A CLINICAL INVESTIGATION OF THIRTEEN CASES OF ANEMIA OF PERNICIOUS TYPE IN PORTO RICO

BAILEY K. ASHFORD and JUAN A. PONS
From the School of Tropical Medicine of the University of Porto Rico under the auspices of Columbia University.

In view of the discussion of the pernicious type of anemia of sprue found elsewhere in this Journal the preliminary remarks introducing the clinical histories of these thirteen cases will be limited chiefly to a summary and a few general observations.

All, save one of these patients, were suffering from typical advanced sprue cachexia with a pernicious type of anemia. They were all adults, four between twenty and forty, six between forty and sixty and three over sixty years of age. The duration of the disease in the twelve suffering from sprue was as follows:

Two months	1
Eight months	2
One year	1
Two years	2
Three years	1
Four years	1
Six years	2
Nine years	1
Ten years	1

Seven of these patients gave a history of recurrent exacerbations, or "relapses."

Of twelve cases, ten were negative for intestinal parasites. Of eleven cases, six were negative for *Monilia psilosis* and five were positive, a common proportion of negative findings in old cachectic and previously treated cases.

Of twelve cases, there was hyperchlorhydria in one, achylia in four, and a normal gastric acidity in seven.

Of the thirteen cases there was a trace of albumin in the urine and a few casts in two, a trace of albumin alone in two, and a normal urine in nine.

BLOOD VALUES

On admission		About a month later		About 2 months later		About 3 months later	
Reds millions	Hb %	Reds millions	Hb %	Reds millions	Hb %	Reds millions	Hb %
1.78	36	1.91	40				
0.44	12	3.50	60				
2 48	50	3 21	70				
2 96	75	3 01	75				
1.70	34	2 27	42				
1.68	35						
0.59	20	1.14	12	1 92	28		
0.49	12	1.63	13	2.49	38		
0.78	30	1.97	48	2.83	48		
2.06	44	2.30	38				
0.58	10	0.54	10	2.02	40	3.5	70
1.92	41	2.17	49	3.68	85	4.38	84
0.11	10	2.39	35	3.28	60	4.7	66
Averages..1.35	31	2.17	41	2.7	49	4.19	73

BLOOD CHEMISTRY

(1) Non-protein Nitrogen.

Average of 13 cases, 36.7 mgms. per cent. Normal considered to be from 25 to 30 mgms. per cent. Ten cases exceeded the maximum for normal.

(2) Urea-nitrogen.

Average of 12 cases, 16.3 mgms. per cent. Normal, 12 to 15 mgms. per cent. Five cases exceeded the maximum for normal.

(3) Uric Acid.

Average of 12 cases, 3.5 mgms. per cent. Normal, 2 to 4 mgms. per cent. Four cases exceeded the maximum for normal.

(4) Creatinin.

Average of 13 cases, 1.47 mgms. per cent. Normal, 1 to 2 mgms. per cent. None exceeded the normal.

(5) Sugar.

Average of 13 cases, 88.1 per cent. Normal from 90 to 120 mgms. per cent. Six cases were below the minimum and one case above the maximum for normal.

(6) Cholesterol.

Average of 12 cases, 131.9. Normal 160 to 200 mgms. per cent. Eleven cases fell below the minimum, six to very low figures, a common phenomenon in sprue.

(7) Serum-calcium (total).

Average of 13 cases, 8.4. Average normal for Porto Rico established by Ashford and Hernández, 9.6 mgms. per cent. Nine cases

fell below this average but it should be remembered that this seems to be a purely nutritional defect and is not peculiar alone to sprue.

(8) Phosphorus.

Average of 9 cases, 2.4 mgms. per cent. Low normal limit considered 3.7 mgms. per cent. Six of the cases fell below the minimum.

(9) Chlorides.

Average of 12 cases, 535 mgms. per cent. Normal between 450 and 500 mgms. per cent. Eight cases exceeded the maximum.

(10) Icteric Index.

Average of 13 cases, 8.5 units. Normal, 2.5 to 5 units. Eleven cases exceeded the maximum.

RETICULOCYTE RESPONSES TO THE SPECIFIC SUBSTANCE PROVOKING RED CELL REGENERATION

Ventriculin * failed to produce a reticulocytosis in ten cases. It produced a faint reticulocytosis in two cases and a normal response in one case.

In seven cases in which liver extract was employed after failure with ventriculin the former also failed to produce a reticulocytosis. In one case liver extract produced a faint response after failure with ventriculin. In one other case both substances yielded a response which was in each case totally inadequate for the blood level at which they were given.

In two cases after complete failure to elicit reticulocytosis by ventriculin, Valentine's aqueous extract of liver (E 29) was given. In one it also failed to produce reticulocytosis; in the other (Case 11) it produced the highest reticulocytosis ever seen in our experience.

In three cases the administration of ventriculin was accompanied by an increase in diarrhea.

The fact of the matter is, we have reached the point where we must see that sprue and Addison's disease are two separate diseases with a common hematologic phenomenon, a macrocytic anemia. In sprue there is often incompetence of the bone-marrow in its blood-regenerating function, tending toward a pernicious anemia.

In the case of Addison's disease, the administration of adequate doses of liver extract or its equivalent in ground, defatted and dried hog stomach will usually cause a remission in two months, preceded by a reticulocytosis in inverse ratio to the red blood cell level. In

* We are obliged to the manufacturers of Ventriculin and Valentine's aqueous extract of liver "E 29" for a gratuitous supply of these products for use in these cases.

sprue which may have developed a pernicious type of anemia—and this occurs generally in the severe cachexia of the disease—such a prompt rise to normal blood value is not so common as a much slower one which is apt to be preceded by a feeble reticulocytosis or none at all. This may be due to lack of absorption of the potent substance by the damaged intestinal mucosa or to a relative incompetence of the bone-marrow due to hypoplasia.

In other respects the two diseases are, as a rule, distinguishable from each other. In pernicious anemia the gastro-intestinal disturbances are less in intensity and different in character from those of sprue in which the picture is almost pathognomonic. In pernicious anemia the cord lesions yield definite pictures which are usually completely lacking in sprue. In fact, numbness of the hands and feet, cramps in the legs, and even functional arthropathies promptly disappear on a proper sprue diet, and later, with these, the whole clinical picture. Dieting has never made any great headway against Addison's disease which practically always shows a complete achylia, the latter a much less frequent condition in sprue than it was thought to be, and one, when it occurs, which seems to be often a temporary aberration of gastric function.

In view of these reflections, it would seem confusing and almost futile to test in Porto Rico the relative potency of a liver extract or a powdered hog stomach supposed to contain an adequate amount of the substance for overcoming the pathogenetic mechanism existing in the bone-marrow of Addison's disease, because, in the first place, it may not be absorbed and, in the second place, if it should be absorbed, the megaloblastic population may be so reduced as to make an increase in blood values by interaction between this substance and the vital medullary elements a physical impossibility.

This paper and these histories in no way prove the inefficiency of ventriculin or liver extract, which are known to be potent in Addison's disease, but the lesson which the writers have drawn is another; namely, that the conditions in the anemia of pernicious type in sprue which are opposed to successful therapy are not always the same as those in Addison's disease. In fact, we have every reason to believe that they are not always the same in these sprue anemias, as autopsies have revealed in some cases aplasia of the bone-marrow; in others, pictures identical with the von Biermer type with marked hyperplasia. This variability is extremely noticeable in comparing cases 5 and 11 of this series, in which, in one, both ventriculin and aqueous extract of liver utterly failed; in the other ventriculin failed and aqueous liver extract yielded a brilliant success.

HOSPITAL CASES

Case 1. G. P., age 28, sex male, Hospital No. 119.

Clinical History: For past five or six years occasional attacks of diarrhea, attacks always relieved by milk and vegetable diet. Became really ill three months ago with soft, yellowish, foamy, generally abundant bowel movements. Great excess of intestinal gas, sore tongue and loss of weight and strength. States that fatty and starchy foods disagree with him. The number of bowel movements average two by night and four by day.

Physical Examination: Cachectic; hair scanty, silky. Teeth in fair condition. Tongue smooth from papillary atrophy; bright red and raw at edges. Fauces and pharynx red and congested. Slight dullness over right upper chest with slight impairment of resonance and rough breath sounds; no rales. Fluoroscopy negative. Heart sounds distant and feeble, soft blowing systolic murmur at apex, not transmitted. Abdomen slightly distended; thin, soft walls; no tenderness, masses, nor ascites. Convolutions of intestine show through belly wall. Liver of normal size. Weight on admission 93½ pounds.

Laboratory Data: Urine, acid; sp. grav. 1017; trace of albumin and occasionl granular casts but few leucocytes.

Feces: Negative for intestinal parasites; *Monilia psilosis* recovered from stools.

Kahn Test: Negative.

Blood Chemistry:

Non-protein nitrogen	46.1 mg. per 100 c.c.
Urea nitrogen	20.2 mg. per 100 c.c.
Uric acid	5.2 mg. per 100 c.c.
Creatinin	1.5 mg. per 100 c.c.
Sugar	102.5 mg. per 100 c.c.
Cholesterol	152.4 mg. per 100 c.c.
Serum calcium (total)	8.4 mg. per 100 c.c.
Chlorides	573.3 mg. per 100 c.c.
Icteric index	8.5 mg. per 100 c.c.
Bilirubin, Van den Bergh	1.1

Duodenal Contents:

Acidity	16 units
Trypsin	2.5 units
Amylase	2.5 units
Lipase	0.1 units

Gastric Contents:

Minutes	R	15	30	45	60	75	90
Total acid	25	61	86	70	60	60	56
Free acid	0	24	48	29	29	20	20

Treatment:

Ashford's diet for sprue. Ventriculin as detailed below. No liver or liver extract. He was also given the following:

(1) Strychnin sulphat	0.10
Acid hydrochloric. dilut	16.00
Pepsin	12.00
Tinct. Cardamoni Comp.	30.00
Aq. q. s. ad.	240.00

M. Sig. One teasponful in water twenty minutes before all meals.

(2) Pancreatin
Takadiastase a. a. 0.3
Magnes. oxid. 0.5
Calcii. carbonat. 1.0
M. et ft. chart. No. 50. Sig. One two hours after each meal.

Course:

Date	Erythrocytes	Hb per cent	Reticulocytes, per cent	Remarks
1/11/30	1.78	36	0.8	No malarial organisms.
1/12/30			0.8	Bowel movements 4 to 10 daily up to 1/17/30.
1/13/30			0.8	
1/14/30			0.7	
1/15/30			0.9	
1/16/30			1.2	
1/17/30			0.9	Biopsy of bone-marrow of tibia revealed typical hyperplasia. Cultures of this marrow yielded *M. psilosis*.
1/20/30	1.35	37	1.8	
1/21/30			0.5	Ventriculin, 30 g. daily until 1/30/30. Bowel movements 5 to 13 daily during this period.
1/22/30			2.0	
1/23/30			0.7	
1/24/30			1.6	
1/25/30			1.6	
1/26/30			0.5	
1/27/30			1.4	
1/28/30			1.9	
1/29/30			0.8	
1/30/30			1.6	Ventriculin, 60 g. daily to 2/6/30.
2/1/30			1.0	
2/2/30			0.8	
2/3/30			0.6	Bowel movements, 18.
2/4/30			0.7	Bowel movements, 19.
2/5/30	1.58	30	0.8	
2/6/30				Stopped ventriculin. Milk diet.
2/9/30				From this date to 2/19/30 only 2 to 3 bowel movements daily.
2/18/30	1.91	40		Eggs and vegetables added to diet.
2/19/30				Ventriculin, 30 g. which was followed immediately by profuse diarrhea.

2/20/30			Stopped ventriculin; cessation of diarrhea and only one movement a day until discharge. Meat added.
2/24/30			Weight 90.25 pounds.
3/5/30	3. 85	68	Weight 98.25 pounds.
3/6/30			Discharged without symptoms.

Diagnosis: Tropical sprue with a pernicious type of anemia.

Comments: In this case ventriculin had to be suspended on account of a severe diarrhea which it is reasonable to suppose was connected therewith. Its administration was not followed by reticulocytosis and the eventual rise in blood values which began nearly a month later could have as well been attributed to the diet.

Case 2. M. R., age 25, female, Hospital No. 126.

Clinical History: This patient was treated by one of us and apparently cured three years ago of a most severe case of sprue with a pernicious type of anemia. It was reported in a series (Case XVI) which formed the basis for a paper on the Anemias of Sprue, delivered at the International Congress of Tropical Medicine and Hygiene in Cairo, Egypt, in December 1928(1[1]). She was then apparently cured. Eight months before admission on this occasion, she lost considerable amount of blood from an injury to her thumb. Following this she noted loss of weight, color and strength. About three weeks after injury she began to experience burning sensation in the tongue and throat with difficulty in mastication and deglutition. There was also much gaseous distention of abdomen but as a rule, no diarrhea. In the last few days she noted some diarrhea, with intensely yellow, small, and at times foamy movements. There were three or four movements during the day but none at night.

Physical Examination: Very pale, weak and thin; weight not determined as she was unable to stand. Hair dry, fine and scanty. Expression dull and stupid. Buccal mucous membrane extremely pale. Bright red, glistening, smooth, raw tongue, from atrophy of papillae. Most of the upper teeth are missing and there is pyorrhea in those which remain. There are a few discrete, palpable submaxillary glands. Lungs negative. Heart sounds distant, feeble and toneless, with soft, blowing, apical, systolic, and pulmonary murmurs, not transmitted. Abdomen slightly distended and loops of intestine visible through wall. Liver definitely small. Extreme pallor of nails. Some pretibial edema. Deep reflexes diminished.

Laboratory Data: Urine, turbid, yellow; acid; sp. grav. 1010; traces of albumin; some leucocytes.

Feces: Negative for intestinal parasites and protozoa; when she was first treated in 1928, her feces were loaded with *Monilia psilosis;* this time she had none (see [4], [5], [6], [25], on the tendency of *Monilia psilosis* to disappear from the feces in severe and long-continued sprue.)

Kahn Test: Negative.

Blood Chemistry:

Non-protein nitrogen	32. 9
Urea nitrogen	14. 4
Uric acid	3. 9

Creatinin	1.5
Sugar	98.4
Cholesterol	141.3
Serum calcium, total	8.9
Phosphorus	2.9
Chlorides	498.4
Icteric index	9.4

Gastric Contents:

Minutes	R	15	30	45	60
Total acidity	17	15	11	7	4
Free acid	0	0	0	0	0

Duodenal Contents:

Occult blood	positive
Acidity	8.0 units
Amylase	2.5 units
Trypsin	2.5 units
Lipase	0.4 units

Treatment: As per Case 1.

Course:

Date	Erythrocytes (millions)	Hb per cent	Reticulocytes, per cent	Remarks
1/21/30	0.44	12	1.2	Leucocytes, 4,250; lymphocytes, 38 per cent; eosinophiles, none.
1/23/30			2.4	
1/24/30			1.2	Biopsy bone-marrow tibia revealed typical hyperplasia.
1/25/30			4.7	
1/26/30			11.1	Ventriculin, 5 g. daily to 1/29.
1/27/30			7.0	
1/28/30	0.88	14	9.3	
1/29/30			6.3	Ventriculin, 30 g. daily to 2/9. Bowel movements 1–3 from 1/29 to 2/6/30.
1/30/30			3.8	
1/31/30			9.0	
2/1/30			20.4	
2/2/30			12.6	
2/3/30			10.4	
2/4/30			5.7	
2/5/30			5.7	
2/6/30	1.85	30	2.8	
2/9/30				Stopped ventriculin.
2/14/30	3.50	60		
2/21/30				Discharged greatly improved.

Diagnosis: Relapse of a former case of severe sprue, with a pernicious type of anemia.

Comments: In this case there was a reticulocyte response to ventriculin but it was far below that established as the normal (55.7 per cent for a red cell level

of 0.5 million and 38 per cent for one of 0.9 million). The dose given on January 25 was an experiment and was changed to the dose considered normal by investigators of this substance three days later.

It is interesting to note that this case presented in her relapse the same relative microcytosis and entire absence of eosinophilia characteristic of her first attack.

Case 3. M. D., age 70, sex female, Hospital No. 132.

Clinical History: Previous history negative. Present disease began abruptly two months ago when she was in perfect health, with nausea, vomiting and syncope. Diarrhea began immediately afterward with excessive intestinal gas, acid eructations and, from the very onset, marked soreness of the tongue and burning of the esophagus and stomach. Occasional epigastric pain, never severe. Diarrhea became worse and worse with four to five stools by day and some by night. Evacuations white, foamy, at times abundant and at others scanty, always very irritating and not very fetid.

Physical Examination: A thin, cachectic old woman. Loss of hair evenly distributed. Arcus senilis. Early cataract right lens. All teeth missing. Tongue fiery red, especially at edges; surface very smooth due to papillary atrophy. Lungs negative. Heart sounds rather feeble and wanting in muscle tone. Blood pressure 158/74. Abdomen slightly distended; wall soft with very lax skin. Loops of intestine seen through the wall and can be rolled under the finger. No masses nor rigidity nor tenderness. Spleen not palpable. Liver small. Skin atrophied and not elastic. Has scabies.

Urine: Acid; sp. grav. 1007; no albumin; sediment, an occasional leucocyte.

Feces: Negative for intestinal parasites. *Monilia psilosis* positive.

Kahn Test: Negative.

Blood Chemistry:

Non-protein nitrogen	33.3
Urea nitrogen	13.4
Uric acid	2.4
Creatinin	1.4
Sugar	93.9
Cholesterol	153.9
Serum calcium, total	8.8
Chlorides	514.8
Icteric index	5.9

Gastric Contents:

Minutes	R	15	30	45	60	75	90
Total acidity	11	37	59	69	58	50	41
Free acid	0	11	25	47	44	32	21

Duodenal Contents:

Occult blood	negative
Acidity	15.0 units
Trypsin	10.0 units
Amylase	2.5 units
Lipase	0.3 units

Treatment: Same as in Case 1.

Course:

Date	Erythrocytes (millions)	Hb per cent	Reticulocytes, per cent	Remarks
1/28/30	2.48	50		
2/4/30			0.4	Ventriculin, 30 g. daily to 2/15/30.
2/5/30			0.7	
2/6/30			0.8	
2/7/30			0.4	
2/8/30			0.2	
2/9/30			0.7	
2/10/30			0.5	
2/15/30	2.18	40		Ventriculin stopped.
2/18/30			0.6	
2/19/30	2.08	46	0.5	Liver extract, 6 vials a day, Lilly.
2/20/30			0.5	
2/21/30			0.7	
2/22/30			0.8	
2/23/30			0.6	
2/25/30			0.4	
2/26/30			0.1	
2/27/30			0.0	
2/28/30	3.21	70	0.9	
3/4/30				Patient discharged, greatly improved. No sore tongue or diarrhea, but tongue still without papillae.

4/25/31 A little over a year from the last examination this patient returned with a relapse. Her blood was as follows:

Hemoglobin	47 per cent
Erythrocytes	2.41 million
Much poikilocytosis, 100 normoblasts per cmm., mean diameter of erythrocytes 8.54 microns, color-index	0.98
Leucocytes	10,000 per cmm.
Polymorphonuclears	30 per cent
Lymphocytes	62 per cent
Mononuclears	4 per cent
Eosinophiles	4 per cent

Diagnosis: Tropical sprue with a pernicious type of anemia.

Comments: The only question might be as to the type of the anemia, but not only was the color-index generally over 1, but the erythrocytes persistently exceeded 8 microns in diameter. In this case, neither ventriculin nor liver extract seemed to have the slightest effect in producing reticulocytosis and her rise in blood values seemed to have occurred as a result of the high nitrogen diet to which she was subjected while in the hospital.

Case 4. F. M., age 48, sex male, Hospital No. 141.

Clinical History: Previous history colorless save that in 1906 he suffered with a slight intestinal disturbance, went to Spain and recovered without treatment. A severer intestinal attack came on in 1912. He again went to Spain and recovered without treatment. Always had indefinite digestive symptoms which subsided on reaching temperate climates. His present illness began about two years ago with increased movements of the bowels, an increase in quantity and frequency. There was a burning sensation noted at times in the epigastrium after meals. He went to the United States and was soon relieved but all symptoms recurred on his return to Porto Rico a few months later. Until 1919 the patient had no regular time nor place for meals. In the last few months he has been getting much worse, with from eight to ten movements of the bowels per day. For six months the stools had been watery; now they are whitish and at times foamy. Last November his tongue was very red and his entire mouth very sore. His usual ration has heretofore consisted of rice, beans, soup and coffee, occasionally with meat.

Physical Examination: Middle-aged, white male; emaciated. All teeth missing. Tongue not inflamed; no marked papillary atrophy. Lungs negative. Heart sounds weak; no murmurs. Abdominal wall flabby; intestinal loops visible and palpable through abdominal wall. Weight 88¾ pounds.

Urine: Acid; sp. grav. 1009; no albumin or sugar; an occasional leucocyte.

Feces: Negative for intestinal parasites and for *Monilia psilosis.*

Kahn Test: Negative.

Blood Chemistry:

Non-protein nitrogen	26.6
Urea nitrogen	10.0
Uric acid	2.8
Creatinin	1.4
Sugar	71.4
Phosphorus	2.1
Icteric index	3.2
Cholesterol	137.4
Total calcium	7.8
Chlorides	479.7

Gastric Contents:

	Minutes	R	15	30	45	60	75	90
	Total acidity	12	12	95	111	156	100	90
(Feb. 5, 1930)	Free acid	0	0	48	59	78	55	50

Duodenal Contents:

Acidity: neutral to phenolphthalein.

Trypsin	10.0 units
Amylase	50.0 units
Lipase	3.1 units

Occult blood, positive.

Treatment:

Sprue diet as heretofore detailed. Calcium lactate by mouth.

Course:

Date	Erythrocytes (millions)	Hb per cent	Reticulocytes, per cent	Remarks
2/4/30	2.96	75		
2/5/30			0.6	
2/6/30			0.7	
2/7/30			0.9	Diarrhea ceased; no diarrhea after this date.
2/8/30			0.3	
2/9/30			0.8	
2/10/30			0.4	
2/11/30			0.9	Calcium lactate, 0.3, t. i. d.
2/12/30			0.3	
2/13/30	3.17	78	1.3	Ventriculin, 30 g. daily to 2/23.
2/14/30			0.9	
2/16/30			1.6	
2/18/30			1.2	
2/19/30	3.40	80		
2/20/30			1.1	
2/21/30			0.9	
2/22/30			0.9	
2/23/30			1.0	Ventriculin stopped and liver, 3 vials, Lilly, given daily.
2/24/30			0.8	
2/25/30			1.8	
2/26/30			1.2	
2/27/30			1.2	
2/28/30			2.6	
3/2/30	3.01	75	2.6	
3/5/30				Discharged greatly improved; no symptoms; weight ninety-one pounds.

Diagnosis: Tropical sprue with a pernicious type of anemia.

Comments: Hematologically, the blood was as stated in the diagnosis; the mean diameter of the erythrocytes on admission was 9.06 microns, the median 10.20 and the double dispersion was 3. We do not expect the achylia of Addison's disease in sprue as a *sine qua non*. Note the hyperchlorhydria in this case and the low cholesterol and serum calcium.

Neither ventriculin nor liver extract had any immediate effect but no reticulocytosis could be expected. If any stimulation of the bone-marrow had taken place, however, we should have at least some rise in blood values during the time of observation.

Case 5. E. V. de B., age 52, sex female, Hospital No. 152.

Clinical History: Father died of carcinoma of stomach at 50 years of age; mother, of apoplexy at 60. One sister died at 18 years, of tuberculosis, but no other case of tuberculosis in whole family. Her general health has been unusually good, save for high blood pressure four years ago, for which she sustained a pure vegetable, salt-free diet for one year. She has never had any dyspnea

of effort nor edema of ankles. Had typhoid 24 years ago following child-birth by a week. Has been ill of present affection two years. She never had any symptoms from her digestive tract up to two years ago and, save as above, never has limited her diet. Has had nine pregnancies.

Physical Examination: Pale, poorly nourished, sickly-looking, middle aged white woman. Very much depressed but perfectly normal mentally. Her face is thin and pale and temporal arteries are thickened and tortuous. Has slight exophthalmus. Pupils react normally to light and accommodation. Lips and mucous membrane of mouth pale. Tongue stripped of papillae, smooth, glossy and whitish at edges which are sore. Gums are somewhat irritated. Fauces and posterior pharynx red and congested. Thyroid not enlarged. No adenopathy. Chest thin; some muscular wasting and prominence of bony structures. Expansion normal. Breath sounds normal. Heart, no visible or palpable impulse. Sounds normal but heart slightly enlarged to the left. Abdomen slightly prominent and flabby. Liver small. Spleen not palpable. Loops of intestine palpated here and there. Reflexes normal. Skin has a muddy, icteroid tint.

Present Symptoms: Her mouth is at times sore; there is burning in the epigastrium and excess of gas in intestines; white, foamy stools; slight gas pains; lack of appetite. Blood pressure 130/80. Her highest weight had been 208 pounds.

Urine: Yellow, clear, acid; sp. grav. 1012; no sugar or albumin; an occasional leucocyte in the sediment.

Feces: Negative for intestinal parasites. Negative for *Monilia psilosis.*

Wassermann Test: Negative for syphilis.

Blood Chemistry:

Non-protein nitrogen	34.6
Urea nitrogen	11.1
Uric acid	4.1
Creatinin	1.5
Sugar	69.6
Phosphorus	3.9
Cholesterol	142.8
Serum calcium, total	8.7
Chlorides	489.3
Icteric index	14.1

Gastric Contents:

Minutes	R	15	30	45	60	75	90
Total acidity	15	31	40	48	44	25	14
Free acid	0	15	19	22	18	10	2

Duodenal Contents:

Acidity	3.0 units
Trypsin	5.0 units
Amylase	50.0 units
Lipase	3.8 units

The above history was taken February 16, 1930 when the patient entered the hospital. Three weeks after her discharge she became an office patient again, May 3, 1930. Her history from May 18, 1929 to February 16, 1930, is as follows:

When she first sought medical attention previous to entering hospital she denied having had sore tongue, although she had suffered much from sore mouth.

The remainder of her history is as above expressed. She then weighed 153 pounds. Her *blood chemistry* at that time was as follows:

Non-protein nitrogen	34.8
Urea nitrogen	11.7
Uric acid	4.8
Creatinin	0.9
Glucose	83.3
Chlorides	510.5
Cholesterol	168.2
Total, serum calcium	9.5
Diffusible serum calcium	5.4
CO_2 Combining power	44.7 cc.
Icteric index	7.7

Gastric Contents:

Minutes	R	15	30	45
Total acidity	22	12	7	7
Free acid	15	8	0	0

Duodenal Contents:

Acidity, neutral	
Trypsin	2.5 units
Amylase	5.0 units
Lipase	3.1 units
No occult blood	

She was placed on the sprue diet of Case 1 and the medicinal treatment was the same as in that case, save that she received a course of liver extract for a month. On the 15th of November, as she had not responded to liver extract and was really no better, she was given a course of *Monilia psilosis* vaccines. By the time she reached her seventh inoculation she had no more symptoms of sprue but as the first five had precipitated such severe diarrhea and sore tongue after each inoculation and she feared these symptoms would return, they were stopped January 16, 1930. On the 8th of February she returned with a full and severe picture of acute sprue and was sent to the hospital. On May 3, when she again took up her office visits it was found that while much thinner she was stronger and had none of the typical signs of the disease. Her anemia, however, was very little improved, so she was enjoined to eat all cereals and a pound of underdone steak daily without grease.

Course:

Date	Erythrocytes (millions)	Hb per cent	Reticulocytes, per cent	Remarks
5/18/29	3.816	62	0	
6/22/29	4.344	74		
9/5/29	2.840	63		
10/15/29	3.648	48		
2/8/30	3.112	34		
2/16/30	1.700	34		Lymphocytes 57 per cent.
2/19/30			0.6	Ventriculin, 30 g. daily to 2/28.
2/21/30			0.5	
2/22/30			0.4	
2/24/30			0.9	

2/25/30			0.6	
2/26/30			0.6	
2/27/30			0.3	
2/28/30	2.035	36		Ventriculin stopped.
3/9/30	1.960	30		Valentine's liquid liver extract, 30 cc. t. i. d.
3/11/30			1.0	
3/12/30			0.8	
3/14/30			0.7	
3/15/30			0.6	
3/16/30			1.1	
3/18/30	2.170	35	0.9	
3/27/30	2.273	42	0.9	Discharged improved. Formed bowel movements for first time in years.

Notes on the course of the disease:

9/5/29 Average diameter of erythrocytes, 8.36 microns. Blood pressure 115/80. Weight 134 pounds.

2/16/30 Weight 121 pounds; average erythrocytes 9.03 microns on admission to hospital.

3/9/30 Valentine's liver extract 30 cc. t. i. d.

Diagnosis: Tropical sprue with a pernicious type of anemia.

Comments: This is the case *par excellence* of hypoplasia of the blood regenerating organs. Neither ventriculin nor liver extract (aqueous, Valentine) had the slightest effect in producing reticulocytosis or raising blood values. And in common with the organs, practically all others were more or less in the same state. The absence of *Monilia psilosis* is explained as is a similar phenomenon in Case 2. Note history of high blood pressure (insufficiency of organs of elimination and faulty metabolism ?), low blood serum calcium, high icteric index, absence of hypochlorhydria. This patient made a sustained and sincere effort to regain her health but died a year after her discharge from hospital.

Case 6. A. Z. C., age 60, sex male, Hospital No. 185.

Clinical History: Previous history of good health save for instrumental infection of bladder from which he recovered. No gastro-intestinal disturbances previous to onset of present illness. Illness began eight months ago with nausea and vomiting; after meals flatulence and flatus. In a short time diarrhea began; three months ago sore tongue made its appearance. Has been gradually getting paler and weaker until now he is incapable of any exertion. No edema of ankles. Bowel movements are yellowish and, at times, foamy.

Physical Examination: A white male, 60 years old, under-weight and very pale. Arcus senilis; pupils normal, but lens slightly opaque. No icterus. Most of the teeth have been removed. Tongue neither shiny nor red. No adenopathies in neck and no rigidity. Narrow, long symmetrical chest. Lungs negative. There is a slight precardial bulging and apex beat is palpable and visible in the fifth intercostal space. Sounds of heart weak; apex displaced to left to axillary line and there is a definite murmur, transmitted to the vessels of the neck and

heard all over the chest with less intensity. Abdomen: wall has lost most of its tone. Spleen and liver not palpable. No tenderness. Both inguinal rings markedly dilated and in coughing bilateral bulging is noted.

Urine: Yellow, smoky, acid; sp. grav. 1008; trace of albumin, no sugar, many leucocytes (patient once had pyelonephritis) in sediment.

Feces: Negative for parasites and occult blood. Negative for *Monilia psilosis.*

Wassermann Reaction: Negative for syphilis.

Blood Chemistry:

Non-protein nitrogen	28.7
Urea nitrogen	16.0
Uric acid	2.1
Creatinin	1.1
Sugar	78.4
Phosphorus	3.9
Cholesterol	159.4
Total, calcium serum	9.1
Chlorides	498.4
Icteric index	0.36

Gastric Contents:

Minutes	R	15	30	45	60	75	90
Total acidity	50	85	98	89	82	52	26
Free acid	0	26	42	39	30	0	0

Treatment: As for Case 1.

Course:

Date	Erythrocytes (millions)	Hb per cent	Reticulocytes, per cent	Remarks
4/1/30	1.685	35	0.4	
4/3/30			0.4	Ventriculin 30 g. daily.
4/4/30			0.4	
4/5/30			0.2	
4/6/30			0.2	
4/7/30			0.2	
4/8/30			0.2	
4/9/30			0.4	
4/10/30			0.1	
4/11/30	1.710	42		Ventriculin stopped.
4/13/30				Liver extract, Lilly, 3 vials daily to discharge.
4/15/30			0.6	
4/16/30				
4/17/30			0.7	
4/19/30			1.5	
4/21/30	1.856	46	2.2	Discharged, improved.

Diagnosis: Tropical sprue with a pernicious type of anemia.

Complication: Valvular disease of the heart.

Comment: Neither ventriculin nor liver extract produced reticulocytosis and the slight rise in blood values may have been due to either the diet and hospital care or to the specific stimulus to the bone-marrow, but the absence of reticulocytosis belies the latter. Note the absence of hypochlorhydria.

Case 7. C. J., age 56, sex male, Hospital No. 196.

Clinical History: Previous history colorless. Present illness began eight months ago with diarrhea and, shortly after, soreness of the tongue. He gradually fell off in weight and became pale. There was great excess of intestinal gas and much acid eructation. Movements from the bowels are large, foamy, and from eight to ten in number a day. The physical examination only revealed a typical sprue cachexia.

Urine: Reddish yellow, clear; acid; sp. grav. 1015; albumin and sugar negative. A few leucocytes in sediment.

Feces: Ova of *Necator americanus;* negative for *Monilia psilosis.*

Wassermann Test: Negative.

Bone Marrow: Biopsy revealed aplasia.

Blood Chemistry:

Non-protein nitrogen	46.1
Urea nitrogen	21.2
Uric acid	1.9
Creatinin	1.8
Sugar	74.1
Cholesterol	122.5
Serum calcium, total	7.9
Phosphorus	1.9
Chlorides	579.4
Icteric index	8.6

Gastric Contents:

Minutes	R	15	30	45	60	75	90	105
Total acidity	12	19	21	17	13	13	13	13
Free acid	0	0	0	0	0	0	0	0

Treatment: Same as for Case 1.

Course:

Date	Erythrocytes (millions)	Hb per cent	Reticulocytes, per cent	Remarks
4/15/30	0.590	20		Four per cent eosinophiles.
4/18/30			1.2	
4/19/30			1.6	Ventriculin 30 g. daily.
4/20/30			4.8	
4/21/30			8.1	
4/22/30			10.8	
4/23/30			7.2	
4/24/30			5.2	
4/25/30			4.2	
4/26/30			2.8	
4/27/30			2.2	
5/1/30	0.747	12		Very profuse diarrhea, 3 to 6 movements. Ventriculin stopped. Given milk diet, tannalbin and opium, bismuth and chalk, and diarrhea was immediately controlled.

5/4/30			Liver extract (Lilly No. 343), 6 vials daily.
5/15/30	1.140	12	No reticulocyte count made.
5/23/30			Liver extract stopped.
5/27/30	1.16	20	
6/2/30			Chenopodium 3 cc. Worms not counted.
6/30/30	1.92	28	
7/2/30			Discharged, improved.

Diagnosis: Tropical sprue with a pernicious type of anemia.

Complication: Uncinariasis (?) worm count not made.

Comments: In spite of the pathologist's report of aplasia of the bone-marrow, ventriculin yielded a feeble reticulocytosis; the response to liver extract, unfortunately, as well as the number of Necators expelled, were not recorded but the failure to rise vigorously in blood values thereafter is pretty good evidence of bone-marrow hypoplasia. Here is a case in which the ventriculin *was* absorbed and yet only a feeble response and negligible rise in blood values ensued, thus confirming the hypoplasia of the marrow. In this case, achylia was apparently present but as no histamin was injected it cannot be assured. The serum calcium was unusually low, as well as the cholesterol. There was a decided retention of non-protein nitrogen and a slightly exaggerated icteric index.

Case 8. F. M., age 24, sex male, negroid, Hospital No. 243.

Clinical History: General health has always been good. The present affection began in 1924 with excess of abdominal gas, marked soreness of tongue, diarrhea, weakness and loss of weight. Under treatment he recovered completely and remained well for one and a half year. He then had a second attack, identical with the first. Similar attacks have occurred about every year since, lasting from six to eight months with from four to six months of relatively good health in the intervals. The present attack began in January, 1930, with gaseous distention of the bowels and a diarrhea which was whitish or yellowish, foamy, irritating, and generally abundant. At times he had gripping abdominal pains. The tongue was extremely sore; much excess of abdominal gas; loss of weight and strength. This attack has been more severe than the previous ones.

Physical Examination: The patient is a young colored male in extreme cachexia, weighing, with a height of sixty and a half inches, only sixty-nine and a half pounds. He is evidently chronically ill. There is a brownish pigmentation of the skin over the forehead and cheeks. The teeth are in fairly good condition, the tongue pale, glossy and smooth from atrophy of the papillae with small brownish spots throughout. The lungs are negative, as is the heart, save for a faint systolic, apical murmur. The abdomen is quite distended, especially in the epigastric region. Distended loops of intestine can be made out through the thin abdominal wall. The epigastrium and both hypochondria are somewhat tender on pressure but there is no mass to be distinguished.

Laboratory data: Urine: Color, yellow; clear; slightly acid; sp. grav. 1,005; albumin, faint trace; sugar, none; sediment, uric acid crystals and an occasional hyaline cast.

Feces: Heavy infestation by *Trichomonas hominis;* negative for *Monilia psilosis.*

Blood: Erythrocytes, 490,000 per cmm.; hemoglobin, 12 per cent; color index, 1.5; leucocytes, 2,000; marked anisocytosis and poikilocytosis; average diameter erythrocytes, 7 microns; one normoblast seen in 100 leucocytes; lymphocytes, 41.6 per cent; polymorphonuclears, 58.4 per cent.

Wassermann and Kahn: Negative.

Gastric Analysis:

Minutes	R	15	30	45	60	75	90
Total acid	12	18	28	42	49	34	30
Free acid	0	0	12	18	29	24	20

Duodenal Analysis:

Acidity	12°
Trypsin	10.0 units
Amylase	25.0 units
Lipase	0.4 unit

Blood Chemistry:

Non-protein nitrogen	36.6 mgm. per cent
Urea nitrogen	14.0 mgm. per cent
Uric acid	3.2 mgm. per cent
Creatinin	1.4 mgm. per cent
Sugar	68.4 mgm. per cent
Cholesterol	122.2 mgm. per cent
Serum calcium, total	8.2 mgm. per cent
Phosphorus	1.1 mgm. per cent
Chlorides	579.4 mgm. per cent
Icteric index	5.2 mgm. per cent

Treatment: As for Case 1, with exceptions noted below.

Course:

Date	Erythrocytes (millions)	Hb per cent	Reticulocytes, per cent	Remarks
6/5/30	0.49	12		6/5 to 6/8, 2 to 4 stools daily.
6/8/30			0.8	Weight 69½ pounds.
6/9/30			0.5	Ventriculin, 30 g. to 6/17. 5 stools. Weight, 66½ pounds.
6/10/30			0.8	3 stools. Opium mixture to 6/17.
6/11/30			0.5	9 stools.
6/12/30			0.6	10 stools.
6/13/30			0.8	9 stools.
6/14/30			0.4	8 stools.
6/15/30			0.7	8 stools.
6/16/30			0.7	4 stools. Weight, 58½ pounds.
6/17/30	0.77	19	0.6	5 stools. Ventriculin stopped.
6/18/30			0.7	Liver extract, Lilly, six vials daily to 6/21. Three stools.
6/19/30			0.5	4 stools.
6/20/30			0.9	5 stools.
6/21/30			0.9	4 stools. Liver ext. stopped.

6/22/30			0.9	1 stool.
6/23/30			1.4	1 stool. Weight, 65½ pounds.
6/24/30			1.9	1 stool. Liver ext. to 6/28; six vials.
6/25/30			2.8	2 stools.
6/26/30			2.6	1 stool.
6/27/30			1.2	1 stool.
6/28/30				1 stool. Stopped liver extract.
6/29/30			0.8	1 stool.
6/30/30				2 stools.
7/1/30			0.4	No stool. Weight, 71½ pounds.
7/2/30				1 stool.
7/3/30				1 stool.
7/4/30				2 stools.
7/5/30				2 stools.
7/6/30				3 stools.
7/7/30				2 stools. Weight, 73 pounds.
7/8/30				2 stools.
7/9/30				4 stools.
7/10/30	1.63	35		5 stools; after this 2 to 4.
7/14/30				Dihydranol, 3 caps. (each containing 0.15 gm. in olive oil—25 per cent solution). t. i. d. to 7/25.
8/7/30	2.49	38		Weight 79 pounds. Discharged improved. No Trichomonas in feces.

Diagnosis: Chronic recurrent tropical sprue with anemia of pernicious type.
Complication: Intestinal flagellosis (?).

Comment: Note small mean diameter of erythrocytes and absence of eosinophiles; possible low-grade nephritis (?); practically normal gastric acidity; high non-protein nitrogen; low blood sugar, cholesterol, and serum calcium. The administration of ventriculin was accompanied by an increase in the diarrhea and neither reticulocytosis nor more than a feeble increase in blood values ensued, the latter explicable by improved diet and hospital care. Liver extract seemed to produce a faint and totally inefficient reticulocyte increase but the rise in blood values seen three weeks later was not only insufficient as a response to the substance stimulating the hemopoietic organs but could have been produced, as in the first case, by better food and care. If *Trichomonas hominis* was responsible for any of the diarrhea it would have been only in the nature of an aggravant. Dihydranol eliminated the flagellate.

Case 9. W. S.; age 74; sex male; white; Hospital No. 229.

Clinical History: His general health has been very good. As a child he had measles and an occasional cold. In 1878 he had typhoid fever and has had malaria several times. In 1917 and 1922 he had pneumonia. He states that he has always had a distaste for meat.

His health was good until 1928 when he began to lose his appetite. During the first few months there were occasional diarrheal movements of apparently

small consequence. Following this, he began to feel weak and at this time took hardly any nourishment. Great loss of weight followed and his weakness increased from day to day. Lately there has been slight edema of the ankles toward evening. Occasionally he vomits but this is preceded by faintness. No fever. Has never had sore tongue.

Physical Examination: The patient is undernourished and very pale. His hair is gray and his face deeply furrowed by wrinkles. The arcus senilis is marked but the pupillary reactions are equal and normal. All teeth are missing. There is marked venous pulsation in the neck. The lungs are normal save for some degree of emphysema. The heart is slightly enlarged toward the left and the second aortic is louder than the second pulmonic sound. There is a soft murmur at the apex, systolic, and transmitted to the neck. The abdomen is scaphoid and there is no tenderness nor can any masses be palpated. The spleen and liver are not palpable.

Laboratory Data: Urine: Color, reddish-yellow; slightly turbid; alkaline; sp. grav. 1,015; no albumin or sugar.

Feces: Negative for parasites; positive for a Monilia which was not *Monilia psilosis.*

Blood: Erythrocytes, 780,000 per cmm.; hemoglobin, 30 per cent; color index, 2.0; leucocytes, 3,100; lymphocytes, 30 per cent; monocytes, 8 per cent; neutrophiles, 62 per cent; marked anisocytosis and poikilocytosis; many macrocytes; one normoblast and one megaloblast in 100 leucocytes.

Wassermann: Negative.

Blood Chemistry:

Non-protein nitrogen	54.5 mgm. per cent
Urea nitrogen	29.6 mgm. per cent
Uric acid	5.5 mgm. per cent
Creatinin	2.0 mgm. per cent
Sugar	90.9 mgm. per cent
Cholesterol	101.0 mgm. per cent
Serum calcium, total	8.8 mgm. per cent
Phosphorus	1.0 mgm. per cent
Chlorides	620.4 mgm. per cent
Icteric index	12.4 mgm. per cent

Gastric Analysis:

Minutes	R	15	30	45	60	75	90
Total acid	8	12	14	11	11	10	10
Free acid	0	0	0	0	0	0	0

Roentgenology: Stomach and duodenum: "both fluoroscopic and radiographic findings point toward a normal stomach and duodenum; the slight retention of barium in the organ six hours *post coenam* can be explained by the sluggish peristalsis shown by the stomach on fluoroscopy."

Treatment: As for Case 1.

Course:

Date	Erythrocytes (millions)	Hb per cent	Reticulocytes, per cent	Remarks
5/24/30	0.78	30		Weight, 99½ pounds.
5/30/30			0.4	
5/31/30			0.7	
6/1/30			0.2	

6/2/30			0.2	Ventriculin, 30 g. daily to 6/13.
6/3/30			0.2	
6/4/30			0.7	
6/5/30			2.5	
6/6/30			3.1	
6/7/30			0.3	
6/8/30			0.4	
6/9/30			0.4	
6/10/30			0.2	
6/11/30			0.2	3 stools.
6/12/30			0.2	4 stools.
6/13/30	0.67	21		Ventriculin stopped. 5 stools.
6/14/30			0.1	Liver ext. 6 vials, Lilly, daily to 6/28. Ten stools, not foamy; vomiting.
6/15/30			0.4	3 stools; not foamy; vomiting; weak.
6/18/30			3.0	Constipation to 6/25.
6/19/30			3.2	
6/20/30			7.7	
6/21/30			4.7	
6/22/30			2.1	
6/23/30			2.6	Weight, 91¾ pounds.
6/24/30			1.1	
6/25/30			1.6	Normal stools from now on.
6/26/30			1.8	
6/28/30	1.97	48		Liver ext. stopped.
7/3/30				Liver ext. 3 vials daily till discharge.
7/12/30	2.83	48		Discharged, much improved. Weight, 97.5 pounds.

Subsequent Course: The patient was instructed on leaving the hospital concerning his diet and urged to continue his liver extract. He was seen again on 8/11/30 and weighed 115 pounds, this in spite of an attack of tertian benign malaria which had reduced his weight six pounds. He was feeling very well at this time. On 9/3/30, while he felt very well, had only 2.87 million erythrocytes and 40 per cent hemoglobin. He had abandoned liver extract until two days before he returned for inspection. On his return, 11/16/30 he had 3.80 million erythrocytes and 68 per cent hemoglobin; was taking one vial of liver extract a day, eating everything, engaged in politics, and feeling perfectly well.

Diagnosis: A pernicious type of anemia of obscure origin, possibly nutritional.

Comments: Clinically, the case did not correspond to the typical Addison's disease in anything save the blood picture; cord lesions were not evidenced and there was extreme loss of weight. Nor did the case correspond to one of sprue; the gastro-intestinal picture was lacking save an occasional loose stool.

Note the high non-protein nitrogen, urea nitrogen, uric acid and chlorides in the chemical examination of the blood, as well as the low calcium and extremely low cholesterol. The icteric index was high. There was no free hydrochloric acid in the stomach contents and the total acid was low.

The reticulocyte responses to both ventriculin and liver extract were extremely feeble, as at the level of the erythrocytes at that time there should have been provoked a reticulocytosis of from 40 to 45 per cent. It is difficult to escape from the conclusion that ventriculin caused in this case an attack of diarrhea, for the patient was habitually constipated and had had no diarrhea save at this time while in the hospital.

Case 10. C. R., age 66; sex male; white; Hospital No. 249.

Clinical history of case when an office patient previous to admission to Hospital: 10/24/28. The patient had on this date a moderately severe case of complete sprue which, he stated, began six months before. There was a general stomatitis, great burning in the epigastrium, an enormous excess of intestinal gas, and severe, white foamy diarrhea. There was no abdominal pain, nausea or vomiting, but the appetite was at times diminished and he had burning in the anus after an evacuation of the bowels. There was great excess of an acid-tasting saliva, alternating with mouth dryness and he stated that he had lost the savour of food. He was weak, nervous and sleepless, depressed and forgetful. There was no numbness of hands or feet nor any muscular cramps in the legs. His complexion was sallow and the skin markedly atrophied with loss of elasticity and deep wrinkles on the face. His normal weight was 155 and he was then weighing 128 pounds. The hemoglobin was 87 per cent and the red cells were normal. He was steadily under treatment with the diet which all of these cases receive (see Ashford's diet for sprue, appended) and simple eupeptics. No liver or ventriculin was ever given this man. On June 13, 1929, his weight was 146 pounds, his hemoglobin 47 per cent, his erythrocytes 5,152,000 and the diameter of the reds averaged 7.8 microns. All symptoms of sprue had disappeared and he declared himself entirely well. He did not return again until June of 1930 when he was found to have 41 per cent hemoglobin, 2,064,000 erythrocytes and 3,800 leucocytes. He was then sent to the University Hospital.

Clinical history in the University Hospital: Patient's father died of a gastrointestinal disease. The patient felt perfectly well until February of 1930 when he noticed slight intestinal disturbances, gas, and inability to digest fats; there was no diarrhea. After this followed acid eructations, flatulence and dizziness. There was never any vomiting or diarrhea; on the contrary, the bowels have been obstinately constipated necessitating frequent enemas after four or five days without a bowel movement. No other symptoms were noted.

Physical Examination: There is no evidence of acute or severe chronic illness, from the appearance of the patient. The pupillary reactions are normal; the teeth are in good condition; the tongue shows no glossitis, nor papillary atrophy, nor glossiness. The vessels over the temples are tortuous and sclerosed. Lungs are normal. Examination of the heart was negative. The abdomen was not distended and its wall was soft. The spleen, liver, and kidneys not palpable. Reflexes were normal.

Laboratory data: Urine: Yellow, clear; acid; specific gravity 1,019; no albumin or sugar; sediment, calcium oxalate and uric acid crystals.

Feces: Negative for parasites; positive for *Monilia psilosis.*

Kahn: Negative.

Blood: Erythrocytes, 2,046,000 per cmm.; hemoglobin 41 per cent; leuco-

cytes 3,800; lymphocytes 71 per cent; monocytes 1 per cent; neutrophiles 28 per cent. (This was the count cited above and amplified in the hospital.)

Gastric analysis:

Minutes	R	15	30	45	60	75	90
Total acid	24	48	62	72	86	98	80
Free acid	9	28	35	42	48	57	40

Duodenal analysis:

Acidity	8°
Trypsin	2.5 units
Amylase	2.5 units
Lipase	0.09 unit

Blood Chemistry:

Non-protein nitrogen	39.9 mgm per cent
Urea nitrogen	12.2 mgm per cent
Uric acid	3.9 mgm per cent
Creatinin	1.6 mgm per cent
Sugar	90.4 mgm per cent
Cholesterol	109.0 mgm per cent
Serum calcium, total	8.1 mgm per cent
Phosphorus	1.1 mgm per cent
Chlorides	509.4 mgm per cent
Icteric index	6.1 mgm per cent

Treatment: Same diet as before recorded, ventriculin and later liver extract.

Course: Usually one bowel movement a day; occasionally none; on four days two; on two days three.

Date	Erythrocytes (millions)	Hb per cent	Reticulocytes, per cent	Remarks
6/25/30	2.06	44	0.0	
6/26/30			0.0	
6/27/30			0.1	
6/28/30			0.2	Ventriculin, 30 g. daily to 7/10.
6/29/30			0.2	
6/30/30			0.3	
7/2/30			0.5	
7/4/30			0.5	
7/6/30			0.3	
7/8/30			0.3	
7/10/30	1.59	42	0.4	Ventriculin stopped.
7/11/30				Liver ext. Lilly, 6 vials daily.
7/12/30			0.5	
7/14/30			0.6	
7/16/30			0.4	
7/18/30			0.1	
7/20/30			0.3	
7/22/30	2.3	38		Discharged unimproved, save for digestion.

Diagnosis: A pernicious type of anemia, sequel of sprue.

Comments: This case illustrates very well an astonishingly frequent type of relapse of the sprue condition after a primary apparent cure. It usually recurs after an unlimited orgy of "food of all kinds", which generally means a return

to the very nutritional unbalance that provoked the original disease, as soon as the patient finds himself in what he considers a cured condition. Note that the weight of the disease falls on the blood regenerating organs and passes over the gastro-intestinal tract without causing diarrhea, sore tongue or excess of intestinal gas. In this case, there was a normal gastric acidity but a low blood cholesterol and calcium. While in this particular case *Monilia psilosis* was cultured from the feces, this is by no means the rule, as these patients are apt to place themselves upon the diet which cured them long before they consult their physician and the fungus is deprived of its enriching medium as well as suffering the effects of a lowered acidity of the intestinal contents. Neither ventriculin nor liver extract seemed to have had any effect on the blood values which rose, probably due to the diet.

Case 11. F. D., age 36; sex male; white; Hospital No. 368.

(This case was worked up by Drs. Ramón Suárez and Juan Pons and reported by the former as case 3 of his series in an article entitled, "El tratamiento del esprú y el uso del extracto acuoso de hígado en su anemia", Bol. Asoc. Méd. de P. R., 23:(186) 74.)

Clinical history: The patient has generally enjoyed good health. He had influenza in 1918 and an operation a year ago for hydrocele. Did not suffer from either diarrhea or constipation. The onset came about a year ago with diarrhea of which there were repeated attacks which would last a day or so and then subside for a month or more. During the last six months the diarrhea has been more or less constant and for the last six weeks, extremely severe. There have been as many as sixteen movements a day, all watery, foamy and irritating to the anus. There has also been severe epigastric burning, acid eructations and a sore tongue. The patient's normal weight has been 145 pounds, but in seven months it has been reduced to 91 pounds. With these symptoms there have gradually developed weakness and pallor, some edema of the ankles, dyspnea of effort, and the last month, a mild attack of jaundice which subsided without treatment.

Physical examination: The patient is emaciated and looks to be suffering from a chronic disease. There is a brownish pigmentation over face on forehead, malar prominences chest and abdomen. The face is puffy and the mucous membranes are very pale. The teeth are affected with pyorrhea. The tongue, not now acutely inflamed, is smooth and glossy. Heart and lungs apparently normal. Abdominal wall soft and flabby; no masses detected. Spleen and liver not palpable.

Laboratory data: Urine: Color, amber; transparent; alkaline; specific gravity, 1008; faint trace of albumin; no sugar; sediment, triple phosphates, no casts.

Feces: Negative for intestinal parasites on three occasions; positive for *Monilia psilosis.*

Kahn and Wassermann: Negative.

Blood Chemistry:

Non-protein nitrogen	36.5 mgm per cent
Urea nitrogen	14.8 mgm per cent
Uric acid	4.3 mgm per cent

Creatinin	1.5 mgm per cent
Sugar	125. mgm per cent
Phosphorus	3.8 mgm per cent
Serum calcium, total	8.0 mgm per cent
Cholesterol	112.4 mgm per cent
Chlorides	525.4 mgm per cent
Icteric index	9.4

Blood: Erythrocytes, 580,000 per cmm; hemoglobin, less than 10 per cent; color index, 1; leucocytes, 3,100; lymphocytes, 58 per cent; monocytes, 1 per cent; neutrophiles, 45 per cent; marked poikilocytosis and anisocytosis; no immature cells.

Gastric analysis:

Minutes	R	15	30	45	60	75	90
Total acid	12	14	15	15	15	12	12
Free acid	0	0	0	0	0	0	0

Duodenal analysis:

Acidity	4°
Trypsin	20 units
Amylase	50 units
Lipase	0.1 unit

Treatment: Ashford's sprue diet, strychnin, hydrochloric acid, pepsin and cardamom prescription and pancreatin, takadiastase, magnesium oxide, and calcium carbonate mentioned in treatment of case 1. To control the diarrhea the following was given:

R/

Tinct. opii deodorat.	4.
Bismuth. subnitrat.	
Cretae preparat.	aa 13.
Syr. acaciae	100.
Aq. cinnamomi	200.

Met Sig. One tablesponful in water every 2 hours until relief.
The rest of the treatment will appear on day administered.

Course:

Date	Erythrocytes (millions)	Hb per cent	Reticulocytes, per cent	Remarks
11/22/30	0.58	10		Wt. 94.5 pounds. Stools, 8.
11/23/30				Stools, 19.
11/24/30				Stools, 6.
11/25/30				Stools, 7.
11/26/30				Stools, 5.
11/27/30				Stools, 4. Wt. 88 pounds.
11/28/30				Stools, 3.
11/29/30				Stools, 3.
11/30/30				Stools, 1.
12/1/30				Stools, 1. Wt. 93.75 pounds.
12/2/30				Stools, 1.
12/3/30				Stools, 2.
12/4/30				Stools, 2. Wt. 89 pounds.
12/5/30			0.7	Stools, 1.

12/6/30				Ventriculin, 30 g. daily to 12/20.
12/7/30	0.51	10	0.6	
12/8/30				Wt. 93.5 pounds.
12/9/30			0.9	
12/11/30			0.8	Wt. 92 pounds.
12/13/30			1.0	
12/15/30			0.8	Wt. 92 pounds.
12/17/30			0.6	
12/18/30				Wt. 96.25 pounds.
12/20/30	0.54	10		Ventriculin stopped.
12/22/30				Wt. 97.75 pounds.

The number of bowel movements from 12/6 to 12/20 was three a day. From this time to 1/4/31, there were from one to four a day.

On January 5, 8 g. of glucose three times a day was added to the diet, and 10 units of insulin injected twice daily.

In addition, on the 7th of January, 1931, the gastric analysis was repeated after a previous injection of histamin, with the following result:

Gastric analysis:

Minutes	R	15	30	45	60	75	90
Total acid	12	12	16	16	12	10	10
Free acid	0	0	0	0	0	0	0

The blood was reexamined and found as follows:

Erythrocytes, 520,000 per cmm; hemoglobin, 10 per cent; leucocytes, 6,200. On the 8th of January, the diet was limited exclusively to fresh fruits and seven ounces of underdone meat. From the 8th to the 10th of January, inclusive, the bowel movements numbered, respectively, 6, 7, and 8.

Date	Erythrocytes (millions)	Hb per cent	Reticulocytes, per cent	Remarks
1/9/31				Liver ext., E 29, Valentine, 90 cc daily.
1/10/31				Stools, 7.
1/11/31			1.1	Stools, 8.
1/12/31				Stools, 7.
1/13/31			18.0	Stools, 5.
1/14/31				Stools, 2. Food calories 1793.8
1/15/31			65.0	Stools, 2. Food calories 2653
1/16/31				Stools, 1. Food calories 2828.
1/17/31			26.0	Stools, from one to two, occasionally three until discharge. Food calories, 2883.
1/18/31				Food calories, 3270.
1/19/31	2.02	40		Glucose and insulin discontinued.
1/21/31				Food calories, 3339.
2/5/31				Wt. 99.75 pounds.
2/10/31				Wt. 102.5 pounds.
2/16/31	2.90	55		Wt. 106.25 pounds.

2/19/31			Wt. 108. pounds.
2/26/31			Wt. 109.25 pounds.
3/2/31	3.5	70	Wt. 112.5 pounds.
3/5/31			Wt. 113.5 pounds.
3/9/31			Wt. 114 pounds. Discharged

The patient was seen again on April 5 and stated that he felt well and was following the diet; only occasionally was there diarrhea of a day or two and at times a little gas. The erythrocytes were 3.40 millions per cmm, the hemoglobin 75 per cent, and the weight 126 pounds.

Diagnosis: Tropical sprue with an anemia of pernicious type.

Comments: Blood Chemistry: Note high non-protein nitrogen, urea and uric acid; high sugar, low cholesterol and serum calcium and high icteric index. There was true achylia gastrica. Ventriculin failed to produce reticulocytosis or increase in blood values while aqueous liver extract produced the highest reticulocytosis we have ever seen, 65 per cent, and a rapid rise in blood values.

OFFICE CASE

Case 12. J. M. S., age 52; sex male; white.

Clinical history: Father, sister and brother all died of typical, uncomplicated tropical sprue. One sister was dangerously ill of the same disease but was cured. The patient has always been malnourished, although a member of a wealthy and distinguished family. His first attack of sprue occurred ten years ago and two years ago he had a bad relapse from which he thought he had recovered, but recently he entered into his third and worst attack. Between these attacks of sprue he always lapsed into the same habits of eating which had preceded each of them. At present he is suffering from sore tongue, burning in the epigastrium, great excess of intestinal gas, and a white frothy diarrhea alternating with constipation. He has no nausea or vomiting, and rarely abdominal pain. Soreness of the tongue alternates with burning of the anus. He has a good appetite and there is no excess of saliva or alteration of taste, but he is apt to suffer from excessive dryness of the mouth.

There is no nervous irritabilitiy but the patient complains of sleeplessness, palpitation of the heart, depression of spirits, severe cramps in the legs during the night, and loss of memory. He is extremely weak and pale; at times there is dizziness but rarely headache. The ghastly pallor is heightened by a symmetrical brownish pigmentation over the forehead, over the eyebrows, around the mouth, over malar prominences, behind the ears, and on the external aspect of the neck. He is 61 inches in height and his highest weight has been 107 pounds. His weight on this date (5/5/31) is 69 pounds.

Physical examination: A middle-aged, undernourished, intellectual man in a state of cachexia. There is a grayish pallor of the skin, which is dry, atrophic and has lost its elasticity. The heart and lungs are normal. The abdomen is distended with gas, and loops of intestine are easily discernible. The liver is small, and the spleen cannot be palpated.

Laboratory data: Urine: Color, dark amber; acid; specific gravity 1,010; no albumin or sugar; excess of indican; strong trace of biliary acids; urobilin 5,652 units.

Feces: Negative for parasites; not examined for *Monilia psilosis.*

Blood Chemistry:

Non-protein nitrogen	32.4 mgm per cent
Urea nitrogen	11.7 mgm per cent
Uric acid	2.9 mgm per cent
Creatinin	1.3 mgm per cent
Glucose	98.9 mgm per cent
Chlorides	552.2 mgm per cent
Cholesterol	128.4 mgm per cent
Serum calcium, total	8.2 mgm per cent
Icteric index	22.4
Van den Bergh's test, indirect	5.5 units.

Basal metabolism: + 15 per cent.

Gastric analysis: (Histamin injected).

Minutes	R	15	30	45	60	75	90	105	120
Total acid	31	31	46	58	62	68	35	10	8
Free acid	10	10	22	32	36	38	10	0	0

Treatment: Diet same as in case 1; also eupeptics. The amounts of ventriculin, liver extract and ferri carbonas saccharatus are stated on the chart and the effect on the blood can be seen.

Diagnosis: Chronic recurrent tropical sprue with an anemia of pernicious type.

Comments: Note the low cholesterol and serum calcium and very high icteric index. There is no hypochlorhydria.

This case demonstrates the apparent failure of both ventriculin and liver extract to affect the bone-marrow, either because the substance was not absorbed from the intestinal canal, or on account of hypoplasia of the blood regenerating organs. The probability is that this failure was due to the latter condition as in the course of an adequate diet, with a pound of broiled steak a day and plenty of fresh vegetables, the improvement gives reason to favor the hypothesis that a proliferation of megaloblasts occurred and that there was a reestablishment of compensation of the hemopoietic organs, powerfully aided by iron which actuated in this case as a food. While this is purely theory, there must have been a production of the substance necessary to provoke the birth of red blood cells and this substance, generated by the secretion from the gastric mucous membrane acting on muscle meat, must have been absorbed. Of course, once the compensation of the bone-marrow should have been restored, the additional amounts of this substance furnished by ventriculin and liver extract must have taken a part, but as the effect was probably gradual, no striking evidence thereof was furnished by a measurable reticulocytosis.

Case 13. J. P., age 48; white; married; poor woman from the country districts. **Hospital Case No. 257.**

Clinical history: This woman had been sent home from a hospital as incurable and one of the writers (B. K. A.) was called to see her. She was semi-conscious and in such a serious condition as to require immediate transfer to the University Hospital. The hemoglobin, taken with a Dare instrument under country conditions in an over-crowded hut by candle light, revealed something below 10 per cent; count of red cells gave 0.11 million per cmm.

The patient does not recall having had any serious illness, but her general health has been poor for the last four years with chronic indigestion and loss of weight, culminating in profound anemia in the last four months. She states that greasy food and cereals are not digested. She has had four or five watery or foamy movements from the bowels daily for several months and a very sore tongue.

Physical examination: An extremely pale, emaciated, cachectic woman of middle age; the skin is atrophied, muddy in color, and pigmented in symmetrical areas on face and arms. The pupillary reflexes are sluggish to light. There is no edema of the face. At present, the tongue is not raw but there is evidence of papillary atrophy as it is small, smooth, and glistening. She is suffering severely from pyorrhea and gums are swollen, bleeding, and bathed in pus. The lungs are the seat of a moderate edema at the bases and she gives a history of cough and dyspnea which elicited a clinical diagnosis of recent date of pulmonary tuberculosis without, however, any positive report from examination of the sputum. The heart is not enlarged but hemic murmurs are pronounced. The liver dullness extends from the 5th interspace to the costal margin. There is muscular rigidity over the gall-bladder region and an indefinite mass at this point on deep palpation. There is no ascites. The spleen is not palpable. The patellar reflex is absent.

Laboratory data: Urine: Pale yellow; clear; acid; specific gravity 1,012. There is no albumin or sugar; sediment is negative.

Feces: Not examined for *Monilia psilosis; Trichomonas hominis* present; no other intestinal parasites found after repeated examination.

Kahn: Negative.

Blood Chemistry:

Non-protein nitrogen	28.4	mgm per cent
Creatinin	1.1	mgm per cent
Sugar	84.4	mgm per cent
Icteric index	5.7	
Van den Bergh's reaction, indirect	0.75	unit
Serum calcium, total	8.4	mgm per cent

Sputum: Negative for Bacillus tuberculosis.

Gastric Analysis:

Minutes	R	15	30	45	60	75	90
Total acid	27	36	44	40	26	20	15
Free acid	5	15	20	20	8	0	0

Much mucus and bile.

Roentgenologic examination: No calculi were located in the gall-bladder whose shadow was very faint. "Films of the stomach and duodenum demonstrate no evidence of extrinsic or intrinsic pathologic change in these organs. The stomach was completely empty five hours *post coenam.*" (8/31/31).

Course: The blood changes are graphically displayed in the charts corresponding to this case. From date of admission, June 6, 1931 until June 20th, the patient ran a temperature between normal and 100° Fahr. which intermitted daily. On June 18 she complained of severe pain in the right upper adbominal quadrant. There was considerable rigidity and tenderness. On the 20th, the calf of the right leg became very painful and exquisitely tender but there was no redness

nor infiltration. On the 22nd of June her temperature rose to 101.6° and on the following day to 102.6°. By the 24th she was afebrile. During this acute period, June 18–24th, she vomited repeatedly, on one occasion with traces of blood; this was accompanied by black and fetid stools.

From June 24th until July 15th, her temperature was usually subnormal but on the latter date she had a chill, followed by a temperature of 100.2° Fahr., with vomiting and pain in the epigastrium very much like an attack of cholecystitis, which we suppose, in fact, that it was.

Treatment: Diet for sprue was immediately begun on admission. From June 12 to 22, ventriculin, 30 g. daily, was administered. From the 17th on, the diarrhea had to be controlled by opiates. On June 24, the two prescriptions of strychnin and hydrochloric acid and pancreatin, takadiastase, magnesium oxide and calcium carbonate mentioned in case 1, were begun and continued until discharge.

On July 17, liver extract (Lilly, 343), three vials a day, was begun and sustained until August 24.

The patient was discharged practically well on September 9, 1931, weighing, however, only 78.5 pounds.

Diagnosis: Tropical sprue with an anemia of pernicious type, severe pyorrhea and cholecystitis.

Comments: This woman was the most gravely ill of all so far seen in our experience to recover from an anemia of this type. She was in semi-coma when brought to the hospital and for a week we were constantly expecting her death from asthenia. In this case, ventriculin produced a normal reticulocyte response and this was followed by a prompt rise in blood values, but she "stalled" at the 50—75 per cent red cell level and, in spite of liver extract, refused to rise further until the last month. This seems to have been due, in part, to her cholecystitis and pyorrhea. She should have been given iron in large doses, as well as the aqueous extract of liver (E 29, Valentine), but it has been impossible to reach her since her discharge.

The most remarkable eosinophilia (see chart of this case under "leucocytes") developed in the course of treatment. The extraordinary peaks roughly correspond to those of the total leucocyte count. Note the absence of achylia gastrica and the low icteric index.

APPENDIX

SPRUE DIET RECOMMENDED BY ASHFORD

Breakfast: Coffee with milk, sweetened with saccharin.
Two soft-boiled or poached eggs.
One of the following fruits: oranges, grapefruit, large bananas, apples, pears, peaches, mangoes, ripe pawpaw. If bananas or mangoes, for which some have an idiosyncrasy of not being able to digest, disagree, omit them from the diet.

Midday meal: Hot bouillon or chicken broth with small pieces of the vegetables allowed in this diet.
A half-pound of beefsteak with a little salt, lightly broiled or lean, rare roast beef or roast chicken. The meat should be as rare as possible. If a tender variety of beef can not be secured, or for the purpose of varying the diet, a good quality of beef can be chopped up, made into a meat ball and seared over a hot fire. It should be turned out on a previously heated plate and eaten while hot. Fresh fish, broiled or baked, is permitted, as well as are eggs.
Fresh vegetables from the garden, baked or boiled; okra, simlins, squash, carrots, spinach, asparagus, beets, tomatoes, turnips, string beans, lima beans, peas and eggplant. If one is living in the Antillian tropics, the following native vegetables can be used: yautía blanca, boiled or mashed; amarillos, roasted or boiled; casabe (baked); chayote; ñame. A salad on the basis of chopped beet leaves or lettuce with tomatoes, celery, asparagus, beets, cucumbers, pawpaw, chayote, cabbage or fruits. These salads should never be omitted and should be eaten in abundance.

Afternoon repast: Tea or coffee with milk, or skimmed chicken broth.

Dinner: As for the midday meal.

Supper: A glass of hot milk or some fruit.

Foods prohibited: Sugar and anything that may contain it, such as pastry, preserves and sweetened canned fruits, raisins,

dried prunes, ice cream and the product of the soda-water fountain.

Bread and anything containing wheat flour, such as cakes, biscuits, and crackers.

All cereals and flours made from grains such as rice, cornmeal, "corn flakes" and other such cereal derivatives with trade names. To this list should be added beans, potatoes, sweet potatoes, alligator pears and pine-apples.

Remarks: Food should be well prepared and well served. Fried food should not be permitted.

The principal object is to increase the nutrition by providing a diet rich in the elements which are to form muscular, glandular, and nervous tissues, as well as in those containing vitamins. No less than a pound of meat a day is recommended.

(Calorie values should be calculated and should not fall below 1800 C. a day).

REFERENCES

1. Ashford, B. K.: (1920) Sprue, Chapter in Oxford Loose-Leaf Medicine, Oxford Univ. Press, American Branch.
2. Ashford, B. K.: (1921) La carencia de ciertos elementos alimenticios como causa predisponente del esprú, pelagra, y beriberi en Puerto Rico. Bol. Asoc. Méd. de P. R., **15**: 249.
3. Ashford, B. K.: (1922) Observations on the conception that sprue is a mycosis superimposed upon a state of deficiency in certain food elements. Amer. Jour. Trop. Med., **2**: 139.
4. Ashford, B. K.: (1923) A clinical investigation of tropical sprue. Amer. Jour. Med. Sci., **165**: 157.
5. Ashford, B. K.: (1924) Tropical sprue in Porto Rico; a synthesis of fifteen years' work of investigation and two thousand two hundred cases. Proc. Int'l. Confer. on Health Problems in Tropical America, held at Kingston, Jamaica, B.W.I., July 22 to Aug. 1, 1924, pp. 686–708. Published by the United Fruit Company, Boston Mass.
6. Ashford, B. K.: (1925) Sprue, Address before the American Congress of Internal Medicine, Washington, March 9, Ann. Clin. Med., **4**: 13.
7. Ashford, B. K.: (1926) With L. G. Hernández. Blood-serum calcium in sprue and other pathologic states in the tropics. Amer. J. Med. Sci., **171**: 575.
8. Ashford, B. K.: (1927) Sprue, Chapter in Russell Cecil's textbook on Medicine, pp. 350–355.
9. Ashford, B. K.: (1928) Certain conditions of the gastro-intestinal tract in Porto Rico and their relation to tropical sprue. Amer.

Jour. Trop. Med., **8**:507. (Address before the New York Academy of Medicine, May 5, 1927).

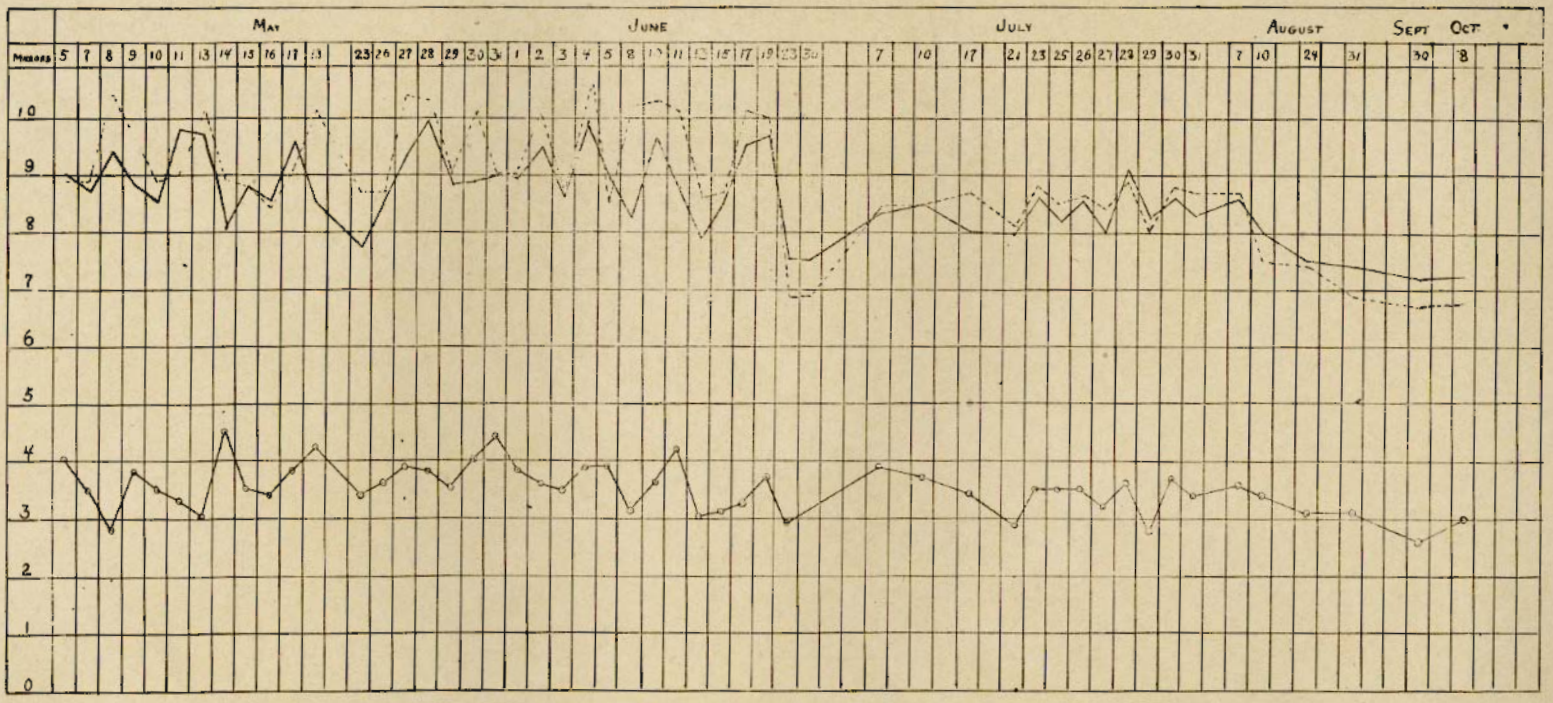
10. Ashford, B. K.: (1928) An evaluation of liver extract in the treatment of the anemias of sprue, J.A.M.A., **91**: 242.
11. Ashford, B. K.: (1929) Mycology of intestinal canal in Porto Rico and its relation to tropical sprue. Trans. Int'l. Congress of Trop. Med. & Hyg., held in Cairo, Egypt, Dec. 1928. J.A.M.A. **93**: 762.
12. Ashford, B. K.: (1930) With E. W. Lord. A severe case of tropical sprue. P. R. Jour. Pub. Health & Trop. Med., **5**: 268.
13. Ashford, B. K.: (1930) The Anemias of Sprue; their nature and treatment. Trans. Int'l. Congress of Tropical Med. & Hyg. held in Cairo, Egypt, Dec. 1928, **2**: 345. Abridged ed. Arch. Int. Med., **45**: 647.
14. Ashford, B. K.: (1931) Sprue, Tice's Practice of Medicine, Vol. IV, Chapter XXVII, W. F. Prior Co., Hagerstown, Maryland.
15. Ashford, B. K.: (1931) The relation of *Monilia psilosis* to tropical sprue and an evaluation of fermentation of sugar as a criterion for specificity. P. R. Jour. Pub. Health & Trop. Med., **6**: 310.
16. Castle, W. B.: (1929) Observations on the etiologic relationship of achylia gastrica to pernicious anemia. I. The effect of the administration to patients with pernicious anemia of the contents of the normal human stomach recovered after the ingestion of beef muscle. Amer. Jour. Med. Sci., **178**: 748.
17. Castle, W. B. and Locke, E. A.: (1928) Observations on the etiologic relationship of achylia gastrica to pernicious anemia. Jour. Clin. Invest. **6**: 3.
18. Castle, W. B. and Townsend, W. C.: (1929) Observations on the etiologic relationship of achylia gastrica to pernicious anemia. II. The effect of the administration to patients with pernicious anemia of beef muscle after incubation with normal human gastric juice. Amer. Jour. Med. Sci., **178**: 764.
19. Isaacs, Raphael: (1930) The physiologic histology of bone-marrow. The mechanism of the development of blood cells and their liberation into the peripheral circulation. Sonderdruck aus: "Folia Haematologica", 40 Bd., Heft ¾, Akademische Verlagsgesellschaft m.b.H. in Leipzig.
20. Isaacs, R., Sturgis, C. C., and Rennie, T. A. C.: (1930) The treatment of pernicious anemia (Addison-Biermer type) with desiccated stomach. "Folia Haematologica", 40 Bd., Helft. ¾ Akademische Verlagsgesellschaft m.b.H. in Leipizig.
21. Isaacs, R., Sturgis, C. C. and Smith, M.: (1928) Tapeworm anemia. Arch. Int. Med., **42**: 313.
22. Minot, George R., Murphy, William P. and Stetson, Richard P.: (1928) The response of the reticulocytes to liver therapy, particularly in pernicious anemia. Amer. Jour. Med. Sci., **175**: 581.
23. Minot, George R., Cohn, Edwin J. and Lawson, Herman A. (1928) treatment of pernincious anemia (Addison-Biermer type) with

upon the production of immature and mature red blood cells. Jour. Med. Sci., **175**: 599.

24. Porter, William B. and Irving Hazelwood: (1929) Reticulocytosis produced by liver extract; two, three and four-hour-interval observations. Arch. Int. Med., **44**: 502.
25. Porter, William B., Williams, Powell J., Forces, J. C. and Irving. Hazelwood: (1929) Aqueous extract of liver; development and use in treatment of pernicious anemia. J.A.M.A. **93**: 176.
26. Porter, William B. and Rucker, J. E.: (1930) The treatment of nontropical sprue with liver extract, a report of two cases. Amer. Jour. Med. Sci., **179**: 310.
27. Sturgis, Cyrus C.: (1930) Recent development in the treatment of pernicious anemia and a consideration of the etiology of the disease. Middleton Goldsmith Lecture, New York Pathological Society. Lancaster Press, Lancaster, Pa.
28. Sturgis, Cyrus C., Isaacs, Raphael, and Smith, Millard: (1928) Limitations of the liver treatment in pernicious anemia. Trans. Amer. Physicians, **43**: 17.
29. Sturgis, Cyrus C. and Isaacs, Raphael: (130) Treatment of pernicious anemia with desiccated defatted stomach. Amer. Jour. Med. Sci., **180**: 597.

Case 12

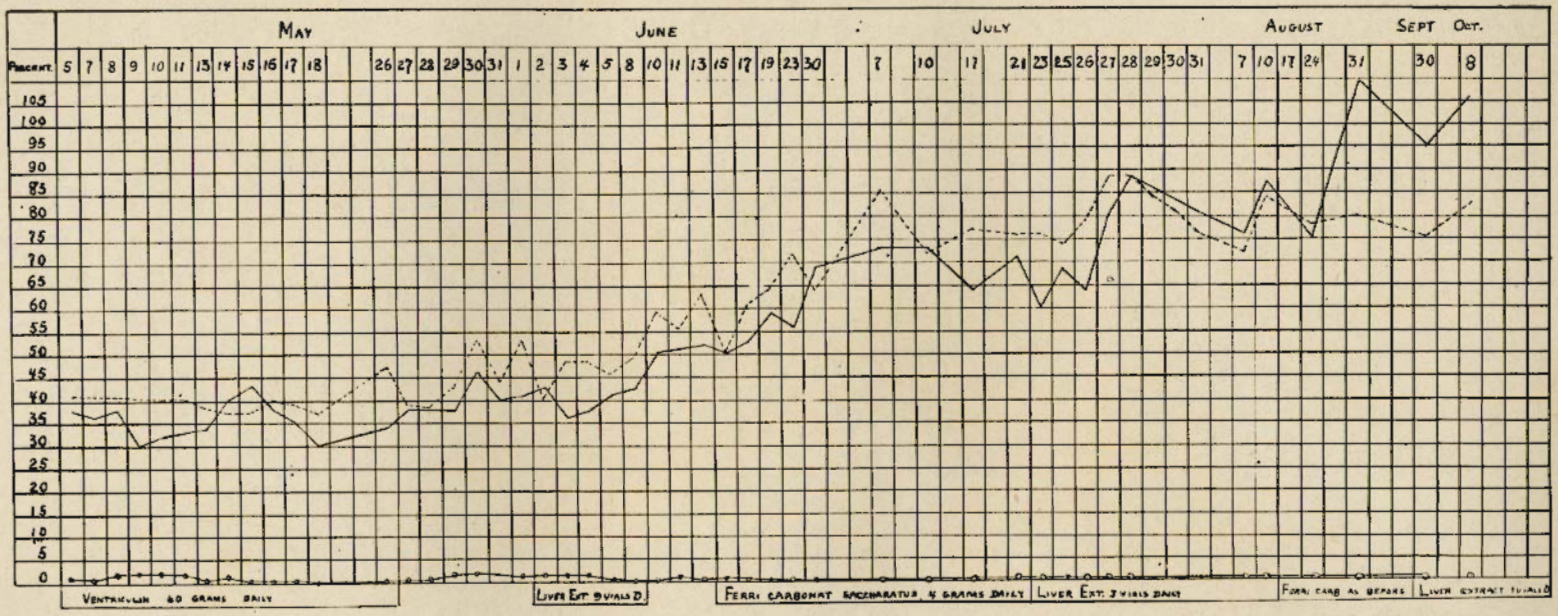
Diameter of Erythrocytes



Mean : Continuous Line
Median: Dotted Line
Double Dispersion

Case 12

Erythrocyte Hemoglobin and Reticulocyte Percentage



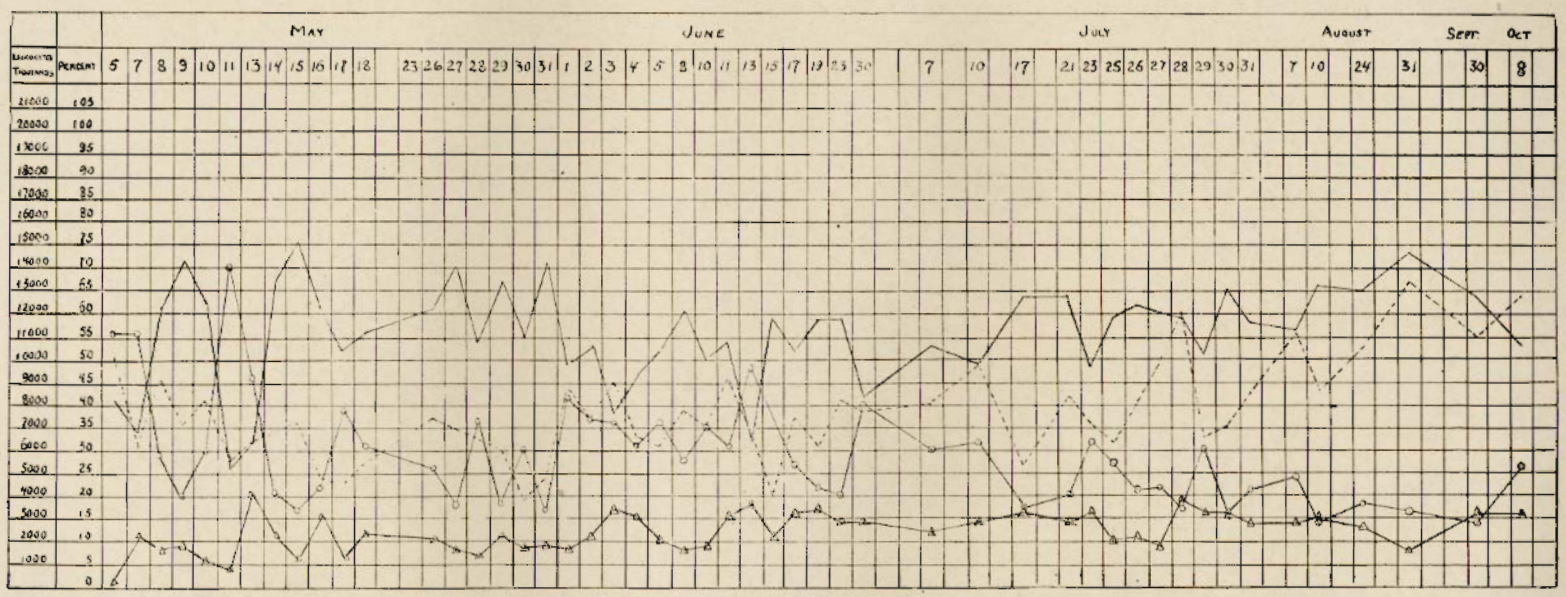
Erythrocytes — Solid line

Hemoglobin — Dotted line

Reticulocytes

Case 12

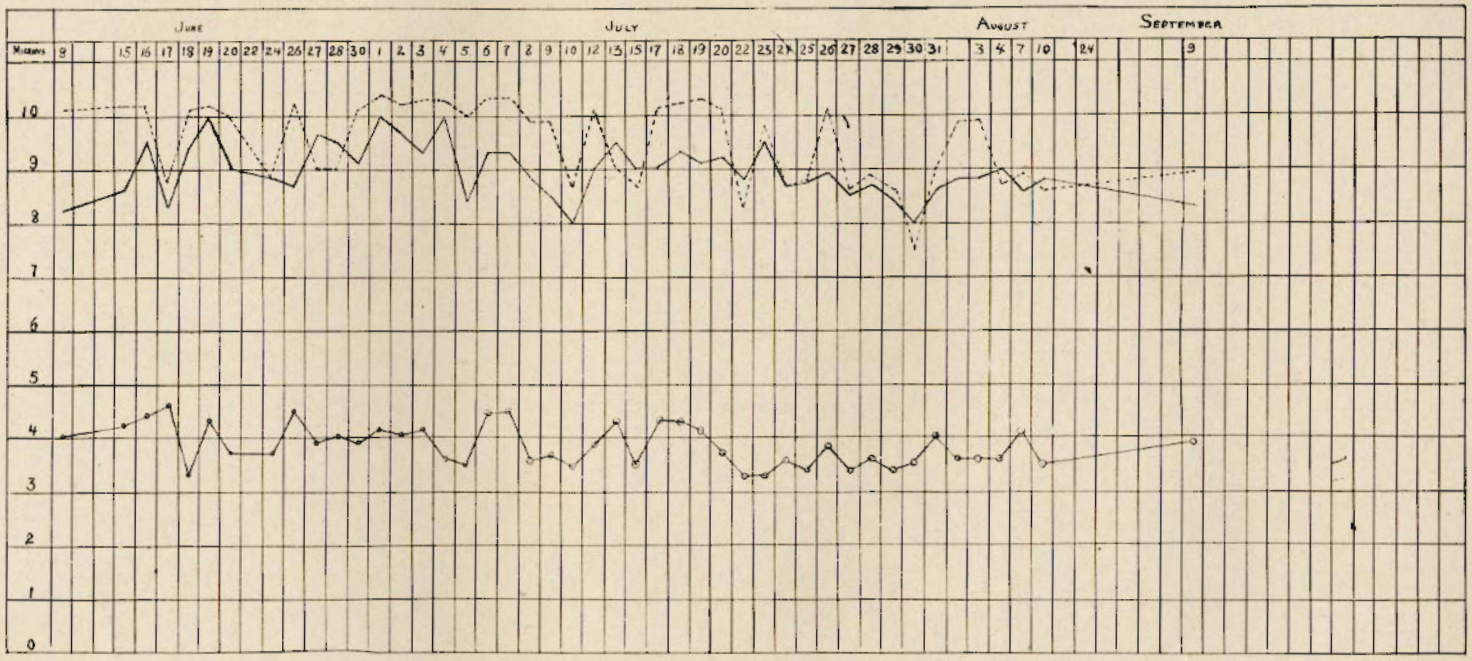
Leucocytes



Leucocytes Dotted Line
Polymorphonuclear Neutrophiles Continuous Line
Lymphocytes
Eosinophiles

Case 13

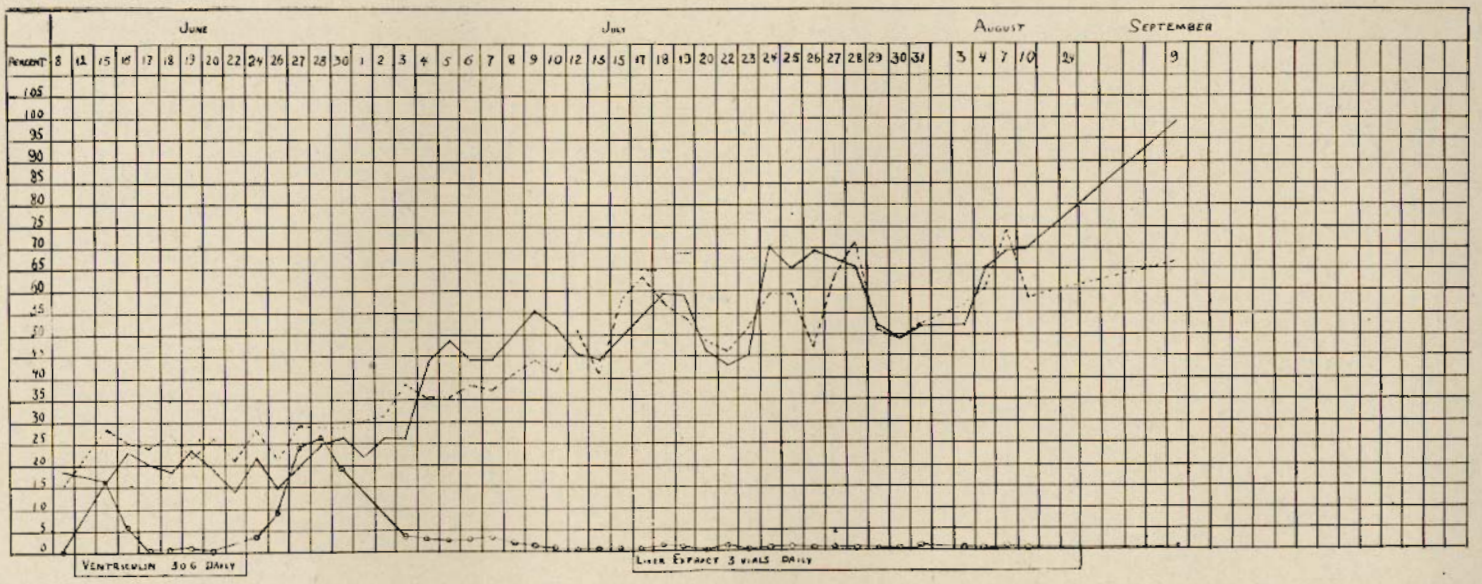
Diameter of Erythrocytes



Mean: Continuous Line
Mcdian Dotted Line
Double Dispersion o——————o

Case 13

Erythrocyte, Hemoglobin and Reticulocyte Percentage



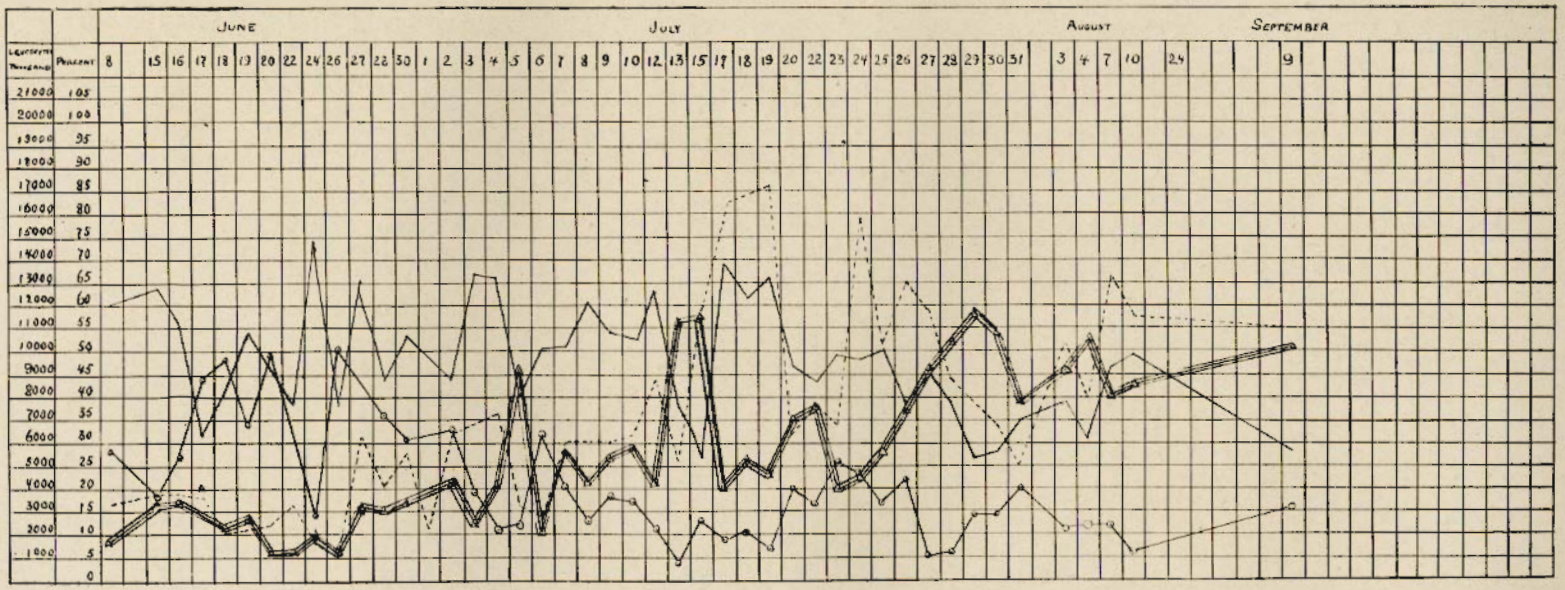
Erythrocytes — Solid line

Hemoglobin — Dotted line

Reticulocytes — ○———○

Case 13

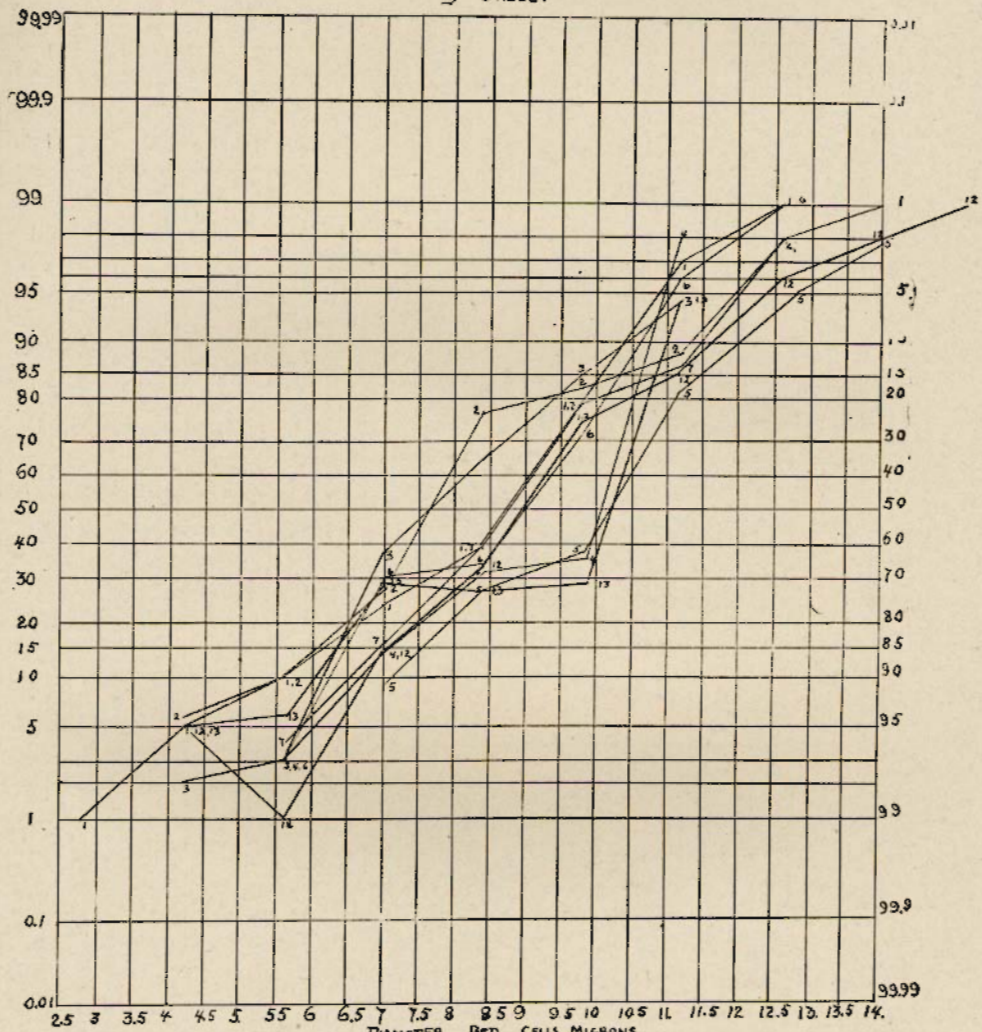
Leucocytes 1



Leucocytes? Dotted Line
Polymorphonuclear Neutrophiles Continuous Line
Lymphocytes. o——o
Eosinophiles.

Price-Jone Curves on Admission

9 cases.



Case	1	2	3	4	5	6	7	12	13
Mean	8.37	8.214	8.06	9.06	9.68	8.44	8.78	9.08	8.19
Median	8.60	7.6	7.6	10.20	10.2	9.0	8.8	8.9	10.4
Double Dispersion	3.9	4.0	3.3	3	3.8	3.9	3.5	4.	4.