

**A CASE OF HYPOPLASTIC ANEMIA, PERNICIOUS TYPE, IN  
THE COURSE OF SPRUE, WITH FREQUENTLY  
REPEATED HEMATOLOGICAL EXAMINATIONS**

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The patient is a well-developed man of florid complexion, fifty-nine years of age. No one would suspect that he is an anemic at first glance, but on closer examination it will be noted that the superficial vessels of the skin of the face and neck are dilated. He is a native of Colombia and while he has suffered the vicissitudes of tropical climate and elevation, at certain periods living in the tropical jungle districts, damp, hot and malarious, for the most part, he has lived at altitudes above 5,000 feet. His residence for the last eighteen years has been Guatemala City at an elevation of 6,000 feet. The fact that he has passed the most of his life at such altitudes may account in part for the dilatation of the vessels of the skin and his ruddy appearance.

His height is  $63\frac{1}{2}$  inches, his movements are normally active, and he is a man who has lived in an excellent social environment, an evidence of which is seen in his selection of words to express his ideas. His normal weight up to the time he began to fail in health, in 1929, was 157 pounds but he now weighs  $118\frac{3}{4}$  pounds. It was the loss of weight, principally, and his indigestion, incidentally, which led him to seek medical advice in 1929.

**Family History.**

The patient's family history is good. His father died at eighty-six years of age; his mother at 100. They had thirteen children of which six still live; he is the thirteenth of the family. Of the deaths, one died in infancy, one of tuberculosis acquired in adult life away from home, one died suddenly after 50; the remainder died at 40, 60, 70 and 73, respectively, of causes unknown.

**Previous History.**

As a child, as is so frequently the case in the sparsely settled country districts in the healthful highlands of Tropical America, the patient had no illnesses, but later, after residence in a malarial region, he acquired malarial fever. His blood has always been nega-



tive for syphilis by the Wassermann and Kahn methods. What may be an important piece of information is his statement that in 1926 he had a sharp acute dysenteroid attack which lasted only a week and which may have been the first evidence of his infection by *Monilia psilosis*.

**Onset of Present Disease and Previous Course.**

About two years ago, he began to lose in weight; with symptoms of what he considered indigestion. In a year he had lost thirty pounds. He states that he had always eaten meat in abundance, although fried in a large amount of grease and that he has had plenty of fresh vegetables. He always has had an abundance of bananas but of other fruits he has had little variety as they did not flourish in the region in which he lived.

By the end of 1929 he presented the following clinical picture:

(1) A sore tongue, at times becoming excoriated, which he attributed to excess of "Chili", and other peppery condiments. (2) Heaviness in the pit of the stomach after eating and burning in the epigastrium. (3) Great excess of intestinal gas. (4) Now and then, a light-colored, frothy diarrhea, with still longer intervals of constipation or apparently normal movements. (5) Great loss of weight and strength.

While pain in the abdomen was not a feature it was not always absent, although not severe, and was probably due to gas. There were no attacks of nausea or vomiting but he suffered from lack of appetite and a great excess of saliva.

He now found himself becoming very nervous and weak, especially in the legs. Pains in the muscles were slight, as were palpitations of the heart. He began to notice numbness in the feet, as well as loss of memory and heaviness in the back of the head and neck. He states that he has never been pale but recalled having been a little dizzy on occasions. Sleep was not affected but despondency became ever more pronounced.

He states that the development of his disease was quite gradual and that after consulting his physicians he was advised to take a trip to Europe. At first, as can be seen from the blood record in Chart I, the anemia did not seem very serious but when he reached Barcelona in the Spring of 1930, he consulted a physician there who told him that the anemia was primary and gave him liver extract with marmalade. As the red cells descended and there was an increase in his indigestion, in the late Summer of 1930 he returned by way of New York. Here he went to see a physician



who gave him liver extract but said that he could not make a precise diagnosis. The liver extract seemed to produce a severe attack of diarrhea and to it the patient attributed his worst relapse, an almost invincible obstacle to my continuance of its further use. As hardly a clinical case is uninfluenced by the particular psychology of the patient, it will be well to note here the unfortunate mental attitude of this one. From the first, the confusing laboratory reports as to the state of his blood, coupled with his ruddy complexion, led him to believe that some incompetence in technique was responsible therefor. The result was that while entirely disavowing any knowledge of medical matters, he became to an extent a mentor to oversee, not only the technical laboratory work of his various physicians, but later to judge their competence in treatment. For instance, on one occasion, after obtaining a blood count from one, he immediately proceeded the same day to have the work repeated by another. A difference of 464,000 red cells per cubic millimeter was to him positive proof that both were in error. As a matter of fact, an even greater instability in these counts from one day to another appears in the charts published with this case report. The alarm in the patient's mind when he is convinced that he has an affection which no one can be entirely trusted to cure probably added a serious psychic interference with normal function, especially of digestion.

He now consulted a physician in New York who found his red cells below a million (patient's statement) and gave him two blood transfusions which acted promptly in restoring him to apparent health. While in the hospital, this physician isolated *Monilia psilosia* and diagnosed sprue.

The patient was now allowed to return to Guatemala with orders to continue acriflavine irrigations of the colon, begun in New York, and to eat without special restriction of fats and carbohydrates (patient's statement). This was in October of 1930.

On reaching Guatemala, while he continued to gain in weight, he soon had a return of sore mouth with a marked slump in blood values and what appears to have been typical sprue stools, whereupon his Guatemalan physicians advised him to consult me in Porto Rico.

The patient arrived, February 19, 1931, and was sent to the University Hospital of the School of Tropical Medicine for observation. He remained here for six days. His temperature throughout this time ran persistently subnormal between 97 and 98.6 degrees



Fahrenheit. The pulse ran irregularly between 68 and 98. The respirations were normal. His consumption of fluids was about 1,600 cc daily. On three days he had three soft movements of the bowels; on two days one; on the remaining two none. He was not confined to his bed but generally kept to his room. The diet given was my standard sprue diet, high in protein, low in carbohydrates, and free from added sugar of commerce, fat, and cereals. His only medication consisted in a teaspoonful of the following mixture, twenty minutes before meals:

R/.		
Strychnin. sulphate	-----	0.1
Acid. hydrochloric. dilut.	-----	16.
Pepsin	-----	12.
Tinet. cardamom. comp.	-----	30.
Aq. q. s. ad	-----	240.

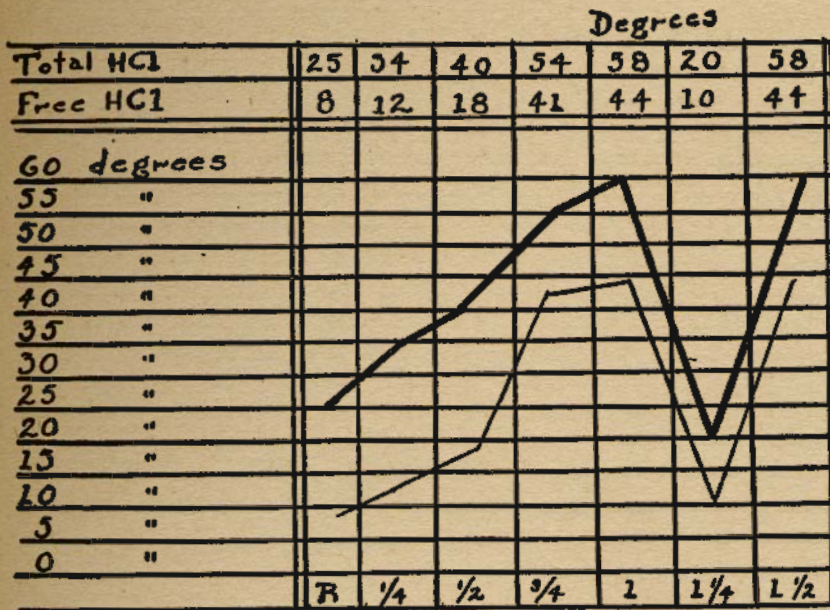
His basal metabolism was found to be -2. The blood chemistry was as follows:

Non-protein nitrogen	-----	38.4 mgm. per cent
Urea nitrogen	-----	15.6 mgm. per cent
Uric acid	-----	4.5 mgm. per cent
Creatinin	-----	1.2 mgm. per cent
Sugar	-----	72.4 mgm. per cent
Phosphor.	-----	4.1 mgm. per cent
Cholesterol	-----	138.4 mgm. per cent
Calcium (serum)	-----	8.9 mgm. per cent
Chlorides	-----	525.4 mgm. per cent
Icteric index	-----	5.6 units

The low cholesterol is rather consistently present in sprue and the low serum calcium values are seen in about half the cases, as well as high uric acid values. The icteric index is slightly above normal. A high icteric index is frequent in sprue.

The Ewald test meal was given before beginning the acid mixture and a fractional gastric contents analysis is as follows:





Thus, on this particular date, the gastric contents were normal save for a sharp drop in the 6th period, followed by an equally sharp rise. This was due to regurgitation of duodenal contents, so common an accident in such estimations of gastric acidity and one which makes previous conceptions as to what happens with the gastric secretion in sprue extremely dubious.

Two urinary analyses were made as follows: Date 2/21/31, normal. Date 2/24/31, faint trace albumin, no casts. Otherwise normal. There is, therefore, no reason to suspect any serious abnormality in the kidney for a man of his age. The feces showed only numerous cysts of *Entameba coli*. *Entameba histolytica* was not present. X-ray examinations of the gastro-intestinal tract had been made abroad already by competent persons and were negative, so they were not repeated. The hematological examination made February 25 was substantially the same as that made by myself, save that I found a slight eosinophilia. It was as follows: Red cells 64 per cent; hemoglobin 70 per cent; color-index 1.09; leucocytes 5,200 per cmm. Differential: Neutrophiles 59 per cent; lymphocytes 38 per cent; mononuclears 1 per cent; eosinophiles 2 per cent. Wassermann and Kahn's serologic tests were 00 and 000, respectively.



He left the hospital on March 3rd and I began to treat him as an office patient. A clinical re-examination on March 4th disclosed: *Digestive system*: No sore tongue; no burning in the epigastrium; much excess of intestinal gas; neither diarrhea nor constipation at the time but he is liable to a shift to either; a small liver; no appetite, and a marked excess of saliva. There was no nausea, no vomiting, no burning of the rectum, no dryness of the mouth. *Nervous system*: The patient is preeminently hypochondriacal and spends much of his time elaborating on inconsequential pains in the body and uncomfortable sensations in the abdomen. He complains of much general weakness and especially of weakness in the legs but sleeps well and has no palpitation of the heart. He has well-marked numbness of the feet and the memory is extremely defective.

#### Physical Examination.

This man's complexion was clear and absolutely free from the usual symmetrical pigmentations of neck, face and arms so often seen in our own sprue cases here. Above all, he had a good color with no suggestion of citron tint in the sclerae. His weight was then  $127\frac{3}{4}$  pounds, or still 30 pounds below normal but he had gained nine pounds in the hospital. No abnormality worthy of note was found on physical examination save a small liver. The knee jerks and other reflexes were normal. His blood pressure was 95 systolic, 60 diastolic.

#### Subsequent Course and Treatment.

He was placed on my sprue diet, first described in 1913-1914, and was given instructions to eat a pound of beef daily, broiled without grease and underdone. This diet was detailed as follows:

#### BREAKFAST

1. Two poached or soft-boiled eggs. 2. Some of the following fruits: oranges, grape-fruit, baked apples, ripe paw-paw, strawberries, melons, grapes, pears, peaches, and, if well tolerated, a good quality of bananas, mangoes, or *nísperos*. 3. Coffee with milk, sweetened with saccharine.

#### MIDDAY MEAL

1. Soup containing the vegetables permitted in this diet, or chicken broth with the floating fat removed. Macaroni, noodles, rice, flour, sauces and all cereal grains should be withheld. 2. Half a pound of tender steak cooked as above described. If there is difficulty in masticating the meat, put it through a meat grinder,



roll it into meat-balls and sear it externally but very superficially; this can be done in a buttered sauce-pan by turning it over as it cooks but only enough butter should be used to grease the pan and prevent the meat from sticking. Fish can be eaten in addition but only such fish as can be boiled or broiled; fried fish is interdicted. The same methods of cooking apply to chicken. Liver, pancreas (sweetbreads), brains, and kidneys are permitted, as are raw oysters. 3. Vegetables should be usually baked or rapidly boiled in previously boiling water. Those preferred are: okra, *chayote*, squash, simlins, carrots, spinach, asparagus, beets, tomatoes, turnips, string beans, lima beans, peas, green peppers, onions, cow-peas, *yautia*, plantains, egg-plant, *yuca* and *ñame*. The only vegetables prohibited are potato and sweet potato. Any fresh green vegetable not mentioned is permissible. Canned vegetables are discouraged but can be eaten if fresh vegetables cannot be secured. 4. Salads on a basis of lettuce or other leaf, with all the vegetables and fruits above mentioned which can be adapted for the purpose. Only a few drops of oil should be used and a little lemon juice or lime juice in the place of vinegar.

#### AFTERNOON TEA

This can be taken with fruit at four in the afternoon.

#### DINNER

Same as at midday. As a dessert saccharinated "jello" can be used.

#### PROHIBITED FOODS

1. Sugar of commerce and all foods to which it may be added, such as, desserts, sweetened canned fruits, raisins, prunes, ice-cream, soda fountain products, etc. 2. Bread and everything which may contain flour, corn or rice, such as biscuits, crackers and mushes. 3. All cereals and grains, such as, rice, beans, corn, and all cereal breakfast foods. 4. All greasy foods. This is the most important of all the prohibitions as they are very badly tolerated in this affection. This prohibition includes lard, butter and oil. It includes pork meat, ham, bacon, cream and the alligator pear. If the exigencies of the case demand, a small quantity of butter, cream or oil, may be tried but much of the success of this diet depends on reducing fat to a minimum.



## GENERAL INSTRUCTIONS

The object of this diet is to rest the fat and carbohydrate-digesting functions, heretofore over-stimulated and now in a state of more or less insufficiency, and to reduce to a minimum the amount of those substances which tend to enrich the gastro-intestinal feeding-ground for microorganisms which take a part in the production of the sprue picture.

He was told that this diet is not a *menu-d'hotel* from which articles are to select at will, but a medical prescription, all parts of which are necessary for the special purpose in mind. It should be properly cooked, tastily served, and well masticated. "Do not attempt to make any changes in this diet without first consulting your physician."

In addition to the strychnine and hydrochloric acid mixture administered while he was in hospital, I am in the habit of giving a powder, two hours after each meal, as follows:

R/.

Pancreatin		
Takadiastase.....	aa	0.30
Magnes. oxid.....		0.50
Calcii carbonat.....		1.00

This latter prescription I now gave but suspended the use of the former in view of the results of his gastric analysis. On the 5th of March he began taking a duodenal extract prepared for experimental use by Lilly and Company. Three vials a day were administered dissolved in orange juice, each vial representing 200 grams of the fresh duodenum.

On March 9th, he complained of such severe diarrhea with pain as to necessitate an opium and chalk mixture with bismuth. After taking 24 vials and not having secured any rise in reticulocytes, I stopped the duodenal extract and on March 19th began Lilly's liver extract No. 343. His fear of this preparation was so great after his experience with it in New York that I had to limit the dose to three vials a day and give an opiate with it on each occasion. This dose was increased in four days to two vials three times a day and it was continued up to April 8th when it was stopped as per explanation given further on in the discussion of his blood records. On this latter date one teaspoonful of saccharated carbonate of iron was administered once a day.

By March 31 he felt perfectly well, save for weakness in his knees and was weighing 133 pounds. On April 16th, the date of



his leaving for Guatemala after 51 days of treatment, his weight was 136 pounds.

#### THE BLOOD

The first blood record of this patient was made in Guatemala, June 3, 1929, and showed a high color-index anemia. Despite treatment, his blood values fell throughout the period June 3, 1929, to March 6, 1930. No malarial organisms or eggs of parasites were found but a slight trace of urobilin in the urine and a one-plus Wassermann were chronicled. His condition became alarming and he embarked for Barcelona where a diagnosis of primary anemia was made. Here his blood was three times negative for syphilis by the Wassermann technique. In June his erythrocytes were 2,800,000 per cmm. but no hemoglobin reading was recorded. He now embarked for New York where a diagnosis of "marked secondary anemia" was made by one laboratory, in view of a temporary low color-index. No measurement of red cells had been undertaken up to this time.

On his return to Guatemala, on November, 1930, he was again examined and found to have only 1,920,000 reds, without normoblasts, megaloblasts, or polychromatophilia. No parasites were found in the feces although the patient states that Oxyuris was once discovered previous to this. At this period he sailed for Porto Rico.

It can be seen that all previous examinations were not continued at short intervals over a sufficient time to permit an exact diagnosis. At first the type of anemia seemed primary, judging alone from the color-index, anisocytosis and poikilocytosis, but later in New York his color-index fell below one, suggesting a diagnosis of secondary anemia.

The *crux* of the whole question was the size of the red cells which apparently were never measured, and in the absence of the Price-Jones curve, no correct diagnosis of this case was possible. Such blood record as could be obtained from the above sources is given in Chart I.

On the patient's arrival in Porto Rico, realizing that the only way to establish the nature of his anemia was to make a series of full blood examinations and erect curves, I determined to make red and white cell counts, differential counts, reticulocyte counts, hemoglobin readings (the Dare instrument was used) and, above all, Price-Jones curves, all more or less daily. The measurement of 500 cells was a physical impossibility, with a daily program such as this, as the work had to be personal. As in a previous series<sup>(1)</sup> only



100 red cells were measured at each blood examination, I decided on the briefer technique. It is realized that these curves are not so exact as if 500 had been measured, but for clinical purposes they are quite exact enough and the consistency of the results as expressed in the charts is evident. Certainly, the error will not exceed one-half a micron in the composite.

Briefly, the average mean of thirty-three successive Price-Jones curves gave 8.57 microns, the median 9.14 microns, and the double dispersion 3.81, the latter a measure of the anisocytosis, this dispersion, normally, being around 2.2 microns. It will be noted that there is a marked absence of the skewness seen in other cases of the same nature.

In Chart II, where color-index the chief criterion, the anemia would appear secondary; but aside from the previous history of a high color-index, the Price-Jones curves show a marked and persistent macrocytosis. On one occasion, a red cell measuring 19 microns in diameter was found.

In these tropics, among those suffering from chronic indigestion due to the prevalent nutritional unbalance of the country, the color-index is also persistently low, but there is generally a normal red cell count or a relative polycythemia and the average diameter of the cells is more likely to be below the normal fixed at 7.7 microns. Moreover, the total dispersion is much less, not usually over 2.5 microns; i.e., there is no anisocytosis.

The most remarkable phenomenon in this blood record is the daily excursion of red cells and hemoglobin. In short, Chart II, as well as some elements of Chart III, show a constant and more or less regular oscillation, with waves of decided improvement, but with only a very slow general upward drive. In explaining this irregularity, much more marked than in any of the other cases of pernicious types of anemia in sprue studied by the writer, one not only thinks of sudden changes in blood volume due to an unstable autonomic nervous system, but of McNee's remarkable work on the functions of the spleen in which he considers intermittent contraction of this organ under emotional stimulus and changes from high to low altitudes one of the sources of hitherto unexplained rises in red cell counts. In the latter case the spleen would seem to act as a reservoir of red cells to be expressed into the blood stream in emergency.<sup>(5)</sup>

Under the circumstances it becomes necessary to immediately evaluate the results of scientific research in terms of treatment. It



will do no good, and perhaps may do harm, to over-force a devitalized and hypofunctioning bone-marrow with the specific hormone. To do so might result in complete exhaustion and an aplasia. The foundation for this conception is based on published and unpublished data of my own and of the Department of Pathology of the School of Tropical Medicine of Porto Rico, in which in similar cases, borings of the marrow showed an extreme paucity of megaloblasts.

The logical thing in this case seems the administration of a diet high in the complete protein molecule (best represented by underdone meat), and, after a month or more of such feeding for the purpose of building up new megaloblasts, then to give a brief and intensive course of the liver hormone. Reference is here made to E. W. Lord's case<sup>(2)</sup>, as illustrative of the success of such treatment.

On the other hand, we must not lose sight of the condition of the liver and stomach also in hypofunction. As one of the functions of the liver is the storage and release of the liver hormone for stimulation of the megaloblasts, it is admissible to predicate a reduction of the output of this hormone in an exhaustive process such as is sprue, as well as a reduction in the production of this hormone by the gastric mucous membrane. Here a high nitrogen diet is also indicated for the same reason as in the case of the lagging bone-marrow; i.e., a rehabilitation of those cells producing and storing the hormone.

Which of the two deficiencies, that of liver hormone or that of hemopoiesis, is paramount in this type of primary anemia cannot be clearly defined for lack of reliable data, but that both work to reduce blood values is evident, as in dysplastic forms of the type of pernicious anemia accompanying sprue the administration of the hormone (Lilly's extract No. 343) produces reticulocytosis and a marked rise in blood values, while on the other hand, biopsies have repeatedly shown, in those sprue anemias of pernicious type not responding to the hormone, a great paucity of megaloblasts in the bone-marrow.

If the irregular curve of red cells and hemoglobin is difficult to reconcile to text-book lore, the white cell count is still more cryptic. In general, the tendency at first was toward leucopenia, followed by a gradual but moderate rise. But the differential counts furnish data for the most diverse theories. Intermittent hypofunction of the sources of neutrophiles would be one. The remissions are strikingly regular but this conception is clouded by the possibility of a



profound dysfunction of the autonomic nervous system, so prominent a feature of sprue<sup>(3)</sup>. Still another source of dysfunction might be ever attributable to psychic influences, also profoundly depressive in this disease.

The one bright spot in these curious curves is the graph of the eosinophiles which is persistently high. That this is of value in prognosis can be seen by reference to cases of anemia of pernicious type due to uncinariasis.<sup>(4)</sup> In the previous blood records made before his arrival in Porto Rico, the patient showed no eosinophilia, and this phenomenon has appeared since the administration of the liver hormone. (For significance of this phenomenon see: Anemias of sprue; their nature and treatment, op. cit.) The hematologic characteristics of a hypoplastic anemia of pernicious type in sprue is well demonstrated in these graphs. No megaloblasts were ever seen. No polychromatophilia was ever observed. The response to liver extract was feeble and fleeting, and a marked macrocytosis with a wide dispersion (anisocytosis) was an outstanding feature.

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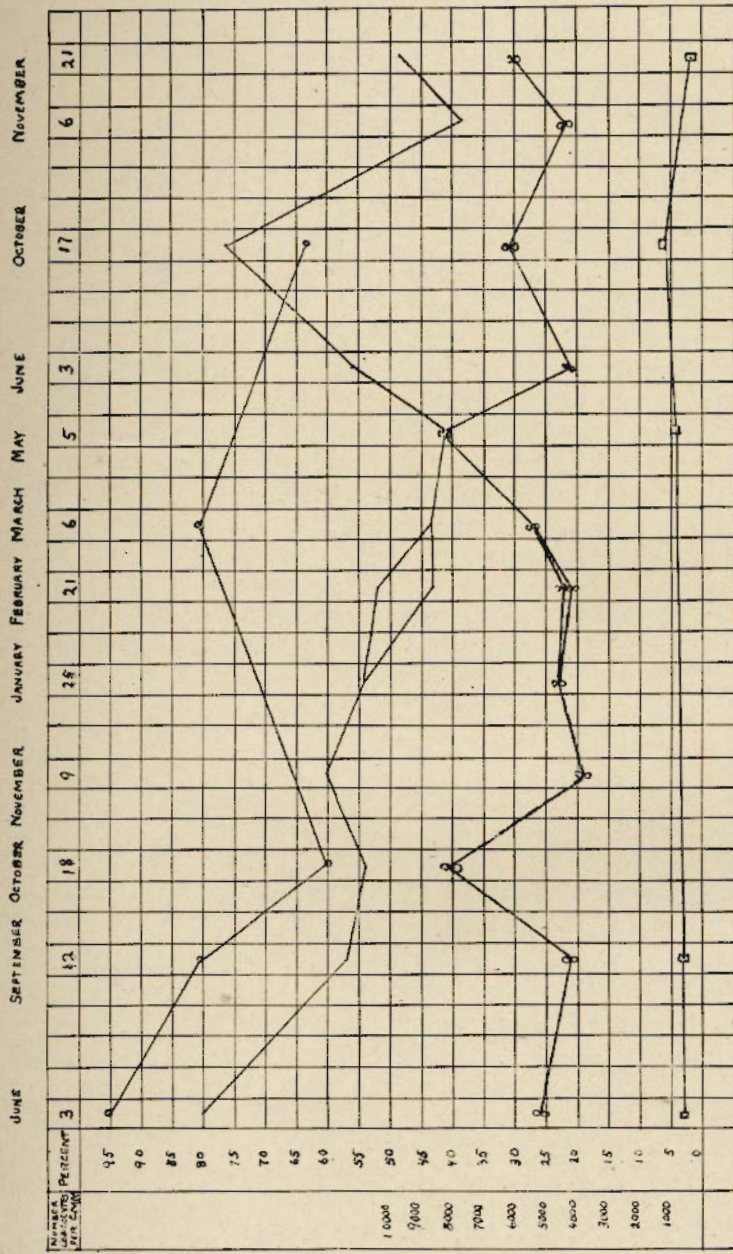


CURVE CONSTRUCTED FROM PREVIOUS BLOOD EXAMINATIONS MADE ELSEWHERE

CHART I

1929

1930

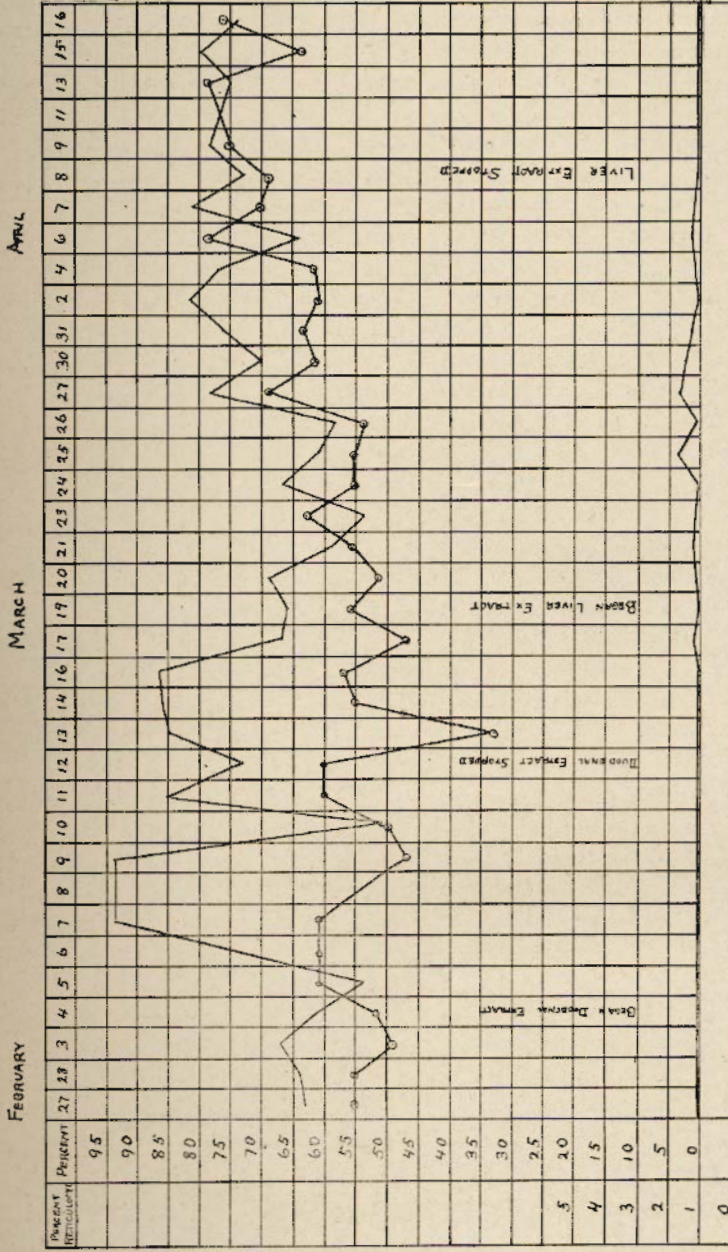


UNBROKEN LINE ○ ERITHROCYTES  
 ○ ——— ○ HEMOGLOBIN  
 ○ ——— ○ LEUCOCYTES PER CMM  
 ○ ——— ○ EOSINOPHILES



CHART II

BLOOD SEQUENCE IN A CASE OF HYPOPLASTIC ANEMIA OF PERNICIOUS TYPE

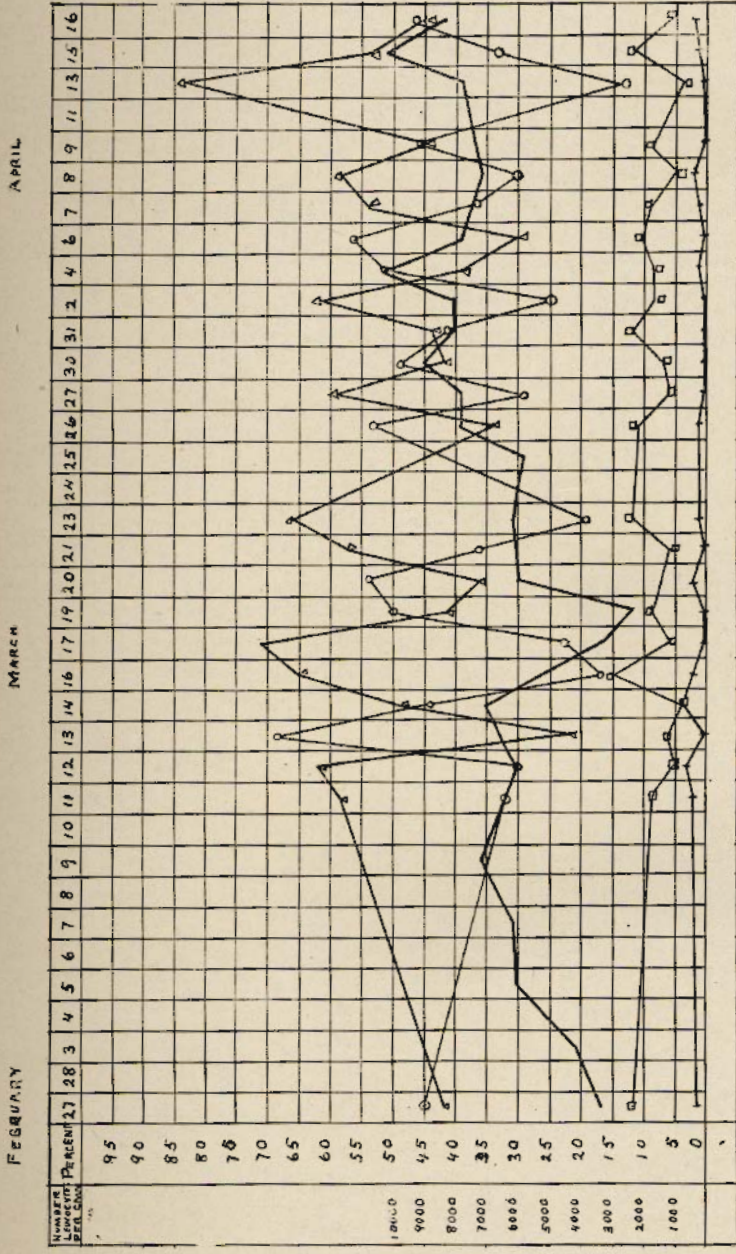


UNBROKEN LINE ABOVE ERYTHROCYTES  
 UNBROKEN LINE BELOW RETICULOCYTES  
 BROKEN LINE, HEMOGLOBIN



CHART III

LEUCOCYTE SEQUENCE IN A CASE OF HYPOPLASTIC ANEMIA OF PERNICIOUS TYPE



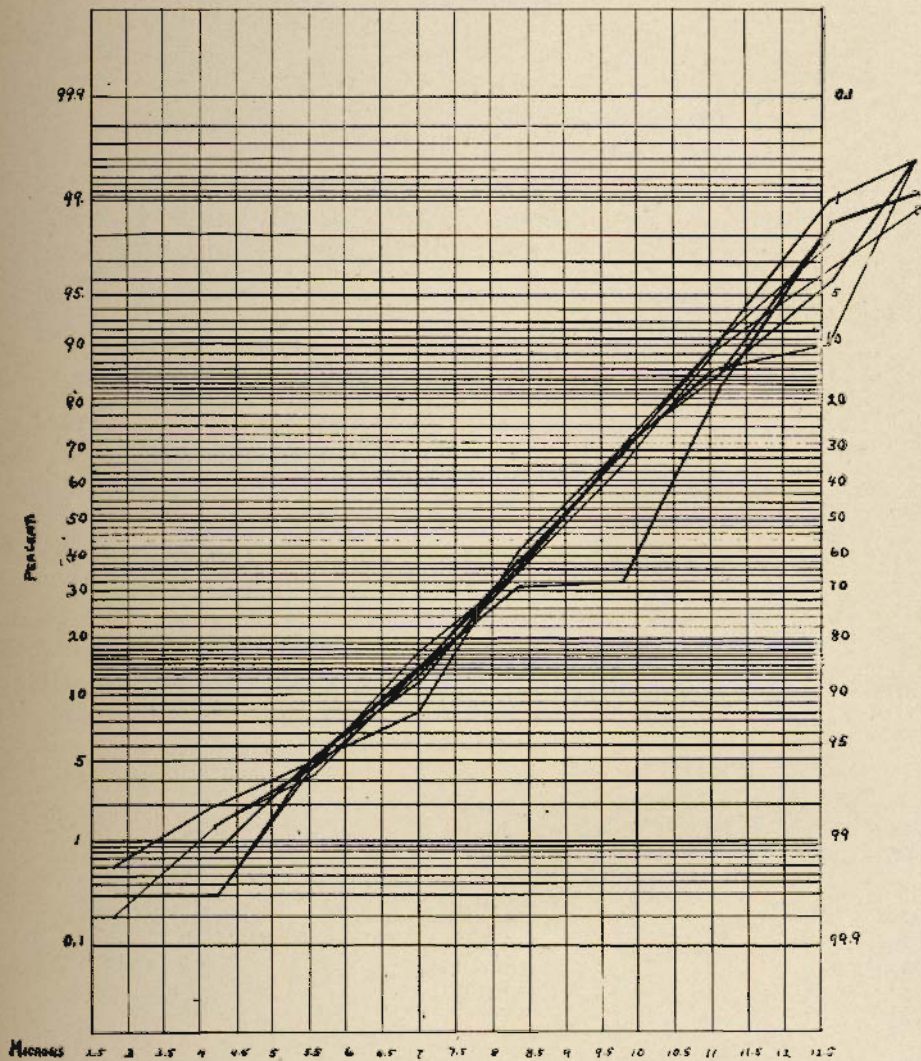
UNBROKEN LINE TOTAL LEUCOCYTES PER CMM  
 ○ NEUTROPHILES  
 □ LYMPHOCYTES  
 △ EOSINOPHILES  
 ┆ MONOCYTES



CHART IV

HYDPLASTIC ANEMIA OF PERNICIOUS TYPE

COMPOSITE OF THIRTY-THREE PRICK-JAMES CURVES CONSOLIDATED IN FIVE-DAY PERIODS



COMPOSITE BY 5-DAY PERIODS	1-5	6-10	11-15	16-20	21-25	26-30	31-33	AV.
MEAN MICRONS	8.79	8.86	8.91	8.85	8.81	9.19	8.7	8.87
MEDIAN "	7.00	7.00	7.00	7.00	7.00	7.00	8.8	7.14
DOUBLE DISPERSION MICRONS	3.80	3.80	3.80	4.00	4.00	3.90	3.7	3.81