PERNICIOUS ANEMIA AND SPRUE *

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The contention that pernicious anemia and sprue are identical diseases has aroused tremendous interest among practitioners of medicine in the tropics. Curiously most writers who are favorably inclined toward a common identity of the two diseases are residents of temperate climates. The diversity of opinion expressed by different observers, which in some instance is founded on insufficient data, has led to much confusion. The aim of this paper is mainly to stimulate interest on the subject and possibly to shed light on the relationship between the two conditions.

In preparing this paper a series of seventy cases of sprue admitted at the Presbyterian Hospital of San Juan, Porto Rico between the years 1925–1931 have been selected. Of these, fifty have been early cases of sprue and twenty advanced cases with cachexia. For a contrast the writer has selected Cabot's(1) classical studies on pernicious anemia based upon the analysis of 1,200 cases which were collected by him from his private practice and from other parts of the country.

Unfortunately few writers have had the opportunity of studying the two diseases at the same time as they are not supposed to occur in the same climate. An exception to this is the southern part of the United States where both conditions are prevalent. In the tropics pernicious anemia is thought to be exceedingly rare. Ashford(2) stated that he had never seen a case a pernicious anemia in Porto Rico.

In order to determine as clearly as possible the criteria which would enable us to classify the cases as pernicious anemia or otherwise, it has seemed desirable to present a brief review of the most important findings in pernicious anemia.

Factors Which Have Been Considered in the Etiology of Pernicious Anemia: Pregnancy and the Puerperal State.—In Cabot's series of 1,200 cases there were 35 in which the disease developed during pregnancy or shortly after parturition. The anemia in such cases

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is apt to be progressive, without remissions, and develops as the result of toxemia brought about by the pregnant state. Removal of its cause is usually followed by a cure.

Syphilis.—Two cases occurred during an active attack of syphilis.

Malaria.—No cases of malaria were found in the series of 1,200 cases. Some Italian observers and Dr. Ewing, of New York, have reported cases of pernicious anemia as having occurred during the course of malarial infection. The anemia which develops in cases of malaria is usually of the secondary type.

Atrophy of the Gastric Mucosa.—Atrophy of the gastric mucosa was found in 61 cases which were autopsied.

Gastro-Intestinal Sepsis.—Hunter and other English writers have tried to show that the cause of pernicious anemia is sepsis and that the foci of infection has its origin in the mouth, stomach or intestines. It has been shown that the microörganisms which they believe causative are common inhabitants of the normal digestive tract. No evidence of specific antibodies has been demonstrated.

Intestinal Parasites.—The anemia produced by hookworm infestation is of the secondary type. The presence of the fish tapeworm (*Dibothriocephalus latus*) in the intestines may produce a disease identical in most respects to pernicious anemia.

Hemorrhage.—Ordinarily the type of anemia seen after hemorrhage is of the secondary type. Small hemorrhages over a long period of time may lead to true pernicious anemia.

Achlorhydria.—Achlorhydria is the most constant and characteristic symptom of pernicious anemia. It has been claimed that the lack of hydrochloric acid in the stomach allows the entrance of hemolytic organisms or toxins. This theory has never been proved. The achylia usually precedes the anemia and may be present during the non-anemic remissions. It has been shown that the subacute combined degeneration of the cord which may precede the anemia is usually associated with the achylia.

Symptoms More or Less Peculiar to Pernicious Anemia.—The appearance of the patient is usually very characteristic. The combination of the lemon-yellow tint of the skin with retention of the fat layer gives a very suggestive picture. The description given by Addison is masterly.

"The disease makes its approach in so slow and insidious a manner that the patient can hardly fix a date to the earliest feeling of that languor which is shortly to become so extreme. The countenance gets pale, the whites of the eyes become pearly, the general frame flabby rather than wasted, the pulse perhaps large, but remarkably soft and compressible, and occasionally with a

slight jerk, especially under the slightest excitement. There is an increasing indisposition to exertion, with an uncomfortable feeling of faintness or breathlessness in attempting it; the heart is readily made to palpitate; the whole surface of the body presents a blanched, smooth and waxy appearance: the lips, gums, and tongue seem bloodless, the flabbiness of the solids increases, the appetite fails, extreme languor and faintness supervene, breathlessness and palpitations are produced by the most trifling exertion or emotion; some slight edema is probably perceived about the ankles; the debility becomes extreme—the patient can no longer rise from bed; the mind occasionally wanders; he falls into a prostrate and half-torpid state, and at length expires; nevertheless, to the very last, and after a sickness of several months' duration, the bulkiness of the general frame and the amount of obesity present a most striking contrast to the failure and exhaustion observable in every other respect."

Gastro-intestinal Symptoms.—These are among the most constant findings. The mouth and tongue become sore and a source of inconvenience. There may be anorexia or eccentricities of appetite. There is a tendency to nausea and epigastric discomfort; this is probably explained by the fact that most of the cases have a marked reduction in hydrochloric acid and pepsin. In fully one half of the cases diarrhea occurs at some time during the course of the disease. There may be constipation, or diarrhea alternating with constipation.

Complaint of palpitation and disturbance of the heart is common. Murmurs are rarely missed, generally hemic and basic. Unusual pulsations of the arteries may occur, so that aneurism may be suspected. There may be enlargement of the liver or spleen.

Nervous System.—There are three groups of cases:

(*a*) Those in which the symptoms of anemia precede those of the cord.

(*b*) Those in which the spinal symptoms appear early or give rise to more discomfort than those produced by the anemia.

(*c*) Those in which the nervous symptoms are slight or absent. In most cases of pernicious anemia there are no symptoms that could be referred to spinal cord disease except numbness, tingling or other abnormal sensations of the hands or feet.

Blood Changes.—The total quantity is much reduced. There is no close parallel between the blood count and the intensity of the symptoms. The hemoglobin is greatly reduced although relatively high in comparison to the red blood cells. The color-index is very constantly and characteristically high in pernicious anemia. *Poikilocytosis.*—Marked irregularity in size and shape of the red cells with many forms is a special feature. There is no other disease in which

marked poikilocytosis is so often seen. *Anisocytosis.*—The average diameter of the cells is increased. The macrocytes measure 8, 10 or even 15 microns. Excess of over-sized cells is the most constant and characteristic change in pernicious anemia. *Polychromatophilia.*—Stippling of the red blood cells in common with dark blue or blackish discoloration upon the yellow or red stained ground of the corpuscles. Nucleated red blood cells are constantly present. There are two types: normoblasts, or the average size, and the megaloblasts, which are much larger. The leukocytes are generally normal or diminished in number. There is a relative increase in the lymphocytes. Myelocytes are frequently present, even up to 8 and 10 per cent. Blood platelets are usually low.

So it is apparent that the cause of pernicious anemia vents itself upon the digestive tract, producing achylia, sore mouth, gastro-intestinal disturbances; upon the spinal cord, and upon the blood. With these points in mind we shall proceed with the differential diagnosis. (Tables 2 and 3.)

DETAILS OF CASES

Age.—In our series of seventy cases of sprue the average age in both sexes was forty-three years, the age of the youngest patient was ten years, while that of the oldest was sixty-six years. The average age of the male patients was fifty years and that of the females forty-one years. In Cabot's series of 1,200 cases of pernicious anemia the highest age incidence occurred between the ages forty-one to fifty years. There were 10 cases in the decade ending with the tenth year, 149 cases under thirty-six years and 922 over thirty-six years.

Sex.—There were 32 males and 38 females.

Onset.—Like pernicious anemia, sprue is also a chronic disease. Wood(5) defined sprue as "a chronic process which makes its appearance so insiduously that it is difficult to obtain an exact account of its duration or its early course when the patient comes under observation". Addison's description of the onset of pernicious anemia is very similar: "The disease makes its approach in so slow and insiduous a manner that the patient can hardly fix a date to the earliest feeling of that languor which is shortly to become so extreme."

Weakness.—Practically every case of sprue complained of marked weakness. Some of the advanced cases were so weak that they were unable to walk.

Change of color.—In our series of cases the colors most commonly

described were: Sallowness to pallor, extreme pallor, lemon-tint and brown pigmentation which was usually symmetrical and more prominent over the cheeks and forehead.

Gastro-intestinal Disturbances.—In Cabot's series of pernicious anemia paroxyms of pain in the epigastrium, with or without diarrhea, occurred in 60–70 per cent of the cases. This condition was present in 80 per cent of the early cases and in 70 per cent of the advanced cases of sprue.

Sore-Mouth.—Definite tongue symptoms were found in 78 per cent of the early cases and in 40 per cent of the advanced cases. The symptoms varied from a sensation of burning to a real raw tongue. In Cabot's series, sore-mouth was a prominent symptom in 42 per cent of the cases. This usually consisted in a diffuse hypersthesia, affecting especially the tongue and associated with a bright-red, beefy appearance. In a few cases there was a definite glossitis, ulceration or herpetic lesions.

In a series of 105 cases of pernicious anemia reported by Christian,(4) sore tongue was a definite complaint in 65 per cent of the cases and only in 16 per cent was the tongue described as being entirely normal.

Diarrhea.—Diarrhea was present in 70–80 per cent of our cases. The stools varied in consistency from solid to watery and were accompanied by flatulence. In Cabot's series diarrhea was present in 40 per cent of the cases.

In relation to the part that gastro-intestinal symptoms play in pernicious anemia, Christian(4) has said:

"In practically all cases of pernicious anemia the gastro-intestinal tract is involved. In some cases the symptoms are very slight, though even here there is usually a moderate degree of loss of appetite associated with some slight gastric distress. The symptoms range from these slight ones to severe persisting gastric pain, and as far as the intestine is concerned, there may be severe diarrhea, constipation, or a combination of the two, diarrhea alternating with constipation. The diarrhea may be related to dietary indiscretion and represent an increased sensibility of the intestine so that food which a normal person would digest without disturbance produces diarrhea or it may be independent of the diet. Not infrequently the patients have daily a few soft, bulky stools and this results from their low gastric acidity. I think it should be recognized that it is not the occurrence of any particular form of gastro-intestinal disturbance that is suggestive of pernicious anemia, but that it is important to realize that most cases of pernicious anemia have some gastro-intestinal disturbances which form a definite part of the picture of pernicious anemia.

In examining these patients for evidence of gastro-intestinal disturbances very commonly one finds changes in the tongue. The patients complain of sore tongue and often it appears red and inflamed, particularly along the margins.

In such a tongue superficial, so-called aphthous, ulcerations are frequently seen. This is a varying condition and the condition will appear, get well, and reappear in succession over a long period of time. After this has continued for some time inspection will show that a progressive atrophy of the mucous membrane of the tongue has been taking place and this continues until finally in many patients the tongue is smooth, pale and glossy. With these objective findings the patients complain that their tongue is very often sensitive to particular foods, as for example, acids cause great distress, or salts irritate. In the later stages of the anemia, as a rule, the sensitivity of the tongue decreases and one has merely the atrophic tongue already described."

Loss of weight.—The average loss of weight ranged from 20 to 30 pounds. Cases with constipation or slight diarrhea showed little loss in weight.

Pyrexia.—The general impression is that sprue is an afebrile disease yet a large number of our cases had temperatures ranging from 99°to 100°F. A few had marked pyrexia.

Cardic-vascular System.—Palpitation of the heart, shortness of breath and edema of the hands and feet were noticed in many cases.

Blood.—In all cases the blood counts reported were those taken on the patients' entrance to the hospital. The average hemoglobin percentage was 44 for the early cases of sprue and 31 per cent for the advanced cases. The average red cell count for the early cases was 1.8 and for the advanced cases 1.4. The lowest count was 0.54 million and the highest 4.4 millions per cubic millimeter.

Color-index.—The average color-index was 1.15, the lowest 0.7 and the highest, 2. It was noticed that the color-index tended to fall as the cases improved and the red cell count went up, while on the other hand the color-index increased as the cases became worse and the red cell count decreased.

Leukocytes.—The average leukocyte count was 4,845 per cubic millimeter, the lowest being 1,300 and the highest 8,100. The average lymphocyte percentage was 41, while the eosinophiles were 2.3 per cent.

Changes in the Red Blood Cells.—The presence of over-sized cells were constant and characteristic especially in the advanced cases. Actual measurement of the cells showed an increased diameter. The nucleated red cells were not so common as in pernicious anemia. A few cases showed polychromatophilia.

Achylia.—Gastric analysis was done in 26 cases only. Achylia was found in six and hypochlorhydria in 9. The other cases showed either normal or increased free hydrochloric acid.

It is evident that in the early cases of sprue the acute gastro-intestinal symptoms overshadow those of the blood whereas as the

case advances the blood changes become more marked and the clinical symptoms less troublesome. (Tables 2 and 3.)

PATHOLOGY

A study of ten cases that came to autopsy with a diagnosis of sprue failed to reveal any lesions which might be considered pathognomonic of the disease and few, if any, which were characteristic of it. In general most of the previous findings reported by Manson-Bahr, P. H. Bahr, Thin, etc., have been confirmed. Emaciation was a constant and marked feature. The subcutaneous fatty tissues were thin and the fat deposits throughout the body greatly diminished. The tongue showed thinning of its covering epithelium with desquamation of the superficial layers. In three cases a mycelial growth was present on the surface and was growing into the epithelial cell-layer. In two of these, a pure culture of *Monilia psilosis Ashfordi* was obtained from the tongue surface. The fungiform and filiform papillae were smoothed out. The posterior one third of the tongue usually remained unaffected. The subepithelial tissues showed varying numbers of lymphoid and plasma cells, eosinophiles and a more or less marked increase in the vascularity. Extension of these changes into the esophagus have been reported, but were not seen in any of our cases.

The gastro-intestinal changes were in accord with those previously described except that there were no ulcerations of the mucosa of the small intestine. The walls were thinned out, generally due to thinning of all coats. This was more marked in the mucosa where atrophic changes were present. Inflammatory changes as evidenced by plasma and lymphoid cells, and eosinophilic infiltration of the interglandular stroma of the mucosa were seen in about one third of the cases. In one of these the changes extended to the submucosa. There was no instance of marked edema of the submucosa accompanied by slight atrophy of the mucosa.

The large intestine showed infiltration of the mucosa with numbers of plasma and round cells, with eosinophilic leukocytes. Atrophy was not clearly in evidence in this portion of the gut. An acute or chronic colitis with or without ulceration was a complicating factor in four cases.

In no instance was a mycelial growth found in the mucosa of the esophagus, stomach or intestine but in one case round bodies similar in morphology to monilia were discovered in the mucosa.

The heart, spleen and liver were usually much reduced in size. The heart and liver were the seat of brown atrophy.

In the liver fatty changes were frequent. There was much iron-containing pigment in the liver cells and in the Kupffer elements. The amount was less than in pernicious anemia. Similar pigment was also seen in the spleen. A diminution in the size of the lymphoid follicles was a striking feature in practically all cases even those of relative young age. The peculiar hyaline degeneration of the venous endothelium of the spleen which P.H. Bahr described in 1912–1914 was not observed and Russell's fuchsin bodies, although present, were not at all numerous.

The parathyroid glands did not show any changes either grossly or microscopically. None of the cases studied presented neurologic disturbances or cord changes. As described by others, they consisted of degeneration of the posterior columns.

The pancreas was invariably normal, except for slight interacinar fibrosis in two cases.

The difficulty encountered by pathologists in differentiating sprue from pernicious anemia is well illustrated by the following autopsy:

"*Case No. 20051.*—Female, white, age 54, entered the hospital on December 5, 1928 and died December 25, 1928.

Present illness: In April 1827 patient developed a severe diarrhea which lasted several weeks. She rapidly lost weight and became very weak. Three months before entering the hospital patient had a marked irritation of the mouth which she attributed to a very strong patent medicine which she was taking at the time. The irritation lasted several weeks. She also had swelling of the ankles, palpitation and dyspnea on the slightest exertion. There were no sensory cutaneous phenomena.

Physical examination: An extremely pale and emaciated old woman, sitting restlessly in bed, moaning and talking to herself, evidently in the terminal stage of a chronic wasting disease.

Hair and scalp: No great hair loss; uniform greying throughout.

Face: Extremely pale listless, expression of suffering, numerous wrinkles, no marked asymmetry or palsy, puffiness of the lower lids.

Eyes: Extreme pallor of palpebral conjunctivae; subicteroid tint of the ocular conjunctivae. Orbital fat preserved. Pupils small, round, equal and regular which do not react to light or accommodation. Ocular movements normal.

Mouth: Lips extremely pale, dry and bluish. Teeth in poor condition, some missing, some infected roots in place. Tongue showed a slight papillary atrophy. Pharynx could not be examined.

Nose and ears: Grossly negative.

Neck: No adenopathy, rigidity or pulsations. No enlargement of thyroid.

Chest: Normal contour, but approaching emphysematous type. Expansion very slight but equal. Tactile fremitus somewhat exaggerated. Percussion yielded slight hyperresonance. Breath very feeble and distant, no rales.

Heart: No visible or palpable cardiac impulse. Increase of dullness both

to left and right. Heart sounded distant and toneless; soft, blowing mitral and tricuspid systolic murmurs. Pulmonic second sound accentuated.

Abdomen: Somewhat protuberant, fat well preserved, no masses palpable, no rigidity or tenderness. Spleen and liver are not palpable. Area of liver dullness is diminished. Uterine anexa not palpable.

Genitals: Not examined.

Extremities: Hands puffy.

Reflexes: All diminished.

Laboratory Findings: Urine: Deep yellow. Specific gravity 1018. Sugar and albumin, negative.

Feces: Negative for parasites and monilia.

Sputum: Negative for tuberculosis and monilia.

Blood: Red cells 880,000. Hgb. 15 per cent, Dare. Microscopic study of the red cells shows macrocytosis, microcytosis, anisocytosis, achromia, nucleated reds, megaloblasts. Forty-five nucleated red cells were found in counting 100 cells. Measurement of red cells:

	Smallest Diam.	Largest Diam.	Mean	Median	Dispersion
Microns	5	14	8.76	8.4	3.45

The autopsy on this case was done by Dr. A. M. Pappenheimer, Professor of Pathology of Columbia University, whose final note is as follows:

"The pathological findings are compatible with either pernicious anemia or sprue, so far as the material at our disposal goes. The active hyperplasia of the bone-marrow is not different from that seen in sprue with advanced anemia. There is a very moderate amount of hemosiderin in the liver, practically none in the spleen pulp, although there is incrustation of the trabeculae. This is perhaps atypical for pernicious anemia. The heart, grossly and microscopically, shows little fat; there is no atrophy of the gastric mucosa, a point likewise against pernicious anemia. On the whole I am inclined to favor the diagnosis of sprue in view of the marked loss of weight."

BONE-MARROW STUDIES

Bone-marrow studies were made in nine of the ten cases that were autopsied. The findings varied markedly in various cases. In four, the bone-marrow was completely aplastic and presented advanced atrophy of its fat. In two cases there was a condition of moderate hyperplasia of all its elements. In three cases, a marked hyperplasia was in evidence and the picture was not distinguishable from that seen in pernicious anemia.

A study of the bone-marrow obtained by drills of the tibia from seventeen living cases of sprue, has in general given similar results to those described above. There was complete aplasia in seven; moderate hyperplasia in one; areas of hyperplasia in an aplastic bone-marrow in one; and active regeneration or hyperplasia in eight.

Evidently there are transitional stages in the pathology of the bone-marrow. Fairley and Mackie(5) believe there are three stages in the evolution of the bone-marrow lesions.

"An early stage where the bone-marrow changes are minimal and only slight anemia is present. An intermediate stage characterized by hyperplasia of variable intensity and culminating in a condition akin to pernicious anemia; there is considerable reduction in hemoglobin and corpuscles, the color-index is high and the anemia is definitely megalocystic in type. The last stage is that of hypoplasia or actual aplasia most commonly seen at autopsy."

Aplastic Anemia.—A certain number of cases of pernicious anemia run a rapid and progressive course, without remissions; and death occurs within a few weeks or months from the beginning of the attack. Instead of hyperplasia of the bone-marrow there is atrophy or aplasia. To these cases the term "aplastic anemia" has been given. It is a sub-type of pernicious anemia with identical clinical features, except that it runs a more rapid course, occurs in younger persons, the color-index is low, and there may be leukopenia.

Although aplasia of the bone-marrow is frequently found in advanced cases of sprue, nevertheless the clinical picture is entirely different from that of aplastic anemia. Furthermore, the aplasia does not seem to be a permanent state, but apparently is susceptible to regeneration under the stimulus of liver therapy. (See Case No. 21320)

THE RESPONSE OF SPRUE CASES TO LIVER TREATMENT

Liver therapy is introduced in this paper not only for the information that might be gained from our experience concerning the response of sprue cases to the use of liver, but particularly as a differential point between the two diseases, inasmuch as liver is considered specific for pernicious anemia. In order to properly evaluate the results obtained from the use of liver in the treatment of sprue and above all to avoid the pitfalls of inexperience, I consider it indispensable to be fully informed in respect to the proper use of liver. I do not know of a better way of finding this information than to glean it from Minot's(6) studies on the use of liver in pernicious anemia. In Porto Rico the general opinion is that few cases of sprue—only the so-called hyperplastic type respond to liver treatment. Upon questioning my colleagues with respect to the amount of liver used I invariably find that the amount prescribed is too small. Liver extract and raw liver are rather expensive in Porto Rico therefore very few patients are able to continue the use

of either one for a sufficient length of time. They either omit it altogether or take it at irregular intervals in inadequate quantities.

The discovery of liver therapy was not accidental but came to fruition through painstaking research which culminated in the experimental treatment by Whipple and his collaborators on animals with anemia, with a diet of liver, and the clinical applications of these principles to patients by Minot.

Minot has shown that liver can benefit essentially all patients with pernicious anemia. The improvement is usually rapid and is heralded by a shower of reticulocytes in the blood during the first two weeks of treatment. The behavior of the reticulocytes suggests that liver stimulates the maturation of the megaloblasts. The reticulocyte increase is inversely proportional to the height of the red blood cells. The peak of the rise occurs about nine or ten days after treatment is begun. The reticulocytes return to normal in about sixteen days. Following the reticulocyte response there is a marked and prompt increase in red blood corpuscles. After two months' treatment the average red cell count may reach 4,000,000 or more per cubic millimeter. Minot has proved that the red blood count may remain between four and five millions per cubic millimeter provided an adequate amount of liver is taken daily. A fall in the red blood cell count is usually accounted for either by failure to take a sufficient amount of liver or by the presence of the complication or infection. The symptomatic improvement of the patient is parallel with the improvement in the blood.

In Table 4 are given the results obtained in ten cases of sprue treated with liver extract. For comparison five cases treated with sprue diet only and three cases which were transfused, are shown. Considering the fact that in no instance was any case given more than three vials of liver extract daily, which is one half of the ordinary dose recommended, the response has been satisfactory and in some cases marked. Minot has shown that when small amounts of liver are fed daily the reticulocyte response is slight. By increasing the amount of liver it is possible to produce a second rise of the reticulocytes. This circumstance suggests that liver given in small amounts may produce slight changes in the bone-marrow, but that the daily dose is insufficient to cause a complete transformation of the bone-marrow. The cases which were treated with sprue diet only showed no appreciable changes in the blood findings. Repeated transfusions will undoubtedly benefit these cases and may be a life-saving procedure. The improvement however is only temporary.

In Table 4, six cases of sprue are shown that have taken liver

for a period of six months or more. In spite of the fact that three of these cases have taken liver poorly the average red blood cell count has remained within normal limits and the clinical improvement is in every way comparable to that expected of pernicious anemia.

ILLUSTRATIVE CASES

"*Case No. 21320.*—Female, white, age 42, entered the hospital December 2, 1929, and was discharged January 10, 1930.

Chief complaint: Distress in epigastrium, weakness, swelling of the lower extremities, pain under the sternum and vertigo.

Onset and course: Patient was in good health until about six months previous to entrance to the hospital when she began to have sore tongue and diarrhea with frequent watery and foul stools. Soon she started to lose weight rapidly and had dizzy spells. Her condition became worse and she was unable to eat very much food on account of epigastric distress and diarrhea. During the next few months her gastro-intestinal symptoms subsided but she grew weaker and weaker.

Physical examination: Patient is a middle-aged woman with a dull expression on her face and lemon-tinted skin.

Tongue: Papillary atrophy and glossitis.

Abdomen: Distended with gas and somewhat tender to deep palpation. Liver and spleen not palpable.

Neuromuscular: Reflexes not elicited.

Laboratory findings: Urine, negative. Blood count: Hgb. D. 20 per cent. Red cells 0.79. White cell count 3,200. Polymorphonuclears 53 per cent; small mononuclear cells 45 per cent; eosinophiles 2 per cent. There were ten nucleated red cells seen in counting 100 cells. Marked achromia, poikilocytosis and anisocytosis.

Bone-Marrow studies: On December 9, 1929, a bone trephining was done and the bone-marrow was sent to the Pathological Department of the School of Tropical Medicine for examination. The report was as follows: "The bone-marrow consists practically of fatty tissue and but a few small groups of blood-forming cells, especially myelocytes, are seen. The blood vessels are engerged and packed with what appears to be blood platelets. Diagnosis: Aplastic bone-marrow."

Nine days later, December 18, 1929 another specimen of bone-marrow was sent for study; meanwhile, patient had been given three vials of liver extract daily. Report is as follows:

"The bone-marrow is very hyperemic and cellular. Many large groups of red blood cells in different stages of development, normoblasts and especially megaloblasts, are seen. Myelocytes and subsequent stages of leukocytic development are comparatively scarce. *The outstanding feature is the large number of megaloblasts*, many of which show very large nuclei with relatively little chromatin. Mitotic figures of megaloblasts can occasionally be demonstrated. Megalocariocytes are rather numerous. Diagnosis: Hyperplastic Bone-Marrow (pernicious anemia)".

Remarks: This case illustrates the fact that aplasia may be only a functional and transitory condition of the bone-marrow, susceptible to activity when properly stimulated by the use of liver.

"*Case No. 18517.*—Male, white, age 58, entered the hospital September 25, 1927 because of extreme weakness, pallor, shortness of breath and diarrhea alternating with constipation. He had been receiving treatment for sprue for four years previous to admission. On entrance the hemoglobin was 63 per cent D., red blood cell count 1.7, white blood cell count 5,650, color-index 1.8. There was a moderate degree of anisocytosis and poikilocytosis.

Treatment: Sprue diet and a transfusion of 250 c.c. of blood. Case was discharged three weeks after admission, slightly improved.

On February 4, 1929 patient was again admitted to the hospital for the same condition. Hemoglobin was 48 per cent, red blood cells 1.3, color-index 1.8. Blood changes were marked and two megaloblasts were seen in counting 100 cells.

Treatment: Sprue diet and three vials of liver extract daily. Patient left the hospital three weeks later with 55 per cent hemoglobin, red blood cells 2.1 and a color-index of 1.3. Patient remained fairly well for a period of two years by the use of small amounts of liver occasionally. On March 13, 1931 his hemoglobin was 37 per cent, red cell count 1.2, color-index 1.5. Patient was then put on the Minot and Murphy(5) diet and advised to take at least six vials of liver extract daily. There was a reticulocyte response of 9.2 per cent. Within a period of seven weeks the red cell count increased to 3.9 per cent and hemoglobin 80 per cent, color-index 1. There was marked clinical improvement."

"*Case No. 18310.*—Female, white, age 49, had had sprue since 1924. Her chief complaints were marked weakness, pallor and vomiting. In July 1927 patient was admitted to the hospital for transfusion. Hemoglobin was 37 per cent, red cells 1.2, color-index 3 +, polymorphonuclears 42 per cent, small mononuclears 37 per cent, large mononuclears 20 per cent.

Patient remained in fairly good health until September 1930 when she had a recurrence of symptoms. Her condition became rapidly worse and she was unable to leave her bed because of weakness and prostration. On December 8, 1930, her blood cell count was as follows: hemoglobin 18 per cent, red cells, 0.9, color index 1. At this time she was put on the Minot-Murhy diet and given six vials of liver extract daily. There was a reticulocyte response of 14.6 per cent. Immediately she showed signs of improvement and soon was able to leave her bed. On February 17, 1931 she was admitted to the hospital and operated on for empyema of the gall-bladder. In spite of the seriousness of the operation and the acute hemorrhagic nephritis which developed as a complication, the patient made an uneventful recovery except for a slight mental disturbance. She left the hospital three weeks after admission with a hemoglobin of 50 per cent and a red blood cell count of 1.6. Since leaving the hospital patient has taken six vials of liver extract daily. There has been a marked improvement in the clinical symptoms, the sore tongue and the diarrhea have disappeared, the icterus index has returned to normal, the countenance has become ruddy, the appetite is ravenous and she has gained 60 pounds in weight. The last blood count taken on May 15, 1931, showed hemoglobin 80 per cent, red blood cells 4.2, color-index .95. The hallucinations and the ideas of persecution which she developed during her stay in the hospital disappeared when the red cell count reached 3.5 per cent."

Remarks: Sprue cases respond to liver treatment satisfactorily and in identical manner to cases of idiopathic pernicious anemia provided large amounts of liver are used. Experience shows that these cases require twice the dose to that of the ordinary type of pernicious anemia.

DISCUSSION

As early as 1897, Thin([7]) commented on the similarity of sprue and pernicious anemia and reported a case of sprue which was diagnosed pernicious anemia by a physician in London. Elders([8]) who has studied both conditions thoroughly has come to the conclusion that sprue and pernicious anemia are deficiency diseases and they have so much in common that it is difficult to accept a different etiology for them. In 1918, Nolen([9]) stated that it was some times impossible to differentiate sprue and pernicious anemia and claimed that most of the blood findings characteristic of pernicious anemia were found in sprue. Manson-Bahr, Low, Newham and Morris have reported blood pictures in sprue cases which in no way can be differentiated from pernicious anemia; not only that, but practically every sign and symptom of pernicious anemia including diarrhea and soreness of the mouth. Vaidya([10]), consulting pathologist of the Bombay Hospital agrees with Elders that both pernicious anemia and sprue are deficiency diseases and the deficiency in the food is for the greater part common to both and in a small part different, resulting in marked gastro-intestinal symptoms in some cases. Vaidya further states that to positively diagnose such a thing as typical sprue is well-nigh an impossibility and this feeling is further strengthened by the fact that clinically, hematologically and in treatment response, the two conditions behave alike. In America, Christian and Wood are perhaps the most ardent advocates in favor of the theory that sprue and pernicious anemia are the same disease. In a monograph on this subject, Christian([11]) writes as follows:

"Evidently pernicious anemia and sprue are closely related, so much so that a patient may be diagnosed sprue by investigators interested in that disease and a short time thereafter, in another clinic interested in pernicious anemia the same patient may be considered as entirely typical of that disease. Again, a patient may be considered as having sprue and a few years later will appear again in the office of the same physician with changes so characteristic of pernicious anemia as to lead to a possible change in diagnosis from sprue to pernicious anemia."

Wood([12]) has expressed the belief that sprue and pernicious anemia are the same condition. He also reports cases of sprue showing subacute combined degeneration of the spinal cord, which hitherto

has been one of the points of distinction between the two diseases. It is of interest to know that Wood has found *Monilia psilosis* in his pernicious anemia cases. Ashford[13] has stated:

> "There is one much neglected subject for the future study in sprue, the blood. Even yet I confess myself unable to make up my mind as to what relation sprue bears to an anemia, pernicious in all but the name, and apt to be associated as it is with achylia gastrica. That a large number of cases of sprue die with a blood picture indistinguishable from that of pernicious anemia is incontrovertible."

Baumgartner and Smith[14] from Clifton Springs, New York, after having studied fifteen cases of sprue came to the conclusion that the two conditions should not be diagnosed as the same disease. However, they make the remark that if achylia is accepted as a necessary observation in the diagnosis of pernicious anemia then only five of their sprue cases could be considered pernicious anemia. Fairley and Mackie[15] having studied a series of sprue cases at the Haffkine Institute in Bombay, came to the conclusion that sprue is a separate entity and that it can be differentiated clinically and by laboratory findings. In their opinion, emaciation and lack of nervous symptoms in sprue are important points in the differential diagnosis of the two diseases. It is true that most cases of sprue lose a great deal of weight. There are cases, however, that reach the cachectic state with a minimum loss of weight. Furthermore, loss in weight is universally reported in cases of pernicious anemia. In regard to the nervous symptoms as a differential point it may be stated that Panton[16] and his colleagues found numbness and tingling in only 18 cases out of 117 cases of pernicious anemia. Elders[8], on the other hand, has reported cases of sprue with ataxia, anesthesia and neuritis. Ashford has reported sensations of cramps and numbness in the lower limbs of some of his sprue cases. In our series of 75 cases we had one case of transverse myelitis.

. *Gastric Secretion.*—In twenty-six cases of typical sprue Fairley and Mackie found achlorhydria in seven and hypochlorhydria in eight cases, while seven were normal. They further state that if their series had been restricted to untreated cases, the percentage of low acid curves would have been higher.

REMARKS

It is peculiar that sprue is a common disease in the tropics where pernicious anemia is considered a rare disease while in the temperate climates pernicious anemia is often seen but the sprue syndrome is unknown. Ashford has shown that *Monilia psilosis* is a constant find-

ing in sprue. Wood has found *Monilia psilosis* regularly in typical cases of pernicious anemia. This finding is in favor of a common identity of the two conditions. In pernicious anemia the achylia gastrica and the cord symptoms occur early in the disease and seem to be closely related to each other. In sprue, the achylia gastrica and the cord changes occur late in the course of the disease. Should these differences be considered so important as to justify the belief that the two diseases are different entities?

CONCLUSIONS

At present it is not possible to definitely state that pernicious anemia and sprue are the same or separate diseases. There are, however, sufficient points of similarity in the clinical symptoms and signs as well as in the blood-picture, pathological findings and response to liver treatment, linking the two conditions so closely together as to justify the belief that the two are manifestations of a common etiological factor. Unquestionably there occurs a gradual but definite transitional stage in the course of sprue cases when the picture of sprue fades away and that of pernicious anemia appears. It is a common experience to see cases of sprue reach a state when the acute gastro-intestinal symptoms, such as sore tongue, diarrhea, etc., subside or practically disappear but on the other hand symptoms of anemia become more marked, the patient finally dying of typical pernicious anemia. It is at this stage that we must stop thinking in terms of sprue and consider the patient a case of primary anemia and as such give him the benefit of the Minot-Murphy diet and liver extract.

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TABLE 1

TABLE SHOWING BLOOD CELL COUNT WITH AGE AND SEX IN 70 CASES OF SPRUE

No.	Age	Sex	Hgb %	R.B.C. per cu. mm.	Color Index	White cell count	Leuco-Diff-Count			Poikylocytosis	Anisocytosis	Polichromatophilia	Nucleated Red Cells
							Polys	Lympho	Eosinophiles				
1....	36	F	75	3.1%	1.2	6100	69%	28%	2%	+	+	−	−
2....	30	F	48	1.9	1.2	4200	62	37	1	+	+	−	−
3....	33	M	60	2.2	1.2	7600	70	20	1	+	+	−	−
4....	20	F	60	2.4	1.2	7300	81	13	2	+	+	−	−
5....	10	M	60	2.9	1.	3600	51	37	13	−	−	−	+
6....	65	M	40	1.8	1.1	5300	41	56	1	+	+	+	−
7....	27	F	50	3.1	.8	5000	60	35	3	+	+	−	−
8....	43	F	60	3.3	.95	6100	52	38	7	+	+	−	−
9....	35	F	65	2.9	1.1	4200	61	36	3	+	+	+	−
10....	55	F	60	2.4	1.2	5900	79	21	1	−	−	−	−
11....	64	F	40	3.0	1.	6400	61	36	3	+	+	−	−
12....	44	M	60	2.6	1.1	5900	67	36	3	+	+	−	−
13....	44	M	72	2.9	1.2	4800	72	27	1	+	+	−	−
14....	23	F	45	1.3	1.2	5900	60	38	2	+	+	+	+
15....	42	F	90	3.7	1.2	2600	77	19	3	+	+	−	−
16....	29	F	55	2.5	1.	3500	40	53	7	+	−	−	−
17....	45	F	55	1.9	1.4	5400	50	47	3	+	+	+	−
18....	21	F	30	1.1	1.2	5000	60	40	4	+	+	−	−
19....	27	F	80	3.4	1.2	4500	50	47	3	−	−	−	−
20....	52	M	30	1.	1.5	1950	72	25	2	+	+	+	−
21....	28	M	25	1.1	1.1	7600	52	41	6	+	+	−	−
22....	28	M	60	3.6	.9	7600	54	36	2	+	+	−	−
23....	58	M	63	1.7	1.8	5650	15	83	1	+	+	+	+
24....	66	M	48	1.3	1.8	4500	62	23	5	+	+	−	−
25....	40	F	20	.68	1.47	1300	55	39	2	+	+	+	+
26....	50	M	33	1.05	1.65	3200	48	48.5	1	+	+	+	+
27....	58	M	40	1.8	1.1	6250	62	31	6	+	+	−	−
28....	32	F	96	.9	1.44	5800	54	46	.....	+	+	+	−
29....	50	M	50	1.8	1.4	3800	50	45	4	+	+	−	−
30....	49	M	50	2.1	1.25	5100	38	58	1	+	+	−	−
31....	58	F	50	1.6	1.56	6000	56	33	7	+	+	−	−
32....	59	M	60	2.4	1.25	6500	60	34	4	−	−	−	−
33....	52	M	20	1.5	1.	8100	60	30	4	+	+	+	−
34....	45	F	45	1.8	1.25	4250	30	66	2	+	+	−	−
35....	29	F	40	1.9	1.05	8000	47	43	9.5	+	+	−	−
36....	40	M	25	1.1	1.1	3600	72	22	2	+	+	−	−
37....	45	F	45	2.5	.9	4400	34	57	1	+	+	+	+
38....	50	M	50	2.	1.25	7600	65	30	3	+	+	−	−
39....	35	F	50	2.25	1.1	4600	50	43	1	+	+	−	−
40....	60	M	38	1.85	1.	2600	35	52	9	+	+	−	−
41....	47	F	30	1.55	1.	2500	27	71	0	+	+	−	−
42....	40	M	60	2.6	1.15	4200	40	56	2	−	−	−	−
43....	47	F	35	1.4	1.2	5100	40	49	2	+	+	−	−
44....	42	M	40	1.6	1.25	3300	46	51	1	+	+	−	−
45....	44	F	33	1.5	1.12	2000	45	50	4	+	+	+	−
46....	57	F	60	3.7	.81	5400	46	49	2	+	+	−	−
47....	53	M	70	3.5	1.	5680	55	42	1	+	+	−	−
48....	45	F	37	1.2	1.54	4100	62	36	2	+	+	−	−
49....	59	M	60	2.4	1.25	6500	60	34	4	−	−	−	−
50....	55	F	37	1.4	1.3	4000	56	43	0	+	+	−	−
51....	40	F	20	.62	.....	3000	68	28	.....	+	+	+	+
52....	62	M	30	.6	2.5	4000	40	53	2	+	+	+	+
53....	65	M	32	.79	1.1	3000	40	57	2	+	+	+	−
54....	58	M	32	.45	4.	3000	62	35	2	+	+	+	+
55....	54	F	15	.88	.9	4000	70	28	1	+	+	−	−
56....	53	F	50	2.	1.2	5000	56	36	8	+	+	−	−
57....	42	F	12	.61	1.5	4000	60	24	.....	+	+	+	+
58....	45	F	47	2.	1.1	4000	70	28	2	+	+	−	−
59....	30	F	65	3.	1.1	5400	64	32	4	+	+	+	−
60....	38	M	35	1.6	1.	3300	42	58	2	+	+	−	−
61....	26	F	55	2.5	1.1	5900	73	25	2	+	+	−	−
62....	42	F	20	.79	1.5	3200	53	45	1	+	+	−	−
63....	50	M	30	1.1	1.3	4500	42	56	2	+	+	−	−
64....	54	F	25	1.1	1.2	3600	40	57	1	+	+	+	−
65....	49	M	48	1.3	1.8	4100	53	43	1	+	+	−	−
66....	39	M	60	2.4	1.2	5000	67	32	1	+	+	−	−
67....	61	F	65	3.	1.1	4800	50	46	2	−	−	−	−
68....	45	M	55	2.7	1.	3700	41	56	1	−	−	−	−
69....	44	M	15	.88	1.	3000	36	60	2	+	+	+	+
70....	38	F	55	1.6	1.7	5200	48	50	1	+	+	+	+

TABLE 2

CLINICAL SYMPTOMS PECULIAR TO PERNICIOUS ANEMIA AND SPRUE

	Age	Sex	Weakness	Gastro intest. crisis	Sore mouth	Diarrhea	Constipation	Diarrhea alt. with const.	Loss of wt.	Edema	Pyrexia	Nervous symptoms
Pernicious Anemia 1,200 cases	41–45	723 M. 343 F	100%	60%	42%	40%	35%	15%	62% 38%	64%	79%	
Sprue 50 cases..	43	32 M 38 F	100%	80%	78%	75–80%	10–15%	10%	95%	50%	40%	
Advanced Sprue 20 cases	44	15 M 5 F	100%	70%	40%	40–50%	10%	10%	80%	75%	100%	Numbness and tingling 20%

TABLE 3

LABORATORY FINDINGS IN PERNICIOUS ANEMIA AND SPRUE

	Hemoglobin	Red cells	Color index	White cells	Polymorphonuclears	Lymphocytes	Eosinophiles	Achylia
Pernicious Anemia 1,200 cases	40%	2—	1+	5,000	Dim.	Inc.	n. +	95–100%
Sprue 50 cases.....	44%	1.8	1.2	5,490	58%	42%	2.7%	23%
Avanced Sprue 20 cases	31%	1.4	1.1	4,200	51%	40%	2%	

TABLE 4

CASES TREATED WITH LIVER EXTRACT AT THE PRESBYTERIAN HOSPITAL

Case		Hgb.	R.B.C.	C. I.	Ret.	Remarks
	On entrance.....	15%	.58%	1.5%		The slight response in the ret. count is in accord with small amount of LE
19885.	2 weeks with 20 cc. LE daily	40	1.1	1.4	4.1%	
	On entrance.....	48	1.3	1.8	0.2	A slight ret. response, yet the R.B.C. count was almost double in 18 days
20282.	18 days with 300 gms. daily.	55	2.1	1.3	5.8	
	On entrance.....	30	1.1	1.3		Left the hospital very much improved
22155.	2 months with 300 gms. daily.	48	2.3	1.0	6.4	
	On entrance.....	28	1.2	1.1	0.3	Ret. count reached peak in 10 days. Marked improvement both clinical & blood-symp.
20742.	3 weeks with 300 gms. daily.	55	2.8	.98	12.4	
	On entrance.....	30	1.	1.5	0.2	Peak reached in four days. Patient decidedly improved.
20269	3 weeks with 300 gms. daily.	55	2.3	1.1	12.7	
	On entrance.....	25	1.1	1.2	1.	Peak of ret. ct. was reached on the 6th day. LE omitted yet R.B.C. ct. went up.
20378.	2 weeks with 300 gms. daily.	55	3.2	.9	26.6	
	CASES TREATED WITH SPRUE DIET ONLY (No Liver Extract)					
	On entrance.....	60	2.4	1.2		Patient's general condition improved but cell count remained the same.
20170.	6 weeks with sprue diet.....	55	2.6	1.	2.	
	On entrance.....	65	3.0	1.1		Slight improvement.
20419.	1 week with sprue diet.....	55	2.8	.9	5.	
	On entrance.....	55	2.7	1.		Admitted for diag. only.
22468.	2 days with 300 gms. daily.	50	2.5	1.	2.	
	On entrance.....	15	.88			Did not receive LE or trans. Blood picture showed marked changes. See autopsy
20051.	Died 4 days after admss....					
	On entrance.....	55	1.6	1.7		Slight improvement
19457.	9 weeks with sprue diet.....	50	2.1	1.1		
	CASES SHOWING THE EFFECT OF TRANSFUSION					
	On entrance.....	63	1.7	1.8		Was trans. once, receiving 250 cc. of blood R.B.C. count remained the same.
18517.	Right after transfusion....	47	2.2	1.		
	On entrance.....	10	.56	1.1	0.1	Improved
22438.	40 days with sprue diet & 2 trans. (250cc)	40	2.2	1.1	10.6	
	On entrance.....	25	.84			Patient showed marked improvement clinically as well as hematologically.
18779.	7 weeks with sprue diet & 4 trans. (250 cc)	74	2.8			

TABLE 4—Continued

CASES TREATED WITH SPRUE DIET AND LIVER EXTRACT

21172.	On entrance.....	40	1.4	1.4		Highest peak in ret. occurred six days after LE was started. Marked improvement
	1 month with sprue diet.....	45	1.5	1.5	2.	
	1 month with liver extc.....	75	3.5	1.0	16.7	
21468.	On entrance.....	45	1.3	1.2	2.	Although the ret. response was not high the R.B.C. showed marked improvement.
	2 months with sprue diet.....	45	2.3	0.9		
	1 month with 300 gms. daily.	60	3.7	1.	7.	
21294.	On entrance.....	60	2.4	1.2	.3	Case showed marked improvement. Ret. response inverse proportion to red cells.
	1½ months with sprue diet.....	64	2.7	1.1	2.	
	2 weeks with 300 gms. daily.	70	3.4	1.	8.	
21320.	On entrance.....	20	.79	White.	1.	Bone-marrow was reported as being *aplastic*. With LE treatment patient showed marked improvement. Second specimen of bone-marrow taken 9 days after LE was given, was reported as *hiperplastic* (pernicious anemia.)
				ct. 3,200		
	4 weeks with 300 gms. daily.	48	2.7	White. ct. 6,400	19.7	

TABLE showing the rate of increase of the corpuscles of six private patients whose red blood cells were below two millions per cubic millimeter when they were placed on Liver diet and who have taken the full amount of liver extract: 600 grams daily.

Time of observation	Average Red Blood Cell Count in millions per cubic millimeter
Before diet begun	1.4
After diet taken about one month	2.9
After diet taken about two months	3.4
After diet taken from four to six months	3.9