

A REVIEW OF THE RECENT LITERATURE ON TROPICAL SPRUE

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RECENT CONTRIBUTIONS TO THE ETIOLOGY OF SPRUE

Sprue is defined by Manson as "an insidious chronic remitting catarrhal inflammation of all parts of the mucous membrane of the alimentary canal, occurring particularly in Europeans who are residing or who have resided in tropical or sub-tropical climates." Dr. Ashford defines it as a "chronic disease characterized by a sore and beefy tongue, a gaseous bowel, a small liver, a pale voluminous diarrhoea, wasting and anemia."

The disease was first described by Hillary in the Barbadoes in 1776. It has been variously called "aphthae tropica, diarrhoea alba, white flux, Ceylon sore mouth, psilosis linguae" and "sprew", the latter being the Dutch name. Kohbrugge in 1901 was the first to describe a monilia (albicans?) as the cause of sprue. Subsequently Manson-Bahr and Castellani carried on important researches on sprue in the far East. In 1915 Dr. Ashford while working at the Institute of Tropical Medicine of Porto Rico described a new yeast-like organism which he named "Monilia psilosis", as the cause of tropical sprue.

In recent years there has been a renewed and wide-spread interest in the subject of sprue, not only as a disease entity but also because it is thought to be possibly identical in its etiology with primary pernicious anemia. The center of interest seems to be focussed on the Monilia psilosis of Ashford and the camps are divided, being for or against this organism as the cause of sprue. Confirming Ashford's work we have the publications of Baumgartner and Smith of Clifton Springs, N. Y., of J. M. Rogers (North Carolina), of E. J. Wood of North Carolina, Bastedo and Famulener of New York, L. W. Smith of the Philippines and of Wm. Krauss of Memphis, Tenn. Those not in accordance with the results of Ashford are: Bovaird of New York, Hannibal and Boyd of the Department of Bacteriology, University of Texas, Manson-Bahr of the London School of Tropical

Medicine, the staff of the Bombay Bacteriological Laboratory (India) headed by Fairley and Mackie, Dold in China, Warthin in Michigan, and Castellani in Ceylon.

A brief summary of two recent papers confirming Ashford's work will now be presented. In a series of eleven cases Baumgartner and Smith found the *Monilia psilosis* frequently in the feces of every one of their patients. In blood cultures negative results were obtained. The cases came from China, India, Korea, Porto Rico and the Philippines. The same monilia were isolated from the stools of primary pernicious anemia, in four out of seventeen cases and from the jejunum of a case of sprue autopsied by them. The authors feel certain from the evidence before them, that the monilia is more than a secondary invader and believe in the etiological relationship of this organism to sprue.

L. W. Smith was able to confirm the work of Ashford and of Michel on complement fixation with the use of monilia antigens. He studied a very small group of cases (eight in all) and agrees with Michel that there must be a toxin in *Monilia psilosis*, since guinea-pigs can be killed by intrapritoneal injection of a saline emulsion of this organism, but not with *monilia albicans*.

From the Bombay Bacteriological Laboratory a comprehensive progress report has recently appeared in the *Indian Journal of Medical Research* (1926) which does not support Ashford's work. The committee was composed of seven members and worked for eighteen months. They isolated *M. ashfordi* in half of their cases of sprue, but also in healthy persons and in non-sprue cases (including various intestinal diseases). This monilia was not found with greater frequency than were the frankly non-pathogenic wild yeast in sprue or in other conditions.

The work of González-Martínez and of Michel was not corroborated by this committee. They were able to obtain positive complement fixation tests only in animals experimentally injected with *M. psilosis* but not in any of eight typical cases of sprue. Furthermore, *M. albicans* and *M. psilosis* gave common group reactions in serological tests.

Regarding the significance of *Monilia ashfordi* in Sprue the following quotation summarizes the opinion of this committee:

"Yeasts multiply more vigorously when the alkalinity of the intestine is decreased. Evidence that any yeast plays a specific role in the etiology of this disease or that sprue is to be regarded as a moniliasis of the digestive tract is definitely lacking. We have never found systemic involvement of the tissues nor demonstrated *Monilia ashfordi* in pathological lesions in the tongue or intestines in cases coming to autopsy. Furthermore, the distribution of *M. ashfordi* in

human excreta in the Bombay series has been so widespread that its presence in sprue feces becomes a matter of doubtful significance. The most that can be said regarding *M. ashfordi* is that during those phases of the diseases in which its increased biological activity can be demonstrated, it can be regarded as a contributory or secondary factor in the production of such features as abdominal distension, flatulency and acid, frothy stools, but never as the primary cause of the disease."

Of further interest in this connection are the studies on the identification of the *M. psilosis* made by L. E. Hines at the McCormick Institute for Infectious Diseases, Chicago (1924). This writer investigated the morphological and bacteriological reactions of old strains of *Monilia psilosis* and concluded that they are not sufficiently characteristic to differentiate them from other closely related non-pathogenic fungi. His conclusions are based upon agglutination and agglutinin-absorption as well as on precipitin tests. Referring to the work of Michel and Ashford who carried out complement-fixation tests in order to prove a pathogenic role for the yeasts present in stools and mouth lesions of sprue patients, Hines says:

"It might be questioned whether this indicates a definite species because the controls did not include strains of other forms of pathogenic yeast such as those found in blastomycosis."

An important contribution by Dr. Warthin, on the etiological relationship of *M. psilosis* to pernicious anemia has just appeared. Dr. Warthin has been unable to produce a hemolytic anemia by feeding cultures of *M. psilosis* to guinea-pigs or by intravenous injection into rabbits. Although he has produced a mycotic septicemia, there was no evidence of toxic or hemolytic action. Similarly, H. W. Smith who injected *M. psilosis* into guinea-pigs never noted any severe degree of anemia, and rarely were lesions seen in the intestine, except in animals fed on a diet partially deficient in vitamins. Thus we see that in spite of much intensive work, the exact etiology of sprue still remains a matter of dispute.

We may take this opportunity to remark that the findings of the *M. psilosis* in the digestive tract of a few or of all cases of sprue does not prove its etiological relationship. For, are not *B. coli* and *B. subtilis* also universally present? And can we not isolate toxins from *B. coli* and kill guinea-pigs with it by intraperitoneal or intravenous injection of massive doses? As has been learned from the recent influenza epidemics, Koch's postulates alone are not adequate for the establishment of an etiological relationship between an organism and a disease. Neither are they absolutely essential. Immunological reactions carefully controlled must be included. We

must furthermore be on guard, as in the case of the bacillus of hog-cholera, to rule out organisms which are constantly associated with a given infection, and which may even be present in the blood stream, and yet not be the causative agent of the disease.

Referring now more specifically to sprue, the investigator must never lose sight of the fact that experimental moniliasis in guinea-pigs or a septicopyemia in rabbits produced by intraperitoneal injections of massive doses of living monilia, is not equivalent to sprue in man. There is therefore, still room for a great deal of carefully controlled immunological and bacteriological work.

RECENT CONTRIBUTIONS TO THE PATHOLOGY OF SPRUE

Opportunities to perform autopsies on sprue patients have been rather limited, and hence we have only a few complete reports and many quotations. Baumgartner and Thomas of Clifton Springs, N. Y., have recently published their notes on one autopsy. This patient had taught in the Philippines from 1905-1924. Before her death she had had an R. B. C. count of less than 2 millions, Hb. 36 per cent and a high color index. She also had had tetany at one time and had shown clinical evidence of degeneration of the posterior tracts of the cord. (This was perhaps a case of pernicious anemia.) The autopsy which was done nine hours after death showed the following: There was slight thinning of the walls of the small intestine. The liver was normal in size. The parathyroids were normal. The thoracic and cervical cord showed slight degenerative changes but no real degeneration. The bone marrow was aplastic. The mesenteric nodes were enlarged. The pancreas was normal. The authors concluded that there is no characteristic pathology to account for the severe symptoms of this case of sprue and that their pathological findings did not confirm their clinical and neurological findings.

Laurence W. Smith found several small superficial ulcers in one case and succeeded in demonstrating mycelia in histological sections of those lesions.

The Bombay committee reports four autopsies. They found gross intestinal ulcers in one case and enteritis of the terminal portion of the ileum in another. The pathological changes were parallel to the general wasting of the viscera. In one case petechial hemorrhages were seen. The lymphatics were normal. There was no demonstrable disease of the pancreas, adrenals or thyroids. There was no involvement of the central nervous system.

The bone marrow showed hyperplasia in one case (with myelo-

blasts, myelocytes, normoblasts and megaloblasts), while in another case there was a complete aplasia with gelatinous, greenish yellow marrow. In a third case (age 62), the picture was like that of a primary pernicious anemia.

Dr. R. A. Lambert (the Director of the School of Tropical Medicine) has recently autopsied two cases of sprue in Porto Rico and we shall await eagerly his thorough and masterly report.

HEMATOLOGICAL STUDIES ON SPRUE

Observations on the blood picture in tropical sprue have been more plentiful, yet we lack papers dealing with the applications of the recent advances in hematology, such as the reticulocyte count, vital staining or the fragility of the cells. There is also very little data on platelets in sprue or on the size of red blood cells. Unfortunately, too, practically all hemoglobin determinations have been reported on the basis of either the Tallquist or the Dare methods which are subject to many errors. There is therefore great need for estimations based upon the recent quantitative chemical methods of Van Slyke and others. Furthermore, there seems to be no consensus of opinion as to the exact type of anemia that sprue represents. Perhaps it is a variable picture, changing with the progress of the disease. A few summaries will now be cited.

Laurence W. Smith writes that the blood in sprue is much like that of primary pernicious anemia. The R. B. C. are usually less than one million and the W. B. C. 3,000 or less. There is a marked relative lymphocytosis, often as high as 85 per cent with a decrease in the polys. A few atypical mononuclears may be seen and rarely basophiles and eosinophiles. There is an absolute decrease in the platelets, the average count being 100,000 to 150,000. A slight microcytosis with no appreciable poikilocytosis, and a high color index (Hb. 30-40% are also observed. The size of the R. B. C. is normal. There is no evidence of marrow activity (no nucleated red cells, no stippling, no polychromatophilia). The number of reticulated cells is normal. Hence the picture is like that of an idiopathic, aplastic anemia.

The report of the Bombay committee states that some cases of sprue ultimately have a color index of plus 1 and end like P. P. A. In a series of 25 cases the following averages were obtained:

R. B. C., 3,243,000
Hb., 65 per cent
W. B. C., 6,360
Color index, 1°

Poly, 49.7 per cent
 Lympo, 42.5 per cent
 Large mono, 4.9 per cent
 Transitionals, 1.7 per cent
 Eosinophiles, 1.2 per cent

In eleven cases the color index was less than 1, in fourteen cases it was greater than 1. The color index may vary from time to time in the same patient. The patients whose color index was greater than one were generally more sick than those whose index was less than one.

Nucleated R. B. C. and megaloblasts were rarely seen. There was usually a leucopenia with a decrease in polys. In the terminal picture there was a dramatic fall in Hb. and R. B. C., producing a clinical condition resembling the blood crisis of P. P. A.

Newham and Morris and Manson-Bahr stress the fact that sprue anemia is secondary to a gastro-intestinal lesion and not due to a disease of the blood-forming organs as in P. P. A. In the latter disease assimilation of food is not affected to the same degree as in sprue, hence emaciation is not a feature. An increase of body fat may actually occur and there is no wasting of the internal organs. The stools, moreover, are of normal size with normal amount of pigment. The toxins of pernicious anemia have definite selective action on the peripheral nerves and the central nervous system with the production of neuritis and of spinal scleriosis, features not associated with the anemia of sprue.

RECENT CHEMICAL INVESTIGATIONS OF SPRUE

Scott (of the London School of Tropical Medicine) has applied the recent observations of the English physiologist Vines to the study of sprue. Vines (1921) had shown that "the calcium in the plasma normally exists in two forms. Of the total (10-11 mg. per 100 cc.), some 60 per cent is readily precipitable by ammonium oxalate, whereas the rest, being bound, probably with a lipoid complex, requires nearly three times the corresponding chemical equivalent. This "bound" or combined calcium is closely concerned with the clotting of the blood. When coagulation occurs the "combined" is converted into "free" or "ionic" state. The parathyroid glands, if functioning properly, prevent the transformation of "free" into "combined" calcium.

In sprue Scott found that the active or ionic calcium is deficient (20-30 per cent below normal), while the total Ca. remains approximately normal. In severe cases, the total may be a little diminished but never to any marked extent. Hence it is not due

to faculty absorption from the gastro-intestinal tract but due to the failure of the tissues to utilize the calcium. This suggests a disturbed parathyroid function. This phenomenon is not limited to sprue, however, for it exists also in cases of malaria and in patients with severe malnutrition.

According to Scott, the percentage of ionic calcium may be utilized as a guide to the therapy of sprue and also in its differential diagnosis.

The committee in Bombay has confirmed Scott's reports of a lowering of ionic calcium in most of their 50 cases, but they did not observe any values of less than 7.4 mg. per 100 cc. Since tetany requires a calcium content as low as 6 mg. per 100 cc., their conclusion is that sprue is not caused by perverted parathyroid metabolism.

Ashford and Hernández made a study of blood calcium in sprue and found that low-total serum calcium values are found not only in cases of sprue but in most cases of serious malnutrition in the tropics.

Other chemical constituents of the blood were also examined by the staff of the Bombay Laboratory. The total non-protein nitrogen, sugar, and chloriods were normal. The total fat, fatty acids, cholesterol and serum albuminus and globulines were low, while the fibrin was a little high.

The importance of ionic calcium determinations as a method of diagnosis and as a guide to the progress of the disease was confirmed. A reading of under 9.4 mg. of ionic Ca. per 100 cc. is considered diagnostic of sprue. A rise in blood calcium was also observed in patients under parathyroid treatment. Valuable as these researches on calcium may be, they must be checked up by a careful study of calcium metabolism, taking into consideration the Ca. content of the diet as well as the output in the stools. As far as we are aware, no metabolic studies of any kind, including determination of the basal metabolic rate in sprue have as yet been reported.

Blood tests for sugar tolerance were made in a limited number of cases by J. D. Thomson. They showed a certain degree of intolerance most noticeable during exacerbation of the disease and during loss of weight. This seems to point to a temporary inefficiency of the glycogenic function of the liver. Cases of glycosuria were given insulin by Baumgartner who found that, although there was a disappearance of the sugar, there was however, no effect on the sprue symptoms.

The bilirubin content of the serum was also determined by the Bombay Committee. High Van den Berg readings (indirect) were

only exceptionally observed by them in sprue. This is suggestive of a secondary and not a primary type of anemia, since in P. P. A. high, indirect Van den Berg readings are the rule.

The sprue anemia was also studied chemically by a British worker named R. M. Morris. He found in two cases with severe anemia that the average daily output of urobilin was much above the normal (in the urine and feces). From his data he calculated that the index of blood destruction was 1.4 to 4.9 times as high as in normal cases.

The fractional test meal was used in 26 cases of sprue studied in Bombay. Four showed hyperchlorhydria, 7 were normal, 8 showed hypochlorhydria and 7 showed complete absence of hydrochloric acid.

There was a definite delay in emptying time of the stomach, but no disturbance in secretory function. "The increase of gas in the intestine brings about an increased intraduodenal tension with relative intolerance for HCl and the pyloric sphincter becomes atonic." The authors also claim that an examination of the fractional test meal for total chlorides, inorganic chlorides and active HCl, provides a means of differentiating sprue from true pernicious anemia. In the latter disease a true achlorhydria exists due to a secretory defect, whereas in the achlorhydria of sprue, HCl is secreted efficiently, but it is neutralized by regurgitated alkaline secretions from the duodenum. (It may be added by way of explanation that the total chlorides afford an index of the secretory function of the stomach; while the inorganic chlorides are an index of HCl which has undergone neutralization by NaHCO_3 of the pancreatic juice.)

An investigation of the duodenal contents made by an English investigator, J. D. Thomson, and independently by a Dutch worker in the East Indies, Van Steenis, in cases of sprue, showed that the pancreatic enzymes are normal. The bile constituents, especially bile acid salts, are lowered. The amount of excreted urobilin was correspondingly lower in two cases.

Ashford and Hernández on the other hand, find an absence of lipase, a normal content of trypsin and a high acidity in the duodenal juices. The content of amylase was irregular.

The feces have been re-investigated by a German worker, Halberkann. He confirms the well-known data of Cammidge and others, that there is a marked increase in the total fats in sprue. They constitute 40-50 per cent of the total weight as compared with a normal of 6-8 per cent. This is not due to the failure of the fat

splitting enzymes, but to an interference with the absorptive power of the upper parts of the intestine.

Manson-Bahr agrees with this view and goes so far as to say that the failure to absorb fats (already digested) will explain almost the whole syndrome of sprue. He considers the ulceration of the ileum the essential lesion. This results in destruction of the villi with consequent atrophy of the mucous membrane. Hence, digested fats can not pass into the lacteals.

NUTRITIONAL STUDIES IN SPRUE

Although there have been scattered remarks in the literature to the effect that sprue may be a disease of dietary insufficiency, there have as yet appeared no definite or systematic laboratory researches on this subject. Elders (a Dutch worker in the East Indies) believes that the diet of sprue patients is deficient in animal proteins, amino acids and vitamins A and B. Ashford has also recently developed the conception that "Sprue is a mycosis superimposed upon a state of deficiency in certain essential food elements."

DIFFERENTIAL DIAGNOSIS OF SPRUE

The disease most confused with sprue in modern medical centers is primary pernicious anemia. As stated above, a common etiology for these two diseases is being sought by many recent investigators. The Bombay committee however, is convinced that sprue is a distinct clinical entity. Unlike P. P. A., emaciation is always a concomitant feature of sprue and the central and peripheral nervous systems are never involved. The following laboratory examinations will be found of great aid: Ionic calcium content of the blood, fractional test meal with examination for total and inorganic chlorides and free HCL., the Van den Berg test and the cytology of the blood.

DISTRIBUTION OF SPRUE

Sprue is now known to be more widely distributed than originally thought to be. It has ceased to be tropical and has become cosmopolitan. Thus from Denmark, Thaysen has just published a report of five cases who have never been outside of the country. Thaysen believes that the disease is often mistaken for pancreatitis.

Many other cases of non-tropical sprue have been recently reported by Wood in the United States. Lambright has published notes on a case which developed in Cleveland.

A series of 13 cases of sprue, which were studied by Dr. David

Bovaird at the Presbyterian Hospital in New York were found to originate anywhere from northern Korea to Ceylon and from Porto Rico to New Hampshire. The disease may occur in natives in tropical countries as well as in Americans or Europeans. The period of stay in foreign lands varied from 2 to 30 years and the symptoms appeared 4 to 24 months after return from the tropics.

EPIDEMIOLOGY

The question has been raised, Is sprue a transmissible disease? Ashford has observed in 36 out of 68 cases that other members of the family were at the same time suffering from or had presumably had sprue. Ashford concludes that sprue is undoubtedly a communicable disease. But it must be recalled that all members of one family usually eat the same diet, and we must rule out the possibility of sprue being a disease of dietary insufficiency.

The Bombay Commission also found multiple "infections" in the same family and among the staff of the same office. To quote from their report, "Certain bungalows and localities also have a most unsavory reputation in this respect. The vast majority of our cases were Europeans or Anglo-Indians. The outstanding predisposing factors in our series of cases were a long residence in Bombay and preceding malaria or dysentery."

RECENT ADVANCES IN THE TREATMENT OF SPRUE

Except for the introduction of a high calorie diet, rich in proteins and vitamins and low in carbohydrates in fats, there has appeared very little new literature in this field.

Baumgartner (1927) confirmed Scott's observations that the content of ionizable calcium of the blood is low but that the total calcium, however, is not decreased. Baumgartner recommends the use of dry parathyroid extract combined with calcium lactate. He reports a rise of blood calcium up to 8 mg. after 5 cc. of Collip's extract of parathyroid gland. Similar reports were made by Shepard and Fleming. Although they have confirmed Scott's findings regarding the lowered content of blood in ionic calcium in sprue and have observed the rise in Ca. under treatment with calcium lactate and parathyroid extract, the Bombay Committee have at no time been satisfied that the new therapy produced results superior to those obtained by adequate dietetic treatment including the use of milk, meats and fruits.

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