM* from 1925 through 1949.

Chapter 2 (Knowledge of TS 1901-1924)

At this time, etiological factor(s) had not yet been determined. Manson stated in his classic book, *Tropical Diseases*, published in 1898: “Personally, I incline to regard sprue as an expression of exhaustion of the glandular structures subserving digestion, the result of over-stimulation by certain meteorological conditions which are found in tropical countries” (32). (In other words, climatic factors not found in northern countries). However, by 1920’s the majority of investigators favored a monilial infection. *Monilia*, a former name for *Candida*, is a genus of imperfect fungi of the family *Moniliaceae*. One group of investigators favored *Monilia albicans*, which had been shown to be causative of both oral and vaginal thrush, conditions which resulted in an overgrowth of yeast (40). The other group, headed by Ashford, favored a newly isolated strain, *Monilia psilosis* [Ashford was held in such high esteem that fellow investigators from Bombay, India used the name “*Monilia ashfordi*” (41). Late in his career, Ashford conceded that *M. psilosis*, *M. albicans*, et al. might be one and the same yeast budding-fungus (11).]. This fungus was a major focus of investigation. Indeed, in 3 of the 27 articles listed in Table 1 (11,16,17) *Monilia* is the central point. Chronologically, the story of *Monilia* overlaps this chapter and the next but for completeness, all will be covered here. In 1915, Ashford isolated a strain of the fungus from scraping of the enflamed tongue of 4 sprue cases (42). This observation was reproduced in other labs which led Ashford to make the claim that *Monilia psilosis* infection was **the** cause of TS (43). However, shortly afterward, other investigators, including Manson, at the prestigious London School of Tropical Medicine, and even some colleagues in Puerto Rico felt that the evidence was weak (11). Ashford, a person who did not take criticism lightly, pulled no stops in validating his argument. In the next few years, Ashford published articles on immunology, complement fixation and agglutination tests, feeding experiments on monkeys and vaccination studies. The vaccine consisted of a 1% suspension of killed *Monilia psilosis* cells and was given in weekly injections for about two months to “volunteer” sprue patients (2). [Related to vaccines, an amusing anecdote was recounted in his autobiography (28).

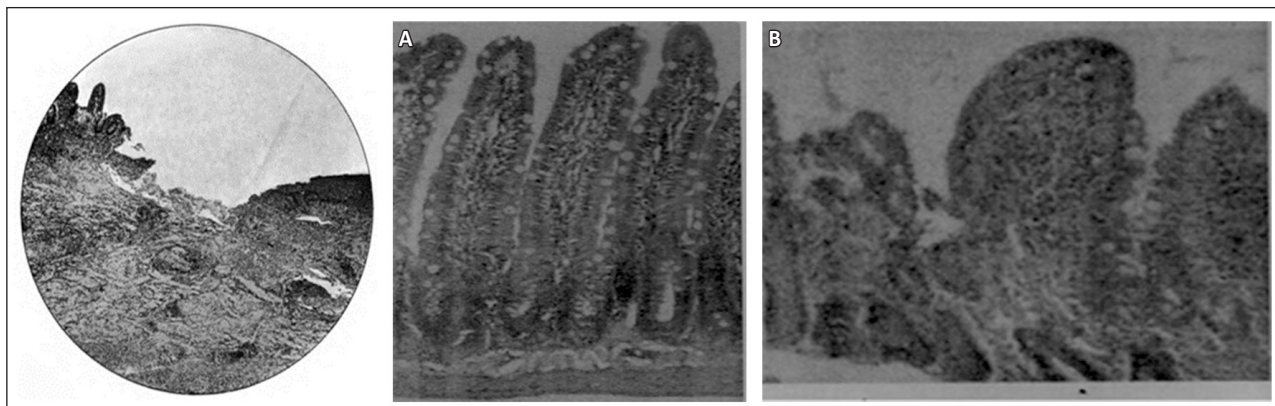


Figure 2. Left - Image of small bowel taken from autopsy of sprue patient circa 1900 showing mucosal atrophy and dense infiltration of submucosa by embryonic cell growth (33). A: Small bowel of normal patient Bottom: Small bowel of sprue patient showing villus atrophy, crypt elongation and inflammatory infiltration of the lamina propria. B: Small bowel mucosal biopsy taken in 2006 (37).

On a visit to Cuba, he was approached by an eccentric landowner suffering from sprue (her home was a refuge for monkeys or apes, Ashford uses both terms) who insisted upon being vaccinated. He did this but when the monkeys were turned loose, he made it known that they had to be caged or he would leave. Reluctantly, she chose Ashford. He also explained that the vaccine was only in the initial stage of development and was not ready to be recommended as a treatment. It never was.]. In Ashford's time, informed consent was not considered an issue although today, these studies would be deemed unethical.

Additionally, while his name does not appear as an author on any of the publications that followed, it is probably no coincidence that his associates chose *Monilia psilosis* as an organism of choice to perform dermatologic (8), immunologic (4) and allergenic (8) studies. However, even after all this work, to Ashford's chagrin, by the late 1920's conclusive evidence could not be obtained so he reluctantly accepted the fact that *Monilia psilosis* was not **the** causative factor although he maintained, even until his death, that it could be **a** causative factor.

Diet

The importance of diet throughout the history of TS cannot be over-estimated. Ten of the 20 chapters of Brown's tome dealt with dietary composition. Eleven of the 27 articles in the PRJPHTM mention diet (1, 2, 3, 5, 6, 9, 12, 13, 20, 23, 25). The standard diet of Puerto Ricans was marginal at best – a high percentage carbohydrate, little meat and inadequate ingestion of Vitamin A, calcium and phosphorous (20). Nutritional therapy was showing great promise, having already ameliorated age-old scourges such as scurvy and beriberi. Consequently, researchers at this time formulated every sort of possible diet from those having a very simple composition, like milk alone or milk and bananas to complex compositions like meat and fruit or milk, meat and fruit plus vegetables with the hope that by chance or luck the formulation might provide the curative substance specific for the particular condition under study. These deficient factors were coined "vitamines" in 1912 by Casimir Funk although the final "e" was eliminated when it was discovered that not all had amine groups (44).

In a publication from 1916 (45), Ashford said of TS: "In the absence of specific treatment, supervision of the diet appears to be the only available weapon we can turn against the disease." This said, however, a hallmark of Ashford's work was the belief that TS was a nutritional imbalance triggered by bacterial infection (46). The TS diet of 1916 has been recently critiqued and found to be inadequate in an essential vitamin, namely B₁₂ (47).

It is curious to note that TS investigators had strong beliefs about the curative power of particular foods. In Ashford's view, for example, bananas were superior in nutritional benefit (45). Brown, on the other hand, favored papayas, calling them "the best of all fruits for the dietetic treatment of intestinal disease in the tropics" (33). They both, however, gave thumbs down to alligator pears (avocados).

Table 2. Sprue diet recommended by Ashford (9).

Meal	Content	kcal	%fat	%protein	Folate (ug)	B ₁₂ (ug)
Bkfst	2 poached eggs + coffee + milk + banana	434	29	18	59	2
Lunch	½ steak, broiled + vegetable salad	977	47	29	131	5
PM snack	Milk	55	49	22	5	0
Dinner	Same as lunch + gelatine	1023	47	29	131	5
Bedtime	Milk + orange	102	24	11	43	0
Total		2591	44	26	369	12
*RDA		2500	25-35	10-30	400	2

*Recommended dietary allowance

Chapter 3 (Knowledge of TS 1925-1949)

Ashford continued formulating eating plans finally settling on the menu presented in Table 2, which shows food ingredients and chemical composition.

Caloric content satisfies the Recommended Dietary Allowance. Folate and vitamin B₁₂ which were at adequate levels, are vital ingredients although Ashford did not know it at the time. The role of folate in the treatment of anemia was not recognized until 1931 (48) after which folate was an essential component of all "sprue diets." Ashford's diet was used in all of the 11 articles cited above with the exception of that listed in reference 13 which used the Minot-Murphy diet.

Founding of the Institute of Tropical Medicine

In 1926, an important event occurred in the advancement of TS research in Puerto Rico. The lifelong dream of Ashford -the establishment of an institute of tropical medicine, which would evolve into the Puerto Rico School of Medicine, was realized. The history of the institution can be found in a series of articles recently published in the *Puerto Rican Health Sciences Journal* (31, 49-52).

Liver extract

In this same year, 1926, there also appeared an article that had profound influence on the etiology, treatment and treatment outcome of TS (53). This was the nutrition classic by Boston researchers, George Minot and William Murphy "Treatment of pernicious anemia by a special diet" which would earn them (along with George Whipple) the 1934 Nobel Prize for Physiology or Medicine. Their summary of the article is as follows:

"The dietetic treatment of pernicious anemia is of more importance than hitherto generally recognized. Forty-five patients with pernicious anemia took a special diet for 4 months to two years. This diet was composed especially of foods, rich in complete proteins and iron, particularly liver and containing an abundance of fresh fruits and vegetables and relatively low in fat. Following the diet, all patients showed a prompt, rapid and distinct remission of their anemias" (53).

It should be mentioned that prior to this study, the pancreas was considered as being implicated in the etiology of TS. An absence of pancreatic secretion had been noted in TS patients (10). However, a pancreatic extract had no curative effect (54).

The success of the Minot-Murphy diet was not lost on investigators of TS in which ailment, a pernicious-like anemia develops as the condition worsened. If the diet was successful for pernicious anemia, why not for TS? Publications about TS consequently burgeoned, reaching a maximum of almost 150 per year in the early 1930's (12-15, 55). The key factor in the Minot-Murphy diet was recognized to be something in liver. This substance, when used for pernicious anemia, induced within a few days a veritable "shower of reticulocytes" (immature red blood cells) followed by marked and rapid rise in both the hemoglobin and red cell count (56). This phenomenon did not occur in other types of anemia. The substance, which proved to be Vitamin B₁₂, was not isolated until 1948 (57). An important consideration is that if liver extract was to be used by labs around the world access to a standard preparation was required. This was accomplished by Eli Lilly Pharmaceuticals which formulated a "liver extract powder No. 343" sanctioned by the Committee on Pernicious Anemia of the Harvard Medical School (3). Figure 3 shows the contents and dosing schedule.

This extract was successfully evaluated in 3 of the 27 articles used as primary reference (2,3,5) including Ashford, who considered the unidentified substance to be a "hormone" (7).

Hematology

The related principal topic, hematology (pernicious anemia), appears in 3 of the 27 articles (13, 15, 22). When combined with an appropriate "sprue diet," results using the extract were almost always positive. In unsuccessful cases, inadequate diet, or non-compliance in terms of use of the extract might have been the reason. Although medical visits were often gratis, patients needed to pay for the extract. Considering that the wages in the early 1920's were 35¢ per day at coffee plantations and 75¢ per day for tobacco workers, coupled with poor economic

policies much of the population suffered severe financial stress (46). [During World War I (called the Great War at the time), demand for sugar increased and prices skyrocketed. The government encouraged growers of vegetables, tobacco and coffee to convert to cane. Unfortunately, the end of the war saw the sugar market go "bust" and growers were stuck with the resulting lack of income and food supplies.].

Epidemiology

Epidemiology appears in reference (6) in Table 1. This study was made in connection with immunological investigations of sprue in Puerto Rico. Data were obtained from the Bureau of Vital Statistics of the Puerto Rico Department of Health from July 1924 through December 1927. In this period of time there were 322 recorded deaths from TS, an average of 92 per year.

Figure 4 shows a map of Puerto Rico with the circled areas representing the locations of confirmed deaths from TS. The population was about 1.4 million and the results were corrected using total inhabitants. Noteworthy are the following:

1. Coastal towns exhibited more cases than did those in the interior of the island [Most of the 350 practicing physicians were concentrated in larger coastal towns so causes of death for inhabitants of the interior of the island, where there was one doctor for every 10,000 persons, could not be accurately certified (6).].

2. Towns along the southern coast had the most cases with Ponce being the highest.

3. Urban areas had more cases than rural areas did, confirming Ashford's observation, made earlier that TS is a disease of the city (56). The authors attributed climate and elevation (hotter in the south meaning greater risk with the mountain towns, at 500 to 3000 feet above sea level having lower risk) as possible reasons for differences. It was also determined that neither the previous diseases of the patients nor parasitic infection were factors. Females, Black and older persons were more susceptible than were males, Whites and younger persons and island-born and non-island born patients shared the same risk. It must be remembered that at this time,

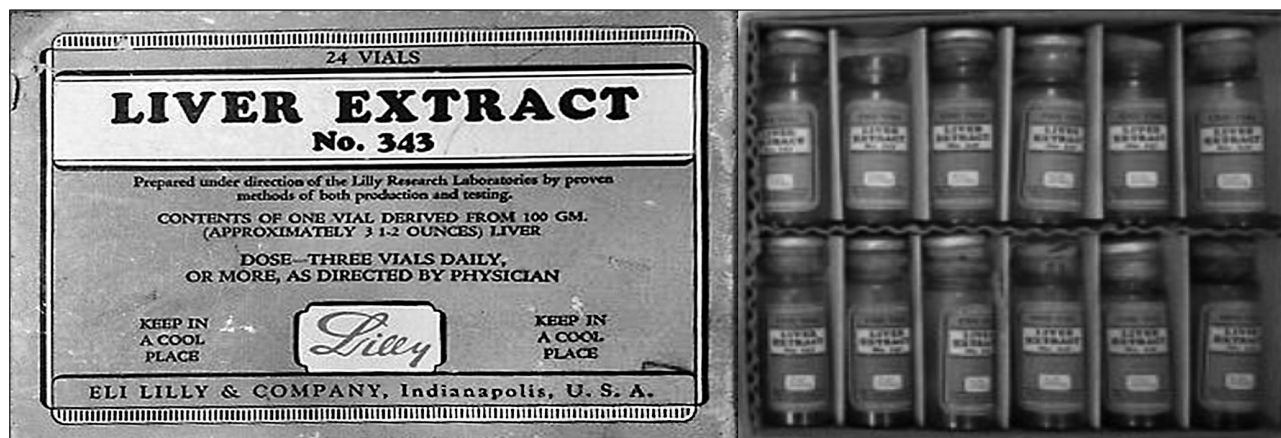


Figure 3. Eli Lilly Liver Extract No. 343 (3). The box contained 24 vials and the dose was 3 vials/day.

Puerto Rico Department of Health arranged for the cooperation of medical specialists conversant with the disease, and for laboratory space and other accommodations. A final report was issued in 1959 (62).

Clinical studies

Four of these studies are included in the 27 principal articles (22, 24, 26, 27). This category might as well have been labeled miscellaneous since it contains a pot-pourri of topics related to TS. The results are summarized in table 3.

Table 3. Clinical Studies of TS and Results

Ref#	Subject matter	Study group	Finding
22	Prothrombin Time (PT)	30 TS patients	Although all patients had severe TS, only 9 had prolonged PT
24	Effect of histamine on the glucose tolerance test	17 TS patients	Failure to produce a reaction with histamine due to low dietary carbohydrate
26	Gasterology	36 TS patients	Atrophic changes occurred due to absence of intrinsic factor
27	Diagnostic aid	TS patients # not given	The sprue rectum presents a definite disease pattern

The Institute remains active

It should be recognized that the *PRJPHTM* was not the only journal publishing articles from the school. In fact, the number of publications of TS authored by researchers at the Institute appearing in offshore journals greatly exceeded the 27 principal articles listed in Table 1. This was especially true for the 1940's when the School of Tropical Medicine was a hotbed of publications on folate and vitamin B₁₂ in relation to TS (63-69).

Ts-Still a problem in parts of the world

The end of the 1940's signaled the termination of the *PRJPHTM's* publication however, TS has persisted and while virtually non-existent in Puerto Rico today, (Personal communication from Esther Torres, MD, University of Puerto Rico, Medical Sciences Campus, Department of Medicine) in other parts of the Caribbean, as well as Northern South America, South Africa, India and South Asia it remains endemic (70-71). Fortunately, In these locations, the morbidity and mortality associated with TS are low. Nevertheless, if acute diarrheal illness occurs, the severe electrolyte abnormalities and dehydration may lead to adverse outcomes (72).

Epilogue

Since the objective of this article is limited to documenting TS-related publications appearing in the *PRJPHTM*, discoveries after its demise cannot be extensively covered. However, so as not to leave the reader in suspense, new findings as to the etiology of TS are available including contributions from investigators from Puerto Rico, whose names appear in references 73-78. Readers

are also encouraged to peruse the content of the XXXII Bailey K. Ashford Memorial Conference which presents a comprehensive review of TS and Ashford's contributions from the standpoint of a clinician (79).

As it turned out, Ashford's original prediction of an infectious cause was correct (46). Researchers now implicate an enterotoxin as the triggering event. However, the initial stimulus, be it dietary, environmental, internal, something to do with the season or even a genetic component, is yet to be established.

To conclude, although progress in the understanding of TS has been painstakingly slow, the emergence of the microbiome and microbiota could shed new light on the disease. Already, with irritable bowel syndrome, a functional disorder, multiple groups have independently reported gut microbiota alterations in patients. The interaction of the microbiome with diet, antibiotics, and enteric infections, all of which may be involved, is consistent with the hypothesis that microbiome alterations could activate or perpetuate pathophysiologic mechanisms in the syndrome (80). Perhaps, the last page of the mystery of TS will finally reveal the disease's true identity.

Resumen

Actualmente entendemos que el esprúe tropical, es un síndrome de mala absorción que responde a tratamientos de ácido fólico y antibióticos de amplio espectro. Esta determinación se llevó a cabo luego de un sinnúmero de años de estudios realizados por una legión de investigadores. Entre los años 1925-1949, se publicaron veintisiete estudios diferentes en el *Puerto Rico Journal of Public Health and Tropical Medicine*, la revista oficial de la Escuela de Medicina Tropical, sobre el esprúe tropical. Esta artículo resume descubrimientos significativos, presentados de una manera cronológica y especula la dirección de futuras investigaciones sobre el esprúe tropical.

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Appendix

Authors

The Institute of Tropical Medicine is frequently mentioned below and so is abbreviated "ITM."

Bailey K. Ashford, MD, Lieutenant Colonel of the Medical Corps. From 1907 until 1935, Ashford was the acknowledged leader of TS research in Puerto Rico. He was dedicated to the betterment of health of all Puerto Ricans, but he had a special affinity for the "jibaros" (country laborers) and admired their innate dignity. Openness was a hallmark of Ashford's concept

of medicine, he gained the confidence of his patients by offering a reasonable explanation of the advised treatment. His accomplishments are aptly described in the article but of equal importance was his mentorship to the next generation of investigators of TS.

Oscar Costa Mandry, MD. "The Father of Medical Technology in Puerto Rico"; his lifetime achievements in the tropics are revealed in the context of his influential role in the ITM and his clear visionary perspective for the creation of the University of Puerto Rico School of Medicine. With his unique and diverse contributions for more than 40 years in the fields of clinical laboratory medicine, public health and medical education, and as an insightful historian, he dramatically influenced and reshaped the Puerto Rican medical and social landscape for generations to come (81).

Rurico S. Diaz Rivera, MD. His only publications in TS were about laboratory experiments in the early 1940's. He performed cardiologic studies in Louisville, KY in the late 40's. He returned to the ITM and was active until the 60's. His research topics of interest were schistosomiasis, leptospirosis, and a wide range of blood disorders. Apart from the Institute, he collaborated with several groups working in clinical medicine.

Frederick M. Hanes, MD. He was graduated from The University of North Carolina in 1903 and was awarded his M.D. degree from Johns Hopkins in 1908. He served in World War I becoming a lieutenant colonel, and serving in France as commanding officer at Base Hospital 65 where he became a friend of Ashford. In 1933 he was named as head of the Department of Medicine at Duke University, Durham, North Carolina, where he taught and conducted research in pathology and neurology. He was also a bibliophile which is probably the reason he was chosen as the executor of Ashford's papers and the author of the posthumous tribute detailed in reference 18.

Luis G. Hernandez. He was an instructor in chemistry and performed laboratory analyses of blood samples for research groups at the PRSTM. He was Ashford's chemist for the serum calcium determination that was described in the methodology section of this article (36).

Federico Hernandez Morales, MD. His lengthy career at the ITM spanned 5 decades (mid 1940's until the early 1980's). He contributed valuable information on TS with results from gastroscopic and recto sigmoidoscopic examinations and with Suarez Calderon in studies with folate. However, his best-known work was in schistosomiasis. He also partnered with various research groups in other areas of parasitology.

Beatrice M. Kasten, MD. She is identified, along with Jenaro Suarez, as having studied the effect of *Monilia* on skin reactions to foods. She was active in dermatological investigations in the 1940's and 50's from her base at the Columbia University Presbyterian Hospital. She had the distinction of being the first woman named to the American Dermatology Association (1951).

Caroline Kreiss Pratt, MD. She was a member of Dr. Hernandez-Morales's group in the mid 1940's with which she was involved in the development of diagnostic tests for TS and

schistosomiasis. Later, she was affiliated with the group of Dr. Suarez and his work with folic acid and TS.

Everett W. Lord, PhD. He was a teacher and later Dean of the College of Business Administration at Boston University. While teaching, he would encourage his students to travel to expose themselves to foreign ideas and cultures. He also advocated for the study of Spanish and Spanish literature in schools. Lord's connection with TS was as a patient of Ashford. He authored his experience from the time he acquired the condition (sometime between 1902 and 1908 when he served as Puerto Rico's Assistant Commissioner of Education) until all the symptoms of sprue disappeared in 1929.

Juan A. Pons, MD. He was Puerto Rico's Secretary of Health in the late 1940's. He received his MD at Sidney Kimmel Medical College - Thomas Jefferson University, Philadelphia, Pennsylvania. Pons published many articles covering health-related issues in the *Boletin de la Asociacion Medica de Puerto Rico* in the 1940's through the 50's as well as being active in the establishment of the University of Puerto Rico School of Medicine. Early in his career he served as medical superintendent at the ITM where he collaborated with Ashford in the preparation of case reports of TS.

Rafael Rodriguez Molina, MD. He maintained an interest in TS research for a 20-year period (mid 40's through mid-60's). He was a member of the Army's 1950's panel investigating TS in Puerto Rico. However, later in his career his interest turned to schistosomiasis and he partnered with Jose Oliver Gonzalez to develop the Circumoval Precipitin test, an inexpensive immunologic assay still in use today.

Angel Rodriguez Ollerros, MD. His contribution to TS was made with an early publication (1938) when he had joint affiliation with the University of Madrid and the ITM. His extensive career, in which he specialized in all aspects of gastrology extended to the 1970's. He collaborated with several groups at the PRSTM and the University hospitals.

Jenaro Suarez, MD. He is identified, along with Beatrice Kesten, as having studied the effect of *Monilia* on skin reactions to foods.

Ramon Suarez Calderon, MD. He was a scientist, cardiologist, educator and hematologist. He studied medicine at the Medical College of Virginia. In 1928 he was named medical director of San Juan's Municipal Hospital and faculty member of the ITM, where he worked with Dr. Ashford. Upon the recommendation of Ashford, the American College of Physicians granted him a fellowship, which enabled him to continue Ashford's work on and investigation into anemia after the latter's death. In 1940, he was named director of internal medicine of the ITM. In 1945, he published his findings on the effective treatment of TS. He was also a member of the Army's 1950's panel to study TS in Puerto Rico.

Rafael Toro. He was identified as a member in the Department of Histology at the University of Puerto Rico.

Charles Weiss, MD, Assistant Professor He performed studies of skin reactions to typical foods in TS patients. He was also interested in immunology and the etiology of TS. Together with his wife, Dorothy Wilkes Weiss, he published the first epidemiologic study of TS in Puerto Rico.

Randolf West, MD. One of the leading authorities on pernicious anemia, he conducted pioneer studies to the cause and cure of this disease. In 1948 Dr. West demonstrated for the first time that vitamin B-1 caused prompt alleviation of the disease's manifestations. He was a member of the Department of Internal Medicine at Columbia University College of Physicians and Surgeons. His work with liver extract was performed with TS patients at the Presbyterian Hospital of Columbia University in 1928.

Dorothy Wilkes Weiss, MD. She teamed with her husband, Charles Weiss, to write the epidemiology study of TS. Her affiliation with the Presbyterian Hospital made it possible for her to collect data on the classifications of 85 sprue patients.