6. This monilia is not only productive of mycotic septicemia in small laboratory animals injected with virulent culture but will produce severe and intractable mycotic ulcers in their tissues when they are relatively immunized to the extent of preventing a mycotic septicemia.

THE OCCURRENCE OF SPRUE IN THE UNITED STATES.\(^1\)

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Tropical sprue, or psilosis, was probably first referred to in American literature in the writings of Dr. John Brickell, a Dublin physician, who was an emissary of the Crown to the Cherokee Indians early in the eighteenth century. In his report he discusses the diseases of the colony of North Carolina, and in addition to yaws he mentions “white flux,” which, in all probability, was the disease described in 1776 by Hillary, in Barbadoes, as sprue. The identity of this West Indian sprue was never questioned by Sir Patrick Manson, though Carnegie Brown still contends that true sprue is limited in its distribution to tropical and subtropical eastern Asia. Fortunately for us many of our medical men, especially of the Army Medical Corps, became familiar with true sprue in the Philippines, and not only brought back with them this intimate acquaintance, but were able to identify the disease known as sprue in Porto Rico as true sprue of the East. In recent years many observers have suspected that sprue existed in the United States, but only in the last decade has anyone had the temerity to actually make the diagnosis except in cases invalided from the tropics. The return of missionaries from China and Ceylon suffering from sprue has given us many opportunities to become familiar with true Eastern sprue and to compare it with the milder type of sprue in the Southern States.

In 1905 St. J. B. Graham,\(^5\) of Savannah, reported four cases of sprue which had originated in Georgia. This observation was based on experience in the Philippines, and the correctness of the diagnosis can hardly be questioned.

In 1907 H. F. Harris,\(^6\) of Atlanta, reported a number of cases of sprue. Later in that same year Searcy, of Alabama, reported

\(^{1}\) Presented at the meeting of the Association of American Physicians, in Washington, May 13, 1915.


\(^{3}\) Tropical Diseases.


\(^{5}\) Georgia Practitioner, August 15, 1905, xi.

\(^{6}\) Tropical Sprue, Report of the Georgia State Board of Health, 1907.
the existence of pellagra, and Harris concluded that he had confused
the two diseases; but a perusal of his careful report will convince
anyone that at least some of his cases were sprue, and it is not
improbable that his cases of pellagra were complicated by sprue.
In a recent personal communication, Dr. Harris says there exist
in Georgia cases which exactly correspond to tropical sprue of the
East.

In 1909 R. Hessler,7 of Logansport, Indiana, published an article
on sprue, but his experience seems to have been limited to cases
invalided from the tropics. In 1911 J. K. Simon,8 of New Orleans,
reported a probable case of sprue.

In 19129 I called attention to the existence of sprue in the United
States in connection with the recognition of pellagra. The two
diseases are greatly confused, for reasons to be mentioned later.

At the last session of the American Medical Association, Hiatt
and Allan10 reported a number of cases of true sprue. Some of the
cases were invalided from Porto Rico, but in one instance, at least,
the case originated in North Carolina and the victim had never
been out of the state. The most valuable feature of this article
is the comparison of the disease brought in from the tropics and the
disease as it occurs in this country. These observers have had the
opportunity to study the disease from the two sources, and their
conclusions are most important in settling this disputed point.

At the School of Tropical Medicine of Tulane University no case
has yet been observed which originated in the United States, though
quite a number from the West Indies have been studied. Notably
among the latter is an unpublished case of Dr. Allan Eustis, with an
autopsy by Dr. C. W. Duval. The case came from the Charity
Hospital in New Orleans.

The place occupied by tropical sprue in medicine at this time is
most unsettled. Manson, Cantile, Begg, P. H. Bahr, and many
others, especially of the English observers, count it a definite dis-
 ease entity, while W. E. Musgrave and T. W. Jackson consider it
a condition or state which may occur in conjunction with or as a
complication of many of the diarrheal diseases of warm climates.
This latter position is chiefly justified by the great variability in the
descriptions of the various writers. Any condition attended with
stomatitis and diarrhea has at one time or another been diagnosed
sprue. Such a state of things is most unfortunate, and will probably
not be corrected until the causative agent of sprue is definitely
determined. Faulty use of synonyms has added greatly to the
unsettled place of sprue in medicine. This is well illustrated in the
use of hill diarrhea as a synonym when a number of observers are

quite emphatic that this disease and sprue are not related in any sense. Manson gives in his list of the synonyms of sprue, Cochin-China diarrhea, while Dr. C. W. Stiles, in a personal communication, says that medical zoologists understand by this term an infection with the Strongyloides stercoralis. This infection was found by Dr. Stiles in a number of the Southern States, with a distribution almost identical with that of uncinariasis.

Leonard Rogers, in discussing the results obtained by him in the treatment of sprue in Calcutta with emetin and a streptococcal vaccine, remarks that the vaccine effect was quite striking, and in explaining it adds, "We should bear in mind that sprue is a purely clinical term, and there may be more than one causative agent, just as in the case of dysentery."

The term sprue has been adopted in the nomenclature of diseases of the Royal College of Physicians. The word was borrowed by Manson from the Dutch word "spruw," which was used in Java to designate the disease. If the original description of Manson is followed closely there need hardly arise confusion from the use of the term. Unfortunately the word has been so loosely used that it has tended to justify the position of those who contend that there is no such disease.

W. E. Musgrave proves one of the most convincing advocates of the view that sprue is merely a condition or state which may occur in various intestinal infections. In spite of this in one of his cases no parasitic cause was found, and the case must be regarded as sprue.

Mayo Robson found that in many cases in which the diagnosis of sprue had been made, the condition was really a pancreatic disturbance of an inflammatory type, and that in other cases pancreatic involvement formed an important complication. In this connection it is interesting to note that Musgrave in one case noted that the pancreas was small and presented a dark, muddy appearance, but without areas of hemorrhage or necrosis. In another of his cases the pancreas was pale and firm. In Eustis's case the autopsy notes by Duval mention a resistance on cutting indicative of interstitial changes of the pancreas. It seems probable that some cases of chronic pancreatitis have been confused with sprue or that in sprue the pancreas plays an important role. It is obvious that much study is needed to clear up the question of the possible relationship of the pancreas to sprue, and that this work must be along the lines of histological study of the pancreas and of pancreatic functional tests.

According to the original description of sprue by Manson there

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11 Two Cases of Sprue Treated by Mouth Streptococcal Vaccines and Emelin Hydrochloride Hypodermically. Lancet. June 6, 1914.
12 Sprue, or Psiloris, in Manila. Amer. Med.. March 8, 1902.
is a definite symptomatology which should save much of the present unnecessary confusion. It is a chronic disease occurring in the tropics and in certain subtropical sections which is characterized chiefly by a peculiar type of diarrhea, by stomatitis, by decrease in the size of the liver, and by marked secondary anemia. There is a tendency to frequent recurrences and the downward course. The diarrhea occurs chiefly in the morning hours, and is unattended by tenesmus, blood, or mucus. The movements are semifluid, though at times more nearly liquid, acid in reaction, and contain much gas. The odor is regarded as peculiarly foul. The color is light, due to a colorless reduction product of hydrobilirubin known as leukobilirubin. In addition to this the large amount of fat in the stool contributes to the light color. The size of the stool is a notable point, one which was emphasized by the late J. H. Musser as a valuable sign in pancreatic disease. In addition to the failure in the absorption of fats it is generally claimed there is a defective carbohydrate digestion. P. H. Bahr found in his Ceylon cases that the fat absorption varied from 70 to 90 per cent., and that there was a complete absence of all pancreatic ferments. In a case of sprue from Porto Rico, Pratt and Spooner found in addition to the intestinal disturbance pancreatic insufficiency which was indicated by the Einhorn-Schmidt thymus test and the Sahli glutoid capsule. The absorption test showed a fat loss of 45 per cent. and a nitrogen loss of 15 per cent. Though the stools were light in color there was a definite reaction for hydrobilirubin by the Schmidt test. The stools were yellow and voluminous, and contained many oil droplets as well as crystals and flakes of fat. It will be noted that these observers found a much greater fat loss than did Bahr. In a recent personal communication, Dr. Pratt mentions a case of sprue without pancreatic insufficiency in which the fat loss was found to be 59 per cent. He thinks that in this case the intestinal lesion is probably responsible for the condition.

The reduction in the size of the liver is not distinctive of sprue, as it occurs in other like conditions, as, for example, pellagra. It is the result of the general condition of malnutrition. Likewise, the anemia and marked prostration are of no particular significance from the diagnostic standpoint.

Sir Lauder Brunton makes small mention of the shrinkage of the liver or the type of diarrhea, but lays particular stress on the aphthous stomatitis. Unfortunately, there is as much diversity in the description of the mouth symptoms as of the character of the feces. The original account of Manson is the most accurate, and should be followed. He recognizes definite stages through which the inflammatory process passes. In the beginning there is simple

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hyperemia, which is followed by denudation of the epithelium, and this, in turn, is followed by the formation of minute herpetic vesicles which occur singly or in groups, and are surrounded by inflammatory areoles. The vesicles rupture, leaving small, superficial erosions which are very painful. Congestion and swelling of the fungiform papillae, particularly about the tip and edges of the tongue as well as superficial cracks on the dorsum, are also mentioned. From this account of Munson the various writers have departed in varying degree. Most writers are content if there is glossitis or esophagitis to pass over the further consideration of the degree or kind of process and count it a positive symptom. Because of this lack of accuracy there is great confusion with a number of conditions, but chiefly with pellagra. It is to be recalled that in pellagra, as a rule, there does not occur definite ulceration, though Crombie's molar ulcer has been noted by H. F. Harris. There is no reference in sprue literature to salivation, which is so conspicuous a symptom in pellagra. The pain from glossitis, pharyngitis, and esophagitis is much more acute in pellagra than in sprue.

W. Allan has called attention to the marked similarity of the symptoms of amebic dysentery and pellagra when the skin eruption of the latter is absent. This same warning should be mentioned in connection with the differentiation of amebic dysentery and sprue. This difficulty is made the greater by the fact that sprue may complicate amebic dysentery. In amebic dysentery the simple fact of the occurrence of stomatitis and diarrhea (the two symptoms so often counted sufficient for a diagnosis of sprue) will lead to error without a study of the feces.

The disease most frequently confused with sprue is pellagra, and it is this fact which justifies this report. There is so much similarity in a portion of the disease picture of sprue that some writers, notably J. Burnet, of Edinburgh, and C. E. Stewart argue that the two are in reality one and the same.

In the United States the diagnosis of pellagra in the absence of skin lesions is made with considerable possibility of error. It may be that in those countries where the disease has occurred for a much longer period, the medical profession has acquired more skill in its recognition, basing their opinions on signs other than the skin manifestations. For the present, at least, we are not justified in making such a diagnosis without skin lesions unless the history of a past outbreak is quite definite. In reviewing my cases, which began in 1905 and include several hundred, I find that at the time of examination the skin lesions were wanting in a large number, and a note is made leaving doubt as to the correctness of the diagnosis. In following up these cases it is interesting to note that a

considerable proportion never developed the necessary symptom for such a diagnosis. A number have died of other diseases and only a comparatively small portion were cases of pellagra. A large part of these cases we now know suffered from tropical sprue, which was supposed not to occur in this country. Emphasis should be placed on the fact that in spite of an experience of several hundred cases of pellagra, extending over a period of ten years, any diagnosis made in the absence of skin lesions at that time was simply guesswork.

In an editorial in the *London Journal of Tropical Medicine and Hygiene* the question of the probability of the identity of sprue and pellagra is strongly argued. The writer finds a marked similarity in the stools in both diseases as well as indicanuria and pathological changes in the intestinal tract which closely resemble one another. Tuczek found in pellagra an attenuation of the intestinal wall as a result of atrophy of the muscular coat and also occasional hyperemia and ulceration of the large intestine. The editorial notes, further, that in sprue the mucosa is almost entirely destroyed and is replaced by a structureless substance containing leukocytes. The submucosa appears much thickened and fibrous tissue is abundant. The muscular coat is greatly thinned. The argument is concluded by the statement that the gastro-intestinal symptoms which are prominent in both conditions are strikingly alike, and that results obtained from examination of the gastric contents, stools, blood, and urine reveal almost identical conditions. The writer thinks that the nervous and mental symptoms which occur in some cases of pellagra have been given undue prominence. Singer, working with the Thompson-McFadden Pellagra Commission, found the incidence of pellagrous insanity to be 40 per cent., which is much lower than the incidence in my own cases in North Carolina. This observer regarded the nervous manifestations as toxic, subsiding with the disease activity. The definite cord degenerations, so well described by Tuczek and so abundantly confirmed in this country in the few years in which such study has been possible, would throw the weight of evidence on the side of a disease to be ranked with syphilis, which it more closely resembles than any other. In one of our earlier cases there was definite degeneration of the columns of Goll and Burdach in the dorsal and lumbar cord. The patient was a negress, aged seventeen years, who was suffering the first outbreak. It is not reasonable to assume that reparation of this organic change would have occurred had she not succumbed. As a rule, organic nervous change does not occur until the victim of pellagra has suffered at least three outbreaks. When it does occur as a consequence of some toxic action it can be counted that the

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disease has reached the stage from which there is no recovery. While there is a toxic pellagrous psychosis unattended by any definite cerebral lesion, it is to be remembered that the spinal cord alone does not bear the brunt of the whole process. The growing tendency to make light of the nervous consequences of pellagra is to be deplored. Equally as much so as syphilis does pellagra attack the nervous system, and it might not be going too far to say, more so. It is probably in this one feature that we see the most distinctive difference between pellagra and sprue, for in the latter the nervous system does not suffer.

In the beginning of the process it is often difficult to distinguish pellagra from sprue. Harris noted that in some of his cases the feces were typical of the sprue type, though the eruption of pellagra was present. It must be remembered in this connection that sprue may complicate pellagra. As a rule, the diarrhea of the two diseases may be readily distinguished. In pellagra the feces are generally more fluid, darker in color, not limited to the early hours of the day, and attended with more or less tenesmus and mucus. In sprue the stool is much larger than normal, quite light in color, acid in reaction, containing much gas, and usually occurring in the early hours of the day. The essential differences, however, are to be found in a chemical study of the feces. For this purpose we used the Schmidt test diet to determine the ratio between the fats and nitrogen intake and the output in the feces. In this work we were guided largely by the advice of Dr. J. H. Pratt.23 We feel justified in the assertion that in pellagra the fat loss and the nitrogen loss in the feces are not abnormal. In one case of great gravity, which resulted in the death of the patient a few days after the observation, we found that the fat loss was 5 per cent. and the nitrogen loss 7 per cent. In another case of long standing the fat loss reached 17 per cent. and the nitrogen loss was 6.63 per cent. In sprue the findings are quite different. It will be recalled that Sir Lauder Brunton, Begg, Mayo Robson, and others found evidences of pancreatic inactivity or actual disease in sprue. J. H. Pratt has called attention to the danger of error in counting a pancreas which is found on examination to be increased in hardness as a diseased organ. A number of these observers have noted the macroscopic findings of interstitial changes in the pancreas, but this alone should not constitute sufficient evidence of organic change. Oftentimes such an organ is capable of full function in spite of this apparent overgrowth of connective tissue. Begg thought that the failure of his yellowed santonin treatment in certain cases was due to complications, chief among which was pancreatitis. Cammidge found that in the urine and feces of fourteen cases pancreatitis occurred six times.

With all of this evidence pointing so strongly to a disturbance

of the pancreas in sprue we carefully studied a number of cases of pellagra to determine this possible relationship. Our findings were entirely in accord with those of Myers and Fine working with the Thompson-McFadden Pellagra Commission. They found that in pellagra there was practically normal utilization of the various foodstuffs. The fat utilization was good in all cases, though in three of their series of fifteen it was slightly below normal. At times we find the stools in pellagra to be acid. The Sahli glutoid capsule test in one case showed no return in the urine in five hours, and in this case there was an excess of meat fibers, but we found this to be exceptional. As a rule, the salicyluric acid appears in the urine in the normal time, the meat fibers are absent. The Schmidt beef-nucleus test, using the silk-gauze bags, was frequently tried, and in no case were there any nuclei to be found on sectioning and staining with eosin and hematoxylin. The test for trypsin showed its presence.

Observers in the tropics hitherto have been unable in many cases to distinguish between sprue and pellagra because of the absence of the skin lesions. The skin lesions of pellagra occupy only a small fractional part of the time of the outbreak, or may be so trivial as to be entirely overlooked. Such confusion may be avoided by a study of the feces. A fatty diarrhea alone would be the best single symptom for the diagnosis of sprue.

**Summary.**

1. Tropical sprue occurs in the Southern States, where it is frequently confused with pellagra.

2. Sprue is a definite disease entity with a definite symptomatology, which when followed should cause no difficulty in diagnosis.

3. There is much evidence tending to justify a further study in order to determine whether the characteristic sprue stool is or is not due to a lesion of the pancreas. The deficiency of pancreatic function in sprue may be due to actual pancreatic change, or a disturbed intestinal function may play a part in the findings.

4. The only certain means of differentiation between pellagra and sprue is a study of the feces. Fatty stools with great fat and nitrogen loss are characteristic of sprue, while in pellagra the fat and nitrogen absorption are about normal even in spite of the diarrhea.

5. Sprue may complicate any of the intestinal diseases and add to the confusion in diagnosis, therefore, for the present at least, the diagnosis of pellagra should not be made in the absence of skin lesions except when the history of a former outbreak is definite.

I am especially indebted to Professor Isadore Dyer, of Tulane University School of Medicine, and to the librarian of that school for many kindnesses. To Mr. George F. Catlett I am indebted for material help in definitely determining the chemical differences in the stools of pellagra and sprue.

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