

OBSERVATIONS ON

CASES OF PERNICIOUS ANAEMIA

WITH SPECIAL REFERENCE TO THE BLOOD CHANGES

by

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I N T R O D U C T I O N .

It has been my fortune to meet with several cases of pernicious anaemia. I propose to give some notes of those I have been able to watch most closely and to give an account of the blood in all the cases with a view to ascertaining what changes are to be found in the blood in the different degrees of anaemia and what indications as regards diagnosis, prognosis and treatment are to be obtained by the blood examination. Much work has recently been done in connection with the subject of pernicious anaemia. Though our knowledge of the condition has been considerably increased, its essential features still remain obscure and perhaps it is this obscurity that renders the subject so attractive.

ETIOLOGY.

Gulland (Encyclopædia Medica I.) writes as follows:- "The antecedents of patients affected with this disease are very various. Improper and insufficient food, bad hygienic conditions, haemorrhages, infective diseases like typhoid fever, syphilis, and osteomyelitis, mental anxiety; among women, pregnancy parturition and lactation, and perhaps, most frequently, gastro-intestinal disturbances of various kinds, have all been regarded as causal factors in the pro-

duction of the disease. They undoubtedly can and do produce anaemia, but why the anaemia in the great majority of cases should be slight and curable and only occasionally pernicious and fatal, we have yet to learn. The unknown factor is the really important one.

Males and females are affected with about equal frequency, and while the condition may occur at all ages, it is most common in adult life, from 30 to 50 years of age."

PATHOLOGY.

There is much diversity of opinion regarding the pathology of the condition.

1. Failure of haemogenesis has been thought to account for the condition. This view has now been largely abandoned, but after Muir (Jour. Path. and Bact. Feb. 1894) called attention to the bone-marrow changes and before these changes were known to exist in conditions other than pernicious anaemia, it found pretty wide acceptance.

The exponents of this view hold that the increased haemolysis of which there is strong evidence, is due to an increased vulnerability of the corpuscles rather than a morbidly exaggerated action of the haemolytic organs.

Russell (B.M.J. Jan. 12th, 1899) found that the nuclei of the liver cells stained more faintly than

usual and concluded that the cells were exhausted by an abnormal amount of work thrown upon them by encountering weakly corpuscles, which they were bound to destroy in the performance of their normal function. He holds that the cells should not show any sign of exhaustion were the blood destruction due merely to exalted function on their part. We must bear in mind, however, that the nutrition of the liver cells suffers in common with the other tissues as a result of the anaemia however produced.

Brakenridge (Edin.M.J., Nov. 1892) after observations on the effect of transfusion wrote:- "I am still disposed to hold that pernicious anaemia is mainly due to a faulty genesis of the corpuscles in the blood-forming organs and a consequent tendency to their early death in the blood destroying organs."

2. Stockman (B.M.J., 1895, May 4th, 11th, 18th), discusses the subject at length and concludes as follows:-

- "1. That pernicious anaemia is not a special disease,
2. but is secondary to numerous exhausting conditions.
3. That these induce an initial anaemia,
4. which is followed in certain cases by degenerative changes in the blood vessels.
5. That capillary haemorrhages result and induce an excessive degree of anaemia.

6. Some cases are due chiefly to external bleeding.
7. That these bleedings account for all the characteristic symptoms and post-mortem appearances.
8. That treatment should be based on etiological considerations.

3. James agrees with Stockman so far, that pernicious anaemia is not a special disease. He writes (International Clinics III., Oct. 1897, p. 169), "While a certain weight must be attached to the theory that pernicious anaemia is a disease of itself in which the red corpuscles are broken down with excessive rapidity in the liver as the result of a ptomaine carried to the liver by the portal system, yet, it may with justice be regarded rather as a symptom than as a disease. Any conditions which tend to impair the nutritive power of the blood may bring it on.

The blood is a tissue which, like every other tissue of the body, is endowed at the beginning of life with a store of vital energy which will enable it to live for a certain number of years. Whatever, therefore, tends to exhaust this store before its time must tend to bring on the disease. Thus the faulty conditions which induce chlorosis may bring it on, and a chlorosis may pass into it; irritative and atrophic changes in the mucous membrane of the stomach or intestine may act as its cause; certain cancers may possibly have the same effect; malarial

conditions, bleedings of any kind, excessive work or worry, may all lead to its occurrence.

Probably as a morbid condition it is much more common than it seems to be. In young people, or in slighter degrees, it no doubt occurs frequently, but, owing to prompt recovery, or treatment, it passes unrecognised.

It is probably true of it, as of phthisis, that as a disease it appears much more formidable than it really is, because it is mainly the more advanced and therefore less curable cases that excite our notice."

4. The most widely accepted view is that the disease depends on excessive haemolysis due to the action of toxic substances in the blood. These toxic substances are generally believed to be absorbed from some part of the alimentary canal. Hunter, the chief exponent of this view, has recently discussed the subject at length. He concludes (Lancet, Jan.27th, Feb.3rd., Feb.10th, 1900), as follows:-

1. Pernicious anaemia is a special form of chronic blood poisoning - a toxaemia.
2. It is the result of a special infection of the digestive tract, especially of the mouth and stomach, and probably, although to a less degree, of the intestines.
3. The chief source of the infection is through the mouth, from long continued and neglected cario-necrotic conditions of teeth, and sometimes possibly from stomatitis arising from other causes.

4. The usual effect of this infection is a chronic infective catarrh of the mouth and stomach, which may in time lead to deeper-seated changes, e.g., ulcers of the mouth and tongue, chronic glossitis and atrophic changes in the tongue, and chronic gastritis with atrophy of gastric glands.
5. Evidences of the infectivity of the organisms of dental decay are overwhelming, and in suitable cases the infective nature of the resulting catarrh of the stomach can also be demonstrated.
6. The infection is chiefly streptococcal and probably derives its special characters from being of a "mixed" character.
7. Such infection the more readily occurs, if the stomach or intestine is already from any cause the seat of disease.
irritation
8. The gastric and intestinal (sickness, retching, vomiting, looseness of bowels, and diarrhoea), so often noticed, and which I find to be even more common than is stated (being recorded in close on 80 per cent. of cases) is the local effect of this infective catarrh, while the excessive destruction of blood taking place in the portal area is the result of the action of the poisons in the blood.
9. The fever so commonly met with is not an accidental occurrence, the effect of weakness, but is a feature of the disease, a result of the infective process itself, and its variations correspond to variations in the activity of that process.
10. Such variations are common from week to week - sometimes from day to day - in the progress sometimes of the disease, even when it is running a fairly progressive course.
11. In addition, however, the course of the disease towards the fatal termination is often marked by one, sometimes by two, periods of marked improvement, lasting, it may be, many months or a year or more, followed by relapses. This character of the disease, I have come to regard as the result of a

relative immunity, unfortunately only temporary in its nature, conferred by the disease itself - an immunity accelerated and greatly strengthened for a time by suitable medicinal treatment, notably by the administration of arsenic.

Still more recently (Lancet, July 21st 1900) with Mr Barker, Hunter has published a case in which extensive suppurative disease of the teeth and ethmoidal sinuses was found post-mortem, although its presence during life had not been complained of, or suspected.

With regard to this view, it may be here stated,

1. That in none of the three cases hereafter noted, on which post-mortem examinations were held, was there any discoverable lesion of the alimentary canal.
2. Several of the cases, hereafter noted, had good teeth.
3. Cases of pernicious anaemia have occurred in elderly persons, who had all their teeth removed in early life.

All of the theories regarding the pathology of pernicious anaemia have so much in their favour that no one of them can be lightly put aside, but so much more can be urged against any or all of them, that it is still more difficult to accept any one theory.

I do not intend to discuss the subject. Much more work has yet to be done regarding it. I venture, however, to state tentatively and with all due caution what I believe regarding the nature of the disease.

1. Pernicious Anaemia is a degeneration of the blood due to exhaustion of the haemogenic function.
2. That exhaustion is due to the increased calls upon haemogenesis caused by the prolonged operation of various morbid conditions, which impair the nutrition of the blood and which in the first instance produce merely what we call secondary anaemia.
3. The degeneration of the blood is indicated by the changes in the red corpuscles and by the presence of embryonic (and, therefore, imperfectly evolved) cells in the blood.
4. When the degenerative changes known as pernicious anaemia are established, the case is as hopeless as a case of degeneration of the spinal cord, though the haemogenic function either spontaneously or as the result of treatment may sufficiently recover to supply healthy looking cells to the circulation for a time.

SYMPTOMS.

The symptoms are fairly definite and, indeed, have not been more clearly or picturesquely described than they were by Addison originally, yet these symptoms are in the main, those of any severe anaemia, and every now and again one meets with cases in which even after careful examination of the blood, the diagnosis must remain, for a time at least, in doubt.

TERMINOLOGY.

In dealing with any subject concerning the blood, we are met at the outset with the vexed question of classification and nomenclature of the white cells. The varieties of leucocytes more commonly met with are as follows:-

- (a) Small lymphocytes which have a relatively large nucleus;
- (b) Large lymphocytes whose nuclei are relatively smaller. (Intermediate groups are also found).

(When Methylene Blue is used, the nucleus in these cells is usually stained more darkly than the surrounding protoplasm, but frequently, the reverse is the case and both varieties may be seen in the same film or even in the same microscopic field. The difference appears to be due to differences in the amount of chromatin in the nuclei and in the number and arrangement of the fine basophile granules in the protoplasm.)

- (c) Polymorphonuclear leucocytes and
- (d) Eosinophiles.

The granules in the polymorphonuclear cells are frequently called "neutrophile".

They undoubtedly stain with acid, and not with basic dyes. Kanthack called these cells "fine granular oxyphiles" and named the cells generally known as eosinophiles, "coarse granular oxyphiles".

The granules in the eosinophiles are larger and more regular in outline than those in the "fine granular oxyphiles", but I am not satisfied that this difference in size and shape is the only one.

The granules of both varieties stain well with Ehrlich's triple stain. Both stain well with eosine when the counter stain used is methylene blue, but only the granules of the "eosinophiles" can be demonstrated when the counter stain used is haematein.

When haematein and eosine are used, the protoplasm of the polymorphonuclear cells appears as a homogeneous pink. (See Plate V.).

Were the difference between the varieties of granules only a matter of size and shape, it would be difficult to understand why the mere presence of haematein should alter the affinity of the small granules for eosine, while it did not affect the reaction on the part of the large granules.

A variety of white cell - the basophilic "mast cell" is found in small numbers in healthy blood. (It is common in spleno-myelogenous leucocythaemia). I have frequently counted a thousand leucocytes without seeing one "mast cell".

The cell is stated by Kanthack to be non-amoeboid. Gulland states that it is amoeboid. The nucleus is generally trilobed, but is often much obscured by the granules. Cabot gives their numbers in health as $1/40$ - $1/2$ per cent.

MYELOCYTES.

Much confusion exists regarding these cells. They are the "markzellen" of the Germans, the "globules blancs hypertrophies" of Hayem. Cornil who first noticed them, called them "Cellules medullaires". Von Limbeck (Gundriss einer Klinische Pathologie des Blutes, 2nd Edit. Jena 1896) writes of them as follows:- "Markzellen are generally very large cells,

whose nucleus fills mostly the whole body of the cell and is very poor in chromatin. They originate in the bone-marrow (Cornil, H. F. Muller). They are partly eosinophile.

In spite of this statement, the cell which is figured by Limbeck as a "mark cell" is a lymphocyte.

Fortunately, recent works are more definite and show more agreement on the subject, but one is disappointed to find in a work of such importance as Clifford Allbutt's system of Medicine, the following paragraph:- "The large hyaline leucocyte or myelocyte as it is also named, possesses a larger amount of protoplasm than the smaller variety. The nucleus is usually spherical or reniform and fairly regular in outline. As it possesses a comparatively small amount of chromatin, it does not stain well with aniline dyes. The cell has not been proved to be amoeboid, but nevertheless seems capable of acting as a phagocyte. In the blood it is less numerous than the lymphocyte, forming usually less than 10% of the haemic leucocytes. Increase in the number of leucocytes is usually accompanied by increase in the total number of myelocytes also, this being specially noticeable in the leucocytosis which accompanies the anaemia of pregnancy, and that which ensues on typhoid fever. In lymphatic leukaemia, however, enormously as the number of lymphocytes in the blood may be increased,

no such increase in that of the **m**yelocytes has been observed. During life, the cell protoplasm is apparently homogenous, but, when dead, staining by means of methylene blue shows it to be full of exceedingly fine granules embedded in a matrix which does not take up the stain." (Copeman, Clifford Allbutt's System Vol. V., page 419).

Now, most of this paragraph holds good regarding the large lymphocytes or "large, hyaline leucocytes", but few haematologists, I think, will agree that the "large hyaline lymphocytes" may be also indiscriminately named "myelocytes". Exception may, further, be taken to the statement that an increase in the number of large lymphocytes - if so, we are to interpret Dr Copeman's use of the word "Myelocyte" - has not been observed in lymphatic leucocythaemia.

I have several preparatibns in which the large forms preponderate. This, however, is by the way.

With most writers the term "Myelocyte" means a marrow cell which is never found in normal blood.

The myelocyte is a spherical cell with a large, round or reniform nucleus embedded in granules which stain with eosine or Ehrlich's triple stain.

(Eosinophile myelocytes also occur). Staining with eosine and methylene blue shows that it seems also to possess fine basophile granules. Of the myelo-

cyte, Cabot (Clin. exam. of blood) writes, "One sees at once how little it differs from the large lymphocytes (simply in having granules) and from the polymorphonuclear neutrophile (only in the shape of its nucleus.)" I refer to this point because pernicious anaemia is one of the few conditions in which myelocytes are found in the blood. We may now recapitulate the varieties of white corpuscles as:- small lymphocytes, large lymphocytes, polymorphonuclear leucocytes, eosinophiles, basophile leucocytes, (mast cells) and myelocytes.

Fortunately, there is not the same confusion regarding terminology in the case of the red cells. The abnormal red cells we shall have to refer to are megalocytes, microcytes, megaloblasts, normoblasts and microblasts and poikilocytes. Highly refractile microcytes which stain deeply with acid dyes are sometimes referred to as Eichhorst's corpuscles.

A word may be said with regard to the methods employed in examining the blood.

All the enumerations of cells were made by means of the Thoma-Zeiss haemocytometer. The haemoglobin was estimated by means of Gowers's haemoglobinometer except in Case IV. All the estimations in that case were made with the Von Fleischl instrument. Coagulability was usually determined simply by manipulating a drop of blood along with a drop of healthy blood on a slide.

The method of fixing the films usually employed was by immersion in formalin 10% in alcohol as recommended by Gulland (Scottish Med. & Surg. Journal, April 1899). Some of the earlier films were fixed in alcohol and ether, some in a mixture of tannic acid, alum and corrosive sublimate. Of these, I have found Gulland's method the most rapid and efficient.

The stains most frequently employed were eosine and methylene blue.

A useful combination of these is Jenner's stain (See Lancet Feb. 18th, 1891). Ehrlich's triple stain and eosin with Mayer's haematein were sometimes employed. The latter combination is not so useful (except for nuclear structure) as the others, but has the great advantage that the veriest novice could hardly mismanage its use.

I venture to make a practical suggestion here, viz:- That when blood specimens are prepared by only one or two methods of fixing and staining, a few unstained films should always be retained for future use.

I have several times noticed points concerning stained films which I have wished to clear up by means of other methods and have been unable to do so for the want of material. *Experientia docet!*

For permission to make use of Cases 1, 2, 3, 5, 6, 7, 8, 13 and 14, I am indebted to Dr James; for permission to make use of Case 4 to Mr A. H. Moxon of Great Yarmouth.

CASES AND COMMENTARIES.

CASE I.

A married woman, aged 27, residing in Leith, was admitted to the Edinburgh Royal Infirmary under the charge of Dr James on the 26th of July, 1899.

She complained of sickness, weakness and jaundice. The notes of her case proceed as follows:-

History: Patient's father died when she was 6 years old. She does not remember her mother.

Her home is comfortable. She has been accustomed to good food. She has two children, the younger of whom is 8 months old.

Previous Illnesses: Disease of childhood. Anaemia at the age of 19. Abscess of the right mamma 2 years ago, and again, 3 months ago. Patient did not suffer from haemorrhage when her babies were born.

Present Illness: Began 9 weeks ago. She first noticed that she was losing strength and became unable to carry her baby.

One morning she fainted and was seen by Dr Calder of Leith.

Her skin became yellow and on several occasions she vomited. (Dr Calder has informed me that at this time she suffered from actual jaundice). She became very breathless and on Dr Calder's recommendation she came to hospital.

State on Admission: Patient is well developed and in fairly good condition, but says she has recently lost flesh. Weight 7 st. $2\frac{1}{2}$ lbs., Temp. 99. The skin and conjunctivae have a slight yellow tinge.

Alimentary System: Teeth bad. Gums very pale. Tongue large and flabby with wide furrows in all directions and slightly coated. Appetite very poor. Patient complains of pain after food, with occasional vomiting. Bowels fairly regular. The abdominal walls are lax. There is slight tenderness all over the abdomen. The spleen can be felt in the left hypochondriac, the epigastric and the umbilical regions.

The upper border of the liver in the nipple line is at the 4th rib: the lower border 1 inch below the costal margin. In the middle line, the lower border is $\frac{1}{2}$ inch below the tip of the ensiform cartilage.

Haemopoietic System: There is no enlargement of the thyroid and no unusual enlargement of any of the lymphatic glands.

The spleen is enlarged and easily palpable. It measures eleven inches in its long axis.

The blood looks watery and does not coagulate readily. Rouleaux formation is slight, fibrin is scanty and there are marked differences in the size and shape of the red cells, but the average size is increased.

The red cells number.....872,000

White cells..... 2,500

Haemoglobin is..... 23%

Stained films show, in addition to the difference in the shape and size, that the red cells are deeply stained, many showing no central depression. A few red cells and a few myelocytes are present. The plates are not increased. (See Fig. 1, 2, 3, and Tables 1 and 2).

Circulatory System: There is marked dyspnoea on the least exertion, accompanied by a feeling of giddiness. On two occasions patient has fainted.

Palpitation is not much complained of.

There is marked pulsation in the neck. No epigastric pulsation is visible. The apex beat is not visible, but can be felt in the 5th left interspace $\frac{3}{4}$ inch internal to the nipple line.

The upper border of the heart is at the 3rd rib, superficial dulness at the 4th rib in the parasternal line. The left border at the level of the 5th rib is just internal to the nipple line.

The right border is at the right sternal margin. On auscultation at the mitral area, the first sound is replaced by a long, loud, blowing systolic murmur. The second sound is loud and slapping.

At the aortic area the sounds are closed, but the second sound is loud and slapping in character. At the pulmonary area, the sounds are closed, but have a slapping character.

There is a loud venous bruit in the neck and a bruit can be heard over the eyeball. The pulse is 100 per minute, regular in time and force. The beat is of fair volume, but the tension both during and between the beats is low.

The arterial walls are not thickened.

The respiratory system appears healthy.

Integumentary System: The skin is slightly tinged with yellow. It feels smooth. Patient says she has sweated more than usual during the last three weeks and states that her linen was slightly stained with yellow when the jaundice was more marked.

Urinary System: No subjective phenomena.

Urine is dark amber in colour; quantity passed 40 $\frac{3}{4}$: reaction, acid; sp. gr. 1013; slight deposit of mucus. Urea $5\frac{1}{2}$ grs. per $\frac{3}{4}$.

Spectroscopic examination shows a faint band due to urobilin between the green and the purple.

Reproductive System: Menstruation is usually regular. Patient has only menstruated once, about five weeks ago, since her baby was born.

Nervous System: Patient complains of stiffness in her joints. She attributes this to lying in bed. She occasionally has numb feelings in her fingers.

There is slight tenderness over the sternum.

The special senses and motor functions are unimpaired.

Treatment and Progress: For the first week, patient was kept on milk. The diet was then gradually improved and after a fortnight, ordinary house diet was allowed. Three days after her admission patient was treated with Liq. Arsenic in 5 minim doses thrice daily.

At the end of the first week arsenic was stopped and Pot. Permanganate in gr.ii pills was given thrice daily for a week. The corpuscles however, fell in number and the permanganate was stopped and Arsenic again given. The dose was gradually increased to m. X. t.i.d.

As Table I. shows, patient now steadily improved.

After the first week urobilin never appeared in the urine. She menstruated on July 28th and again on August 5th, the discharge on each occasion lasting three days.

The temperature usually varied between 98.8 and 100.

On the evening of August 21st, it reached 102°F. On August 25th, it fell to 99 and during patient's stay in the Infirmary was never again higher.

On September 7th, she was sent to the Convalescent home. Her weight was then 7 st. 4 lbs. She expressed herself as feeling strong and well. The spleen was just vaguely palpable; the cardiac and venous murmurs had disappeared. After three weeks, patient was again seen. Her complexion was now almost ruddy and her red cells and haemoglobin had made a further slight increase. She was advised to continue to take arsenic and no more was heard of her till about a year had elapsed.

In June 1900, she applied for readmission to the Infirmary, but died before she could take advantage of the bed that had been reserved for her. Dr Philp of Inverkeithing was kind enough to give me the following notes regarding her:-

"She was confined prematurely, on June 7th, and was attended by a midwife. There was no great loss. For ten days before, she had been in bed and was taking arsenic which she had previously stopped. After confinement, she stopped the arsenic owing to sickness.

The puerperal discharge was slight and had ceased before death. There was no milk. There was intense anaemia and the skin was of a lemon-yellow colour. No diarrhoea, no haemorrhages; Temp. from 100 to 102. No enlargement of liver or spleen. The blood and urine were not examined. There was slight oedema of the ankles. Patient was occasionally delirious and died on June 20th. "

TABLE I.

Date	Red Cells per cmm.	White cells per cmm.	Hb. %	Colour Index.
July 28th	872,000	2,500	23	1.3
Aug. 3rd	1,182,000	4,375	23	1
" 11th	800,000	3,125	23	1.4
" 18th	1,000,000	3,735	21	1
" 24th	1,500,000	1,562	30	1
Sep. 7th	2,316,000	1,850	43	.9
" 26th	2,800,000		48	.8

TABLE II.

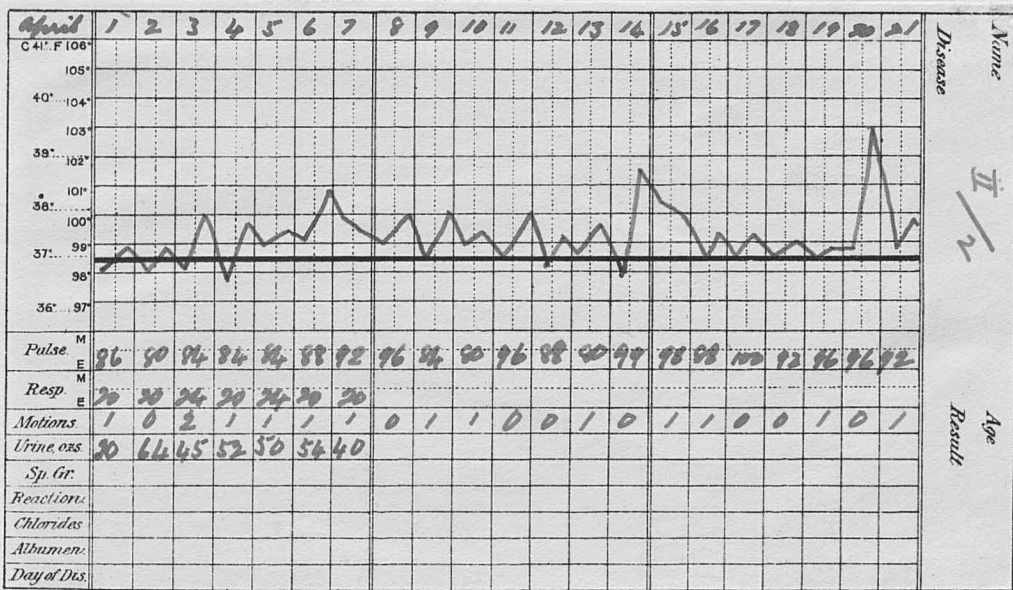
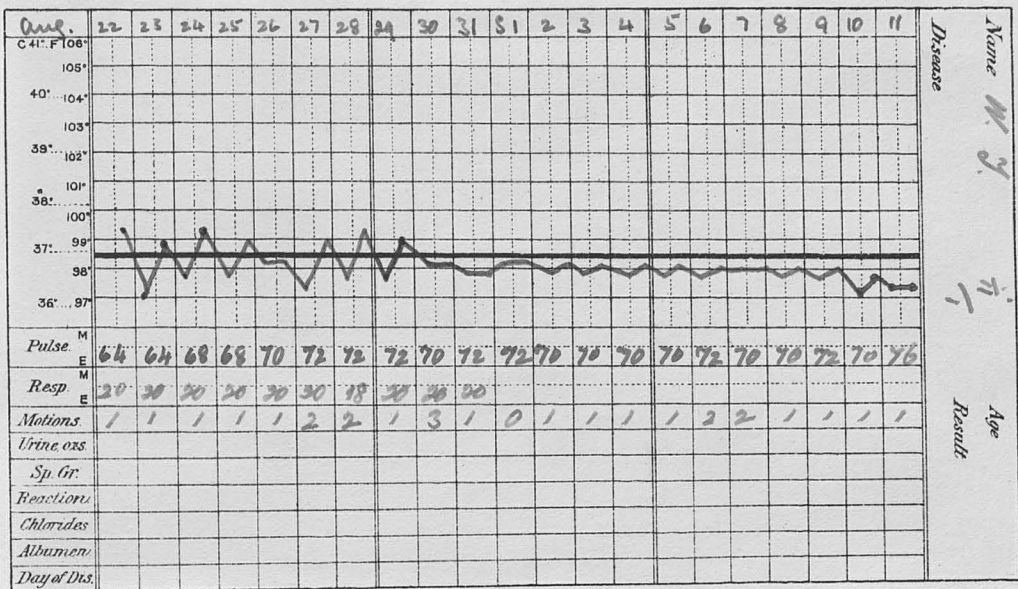
	<u>Percentages of White Cells.</u>				<u>Number per 1000 White Cells.</u>	
	Polymorpho- nuclear.	Lympho- cytes.	Eosino- philes.	Myelo- cytes.	Normo- blasts.	Megalo- blasts.
th	67	26	5	.6	8	56
rd	53	46	1		10	20
th	53	46	.5	.5	10	20
th	55	43	2	.5	10	10
st	49	46	4			2
th	44	52	4			

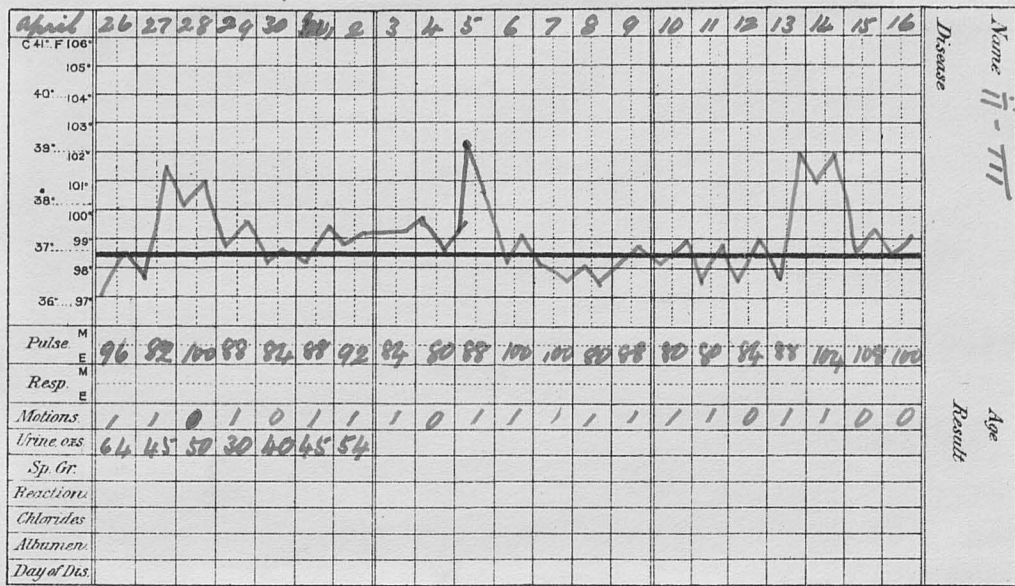
Some points in the case may now be referred to.

It is interesting to note that symptoms were first noticed six months after confinement and that the fatal relapse was also associated with pregnancy and childbirth, though in neither instance was there a history of haemorrhage.

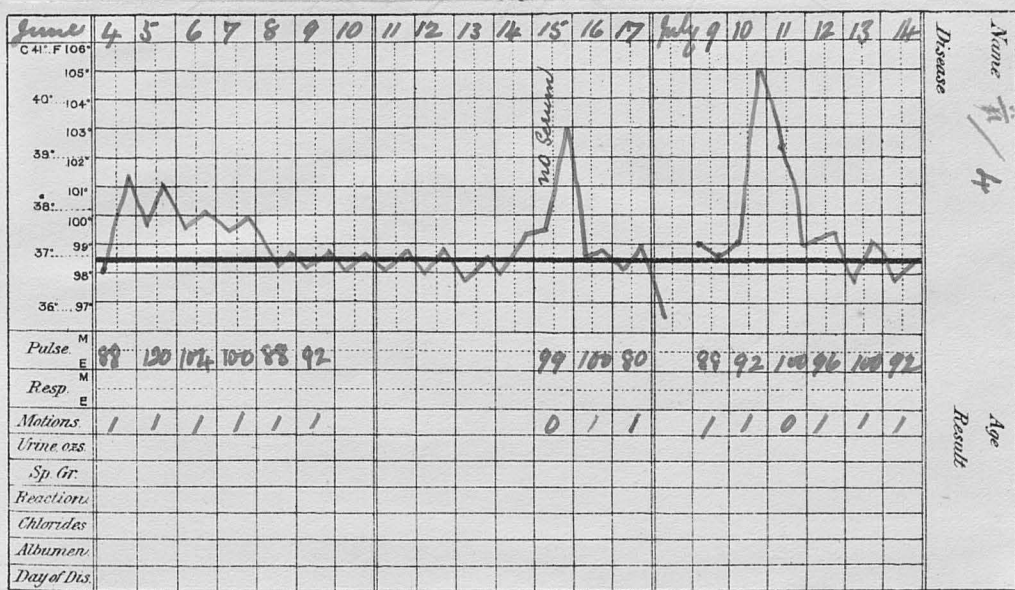
Regarding the blood changes, we may note the continued low leucocyte count and the curious fact that while the number of red cells was increasing and that of the abnormal cells decreasing, the percentage of lymphocytes was going up at the expense of the polymorphonuclear cells.

The steady rise of red cells coincident with the administration of arsenic and their fall during the week that arsenic was stopped is worthy of note. During the week, however, patient menstruated, but the loss was no greater than that of the previous week during which the corpuscles rose in number.





Name II - III
 Disease
 Age
 Result



Name II / 4
 Disease
 Age
 Result

CASE II.

An engineer, aged 43, residing at Roslin was admitted to the Royal Infirmary under the charge of Dr James on August 22nd 1899, when the following notes were taken.

Complaint: "Pain in the back and chest, tingling in the fingers and toes, shortness of breath and weakness."

History: Patient's family history is good. He is temperate in his habits, has a comfortable home and was regularly at work till four years ago.

Previous Illness: Fourteen years ago, patient had an attack of typhus fever.

Present Illness: Began four years ago. Patient attributes its onset to excessive cycling. He first noticed numbness at the points of his fingers and a year later, he noticed the same sensation in his toes. He became gradually weaker and got breathless and had to give up work for some time. He saw a doctor, and after a few weeks he was able to resume work, but ever since he has been obliged to give it up at intervals owing to weakness.

State on Admission: Patient is well developed and looks well nourished though the muscles are soft.

Height 5 ft. 8 $\frac{1}{2}$ in.; weight 10 st. 2 lbs.

Temperature 98.6

Alimentary System: Teeth neglected and dirty, but not carious. Tongue slightly furred. Appetite poor. No trouble with digestion. Bowels tend to be confined. The abdomen on inspection and palpation seems healthy.

The liver is slightly enlarged and can be felt two inches below the costal margin in the nipple line.

Haemopoietic System: The spleen is not enlarged. None of the lymphatic glands are enlarged. The blood (Plate IV) looks pale and watery and coagulates slowly. There is slight poikilocytosis and rouleaux formation is impaired. The red corpuscles number 2,100,000, white 7,300 p. cmm. Haemoglobin 52%. Megaloblasts and normoblasts are present. The plates are diminished.

Circulatory System: There is at times pain over the heart. There are palpitation and dyspnoea on slight exertion. There is pulsation in the neck. The apex beat is in the 6th interspace $\frac{1}{4}$ inch outside the nipple line. The upper cardiac border in the parasternal line is at the 3rd rib. The left border is half an inch to the left of the nipple line. The right border at the 4th rib is $\frac{1}{4}$ inch to the right of the right sternal margin. A Systolic murmur can be heard over the mitral, aortic and tricuspid areas. The pulmonary 2nd sound is accentuated. The pulse is 68 per minute, regular in time and force. Tension is low, volume small. The wall is not thickened.

Respiratory System: There is a slight cough, not accompanied by expectoration. Respirations are 20 per minute. The chest is well-formed and on percussion and auscultation seems healthy.

Integumentary System: There are no swellings or haemorrhages.

Urinary System: There are no subjective phenomena. The urine is straw coloured, acid, sp.gr. 1014. There is a slight cloud of mucus.

Nervous System: Patient complains of feelings of tingling and numbness in the fingers and toes. These sensations are not affected by exposure to heat or cold and are not constantly present.

There is slight tenderness on tapping the shins.

The motor functions, special senses and reflexes are not impaired.

Patient was treated with gradually increasing doses of Liq. Arsenicalis and an iron and aloes pill twice daily. He was three weeks in Hospital.

During that time he showed very little change. The blood condition showed very slight alteration.

The temperature never rose above 100. The bowels acted regularly. The pulse ranged from 64 to 92 per minute. The Cardiac murmurs became less marked and his weight increased by $3\frac{1}{2}$ lbs. He was then discharged.

On March 30th 1900, patient was re-admitted.

He complained of great weakness, eructations and occasional vomiting and loss of sensation in the fingers.

He was troubled with constipation and occasional diarrhoea. The vomited matter consisted of partially digested food. The liver was found one inch below the costal margin in the nipple line.

The spleen was slightly enlarged and measured $6\frac{1}{2}$ inches in length and $3\frac{1}{4}$ in breadth.

Patient complained of throbbing in his temples, palpitation and faintness. The apex beat was palpable in the nipple line. There was a soft, systolic murmur not propagated to the axilla and a bruit de diable could be heard in the neck. The pulse was 80 per minute, regular in time and force, but of low tension and small volume. He had a cough with slight muco-purulent expectoration accompanied by a feeling of soreness in the chest.

No percussion dulness or accompaniments on auscultation could be made out. The urine was pale: sp.gr. 1016; reaction, acid. It contained no abnormal constituent.

Patient complained of great numbness and loss of sensibility in the fingers, and pains in his bones. He said he at times dropped coins as he could not feel them.

Sensibility to touch was impaired. Sensibility to pain, heat or cold was not affected. For the last two months, he has suffered from slight deafness and his sight has been rapidly failing. The pupils reacted well to accommodation and light. Both fundi seemed healthy.

The patellar jerks were very slight. Muscular power was only slightly diminished but patient was very easily exhausted.

From March 30th till April 12th patient was treated with Liq. Arsenicalis in ~~m~~ V doses thrice daily. He had in addition two injections of Brown Séguard's bone marrow and spleen juice at intervals of a week. During this time his condition showed little change. His temperature was never above 101 F.

On April 14th arsenic was stopped and iCC of antistreptococcus serum was injected once a week. About three hours after each injection the temperature rose a few degrees, e.g., from normal to 101.5, from normal to 103 from 97 to 101.5 and from normal to 102.5.

There was almost no alteration in the rate or tension of the pulse and differential counts of the leucocytes before the injection and during reaction showed a very slight increase of the polymorphonuclear cells.

A curious point is that on June 15th, the usual day for the injection, the serum was not given, yet the temperature rose from normal to 103 in the afternoon and fell again before evening.

Patient always expressed himself as feeling better after getting the serum. On July 17th, the blood had lost its streaky appearance and looked a good colour. Arsenic was again administered and on July 18th m X of tincture of the perchloride of iron thrice daily were also commenced. Patient was sent to the convalescent home on July 30th.

On August 3rd, he was sent back to the Infirmary. He said he had caught a chill by getting up through the night. His temperature was 104 and he was suffering from diarrhoea.

He was ordered 10 grs. of Sulphate of Quinine thrice daily, and the next day the temperature fell to 100 and the next to 98. On August 9th an injection of 1 cc. of antistreptococcus serum was given. On this occasion there was no reaction.

Patient's symptoms rapidly improved and he went home on September 22nd, 1900.

TABLE III.

Date.	Red Cells per cmm.	White Cells per cmm.	Hb. %	Colour Index.
1899.				
Aug. 22nd	2,100,000	7,300	52	1.2
Sep. 14th	2,066,400	2,187	48	1.1
1900.				
Mar. 30th	1,500,000	2,500	35	1.1
May 8th	1,875,000	2,500	27	.7
" 22nd	1,972,400	(2,500 3,125)	30	.7
June 4th	2,012,250	4,166	48	1.2
" 15th	2,480,000	2,812	35	.7
July 17th	2,880,000	2,187	42	.7
" 30th	2,500,000	2,500	38	.7
Aug. 7th	1,625,000		30	.9
Sep. 3rd	1,460,400		30	1

TABLE IV.

Percentage of White Cells.

Number per 1000
White Cells.

	Polymorpho- nuclear.	Lympho- cytes.	Eosino- philes.	Myelo- cytes.		Normo- blasts.	Megalo- blasts.
1899.							
Sep. 4th	54	42	3	0		10	15
1900.							
May 22nd	{ 43	{ 56	{ 1	0		0	4
After Serum	{ 59	{ 40	{ 1				
June 20th	64	34	2	0		0	0
July 17th	49	48	2	5		0	0
" 30th	54	38	8	0		0	0

This case is remarkable for its uneventfulness during a period of observation of over a year and during the previous four years of patient's illness.

The number of red cells shows very little variation.

The febrile attack which patient suffered from at the convalescent home seemed to have had the effect of reducing the red cells to a lower number than they had ever before reached.

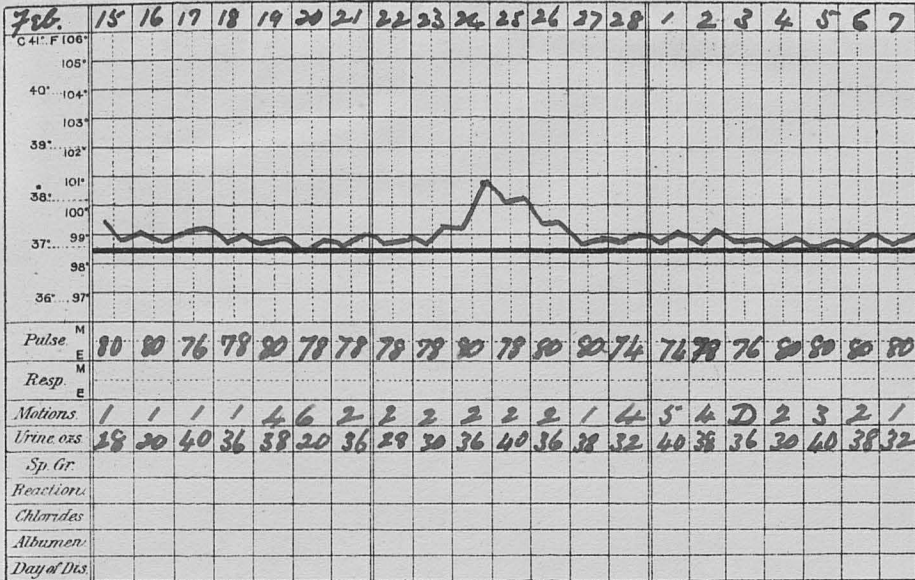
Unfortunately, I was unable to make observations of the blood after that period. Though nervous symptoms were complained of, no sign of gross lesion could be detected.

The case illustrates what I have subsequently noticed, viz:- that after treatment the symptoms may be immensely mitigated although the blood shows little improvement. No demonstrable improvement of the blood followed the administration of antistreptococcus serum.

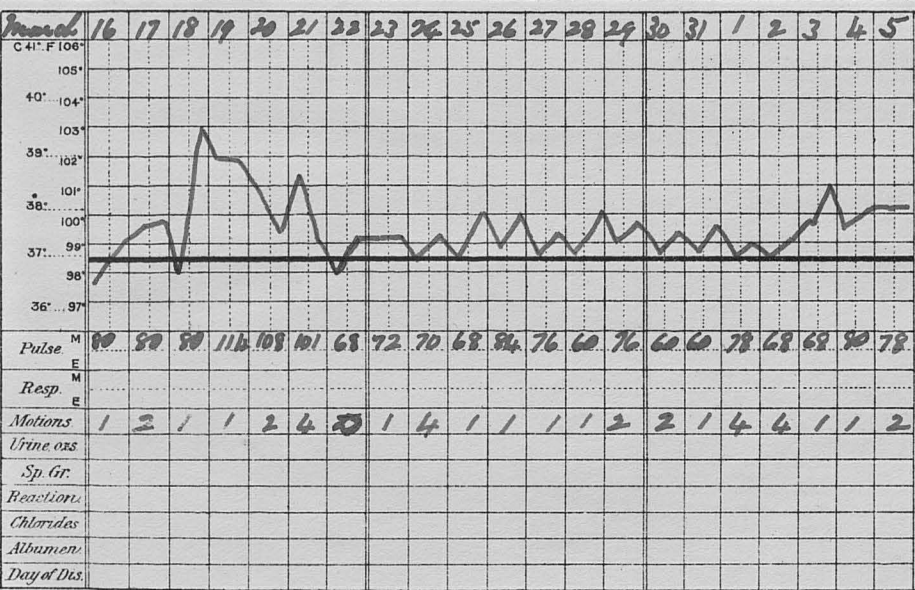
CASE III.

A railway porter, aged 47, residing at Cupar, Fife, was admitted to the Royal Infirmary under Dr James's charge on February 15th, 1899.

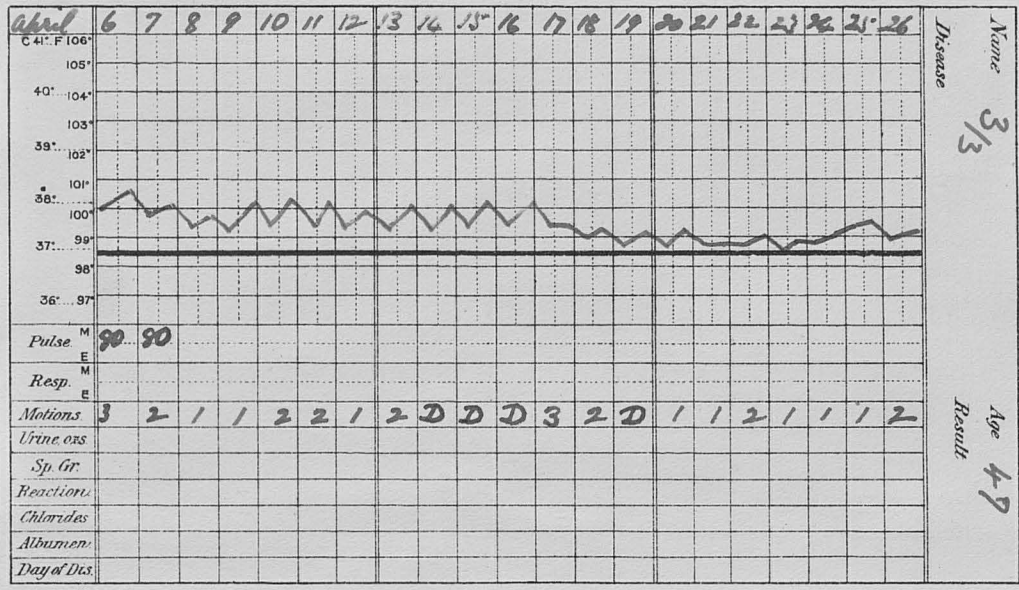
He complained of pain in the chest, prickling sensations in the legs and fingers, weakness and listlessness of $2\frac{1}{2}$ years duration.



Name
Disease
3/1
Age
47
Result



Name
Disease
3/2
Age
47
Result



Name 3/3
 Disease
 Age 49
 Result



Name 3/4
 Disease
 Age 47
 Result

History: Family history good. Patient is married and is comfortable at home and is temperate as regards alcohol and tobacco. He has had no previous illnesses of importance.

Present Illness: Began over two years ago. Patient began to feel vaguely out of sorts and became gradually weaker, but was able to work till December 1898. He then saw a doctor who ordered rest and gave him medicine. Patient did not improve and was recommended to come to Hospital.

State on Admission: Patient is well developed. Muscles soft. There is marked pallor with a slight yellow tinge. The sclerotics are very white. Temperature normal.

Alimentary System: Lips dry, gums pale, teeth good. Tongue pale and moist, shows a slight coating of fur. The appetite is fair. Bowels regular. Stomach slightly dilated. Liver not enlarged.

Haemopoietic System: No unusually enlarged glands. Spleen not enlarged.

Red blood corpuscles, 848,000 p.cmm.

White Corpuscles 5,313 "

Haemoglobin 30% Blood looks pale, and coagulates slowly. Fibrin is diminished. The average size of the red corpuscles is increased.

There is marked poikilocytosis. Megalocytes and microcytes are numerous, megaloblasts and normoblasts are present in considerable numbers. Polychromatophilia is not marked. (Plate V.)

Circulatory System: There is slight dyspnoea. No abnormal pulsation is visible. The apex beat is between the 5th and 6th ribs $\frac{1}{2}$ inch internal to the nipple line. There are no signs of cardiac enlargement. On auscultation, the sounds are feeble in all the areas. There is a soft, systolic, mitral murmur and a bruit can be heard in the neck.

Pulse 72 per min. regular, wave small, tension low; wall not thickened.

Respiratory: Breathing, 19 per minute. There is no cough. The chest is rather long and rounded. Movements fairly good, but vocal fremitus is diminished. The sounds are faint with no accompaniments.

Integumentary System: The skin is pale yellow in colour. There is slight eodema of the eyelids, legs and ankles.

Urinary System: The urine is dark amber in colour, acid, sp.gr. 1013. There is a well-marked absorption band due to urobilin on spectroscopic examination.

The Nervous System except for "prickly" sensations in the fingers seems healthy.

Treatment and Progress: For the first fortnight patient was treated with arsenic (Liq. Arsenicalis M.V t.i.d.) and an injection of Brown-Séguard's bone marrow and spleen juice every third day.

At the end of that time, Liq. Ferri Pernitratidis in M.XX doses thrice daily was substituted for the latter. During the first four weeks patient improved considerably but occasionally suffered from diarrhoea.

On March 18th, he had a rigor and complained of pain in the left side. The temperature rose to 103 F., pulse to 120 and respirations to 40 per minute. Next day patient began to cough up viscid, rusty coloured sputum which was found to contain pneumococci. Percussion dulness and tubular breathing could be detected at the lower part of the left lung.

In the evening patient became delirious. Next day patient was again sensible. Crepitations could be heard over the dull area.

The condition evidently was pneumonia limited to the left base. The arsenic and iron were stopped and digitalis and ammonia were administered.

Patient had a crisis on the 4th day, (March 22nd) The pulse, however, became very poor in volume and tension, On March 28th as there had been an increase in the dulness an exploring needle was inserted into

On April 2nd, 44 ounces of fluid were drawn off. The fluid was clear yellow in colour with a few flakes of fibrin. Its specific gravity was 1014.

On April 3rd, the temperature rose, loud friction was heard on the left side and a patch of catarrhal pneumonia was detected on the right side.

There was, however, no marked change in patient's symptoms except that he was gradually getting weaker and more breathless, till April 14th. From that date till the 20th, he suffered greatly from diarrhoea, consequently he was treated with simple astringents and all other medicines were stopped.

After this period arsenic was resumed, but fluid was evidently re-accumulating in the left pleura. On May 4th, blood-stained pus was found and 30 $\frac{3}{4}$ were drawn off through a large trocar and a tube was then inserted between the 5th and 6th ribs.

No great improvement followed. Patient got weaker and weaker. On May 7th, the left side was oedematous and the oedema soon spread to the back.

On June 8th Patient died after a paroxysm of coughing.

TABLE V.

Date.	Red cells per cmm.	White cells per cmm.	Hb. %	Colour Index.
1899				
Feb. 15th	848,000	5,313	30	1.8
" 20th	1,440,000	5,200	25	.8
Mar. 3rd	2,400,000	8,400	35	.7
" 10th	3,916,000	7,000	45	.5
" 18th	2,000,000	5,620	50	1.2
Apr. 20th	2,720,000			

TABLE VI.

	<u>Polymorphonuclear</u>	<u>Lymphocytes</u>	<u>Myelo-</u> <u>cytes.</u>
1899.			
April 28th	79	20	.2

A post-mortem examination was made by Dr Welsh and the following notes were taken.

Body well nourished; no great pallor: marked rigidity; slight lividity. Thorax.- Pericardium distended with clear serous fluid. Left pleura healthy along the anterior margin. All the posterior part cut off by fibrous adhesions and containing over 20 ounces of pus.

Right pleura healthy.

Heart: Epicardial fat degenerated and mucoid. Arterial valves competent. Aortic segments thickened along with the attached and free margins. Mitral

cusps thickened from chronic endocarditis extending to chordae tendineae and apices of the papillary muscles.

Endocardium of left ventricle thick and opaque. Cavities slightly dilated. Muscle flabby and anaemic, with slight fatty degeneration.

Left Lung - Emphysema along anterior margin. Collapse posteriorly.

Right Lung - Emphysema and anaemia.

Abdomen - Peritoneum healthy.

Liver - Periphery of lobules yellow from fatty infiltration. Centres dark red from chronic venous congestion. Marked pigmentation to naked eye. Iron reaction with potassium ferrocyanide and hydrochloric acid, at periphery of lobules.

Spleen, enlarged, soft, pale and diffluent.

Kidneys somewhat enlarged and pale showing cloudy swelling and fatty degeneration.

Osseous. Bone marrow of femur all transformed to red marrow, and the bony trabeculae were being absorbed around the medullary canal by the increase in bulk of the marrow.

The pus showed only a few degenerated cocci of uncertain nature.

The points worth noticing about this case are its insidious onset and apparent causelessness and the effect of a complication which, in a more healthy person, would have been a comparatively slight

illness - an attack of pneumonia which did not affect the whole of the left lower lobe and which was followed by a crisis on the 4th day.

This was followed by pleurisy which subsequently became purulent.

As patient's condition did not appear to permit a more serious operation, a tube was inserted between the ribs. In a few days the side of the chest was boggy and oedematous.

The progress of this case seems to indicate that wounds whether traumatic or surgical are of very serious import owing to the poor nutrition of the tissues, apart from the danger of haemorrhage.

It may be that the diminished number of leucocytes may result in a lessened resistance to the action of organisms.

It is specially unfortunate that some of the data and nearly all the blood films from this case have been accidentally destroyed. A study of the effects of a complication such as pneumonia which has marked effects on the blood in a case of pernicious anaemia, authenticated by post-mortem examination, should otherwise have made Tables V. and VI. the most interesting of the series.

CASE IV.

A girl, aged 21, a silk-factory hand came to the Outpatient Department, of Great Yarmouth General Hospital on January 19th, 1900.

She complained of weakness and sickness and swelling of both wrists.

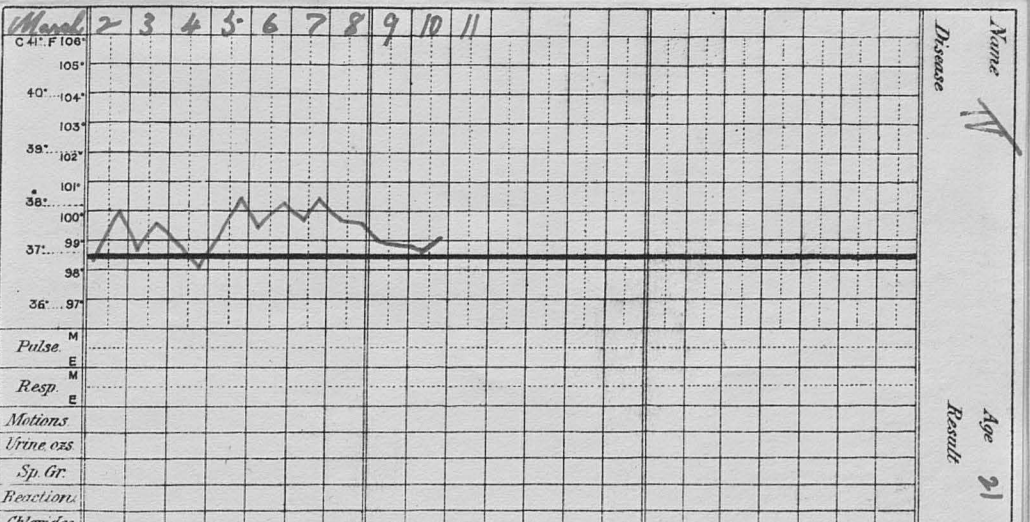
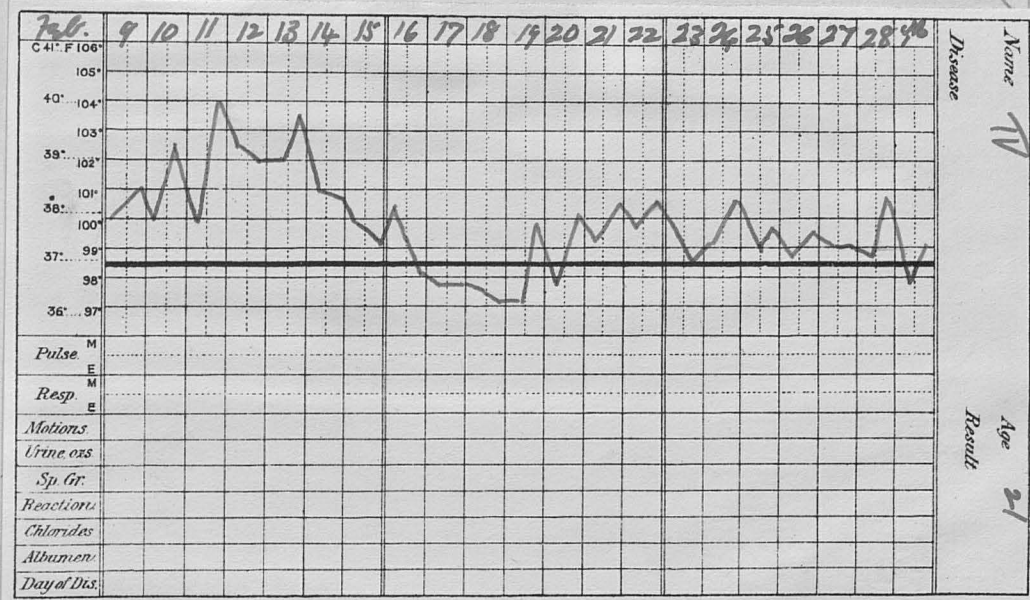
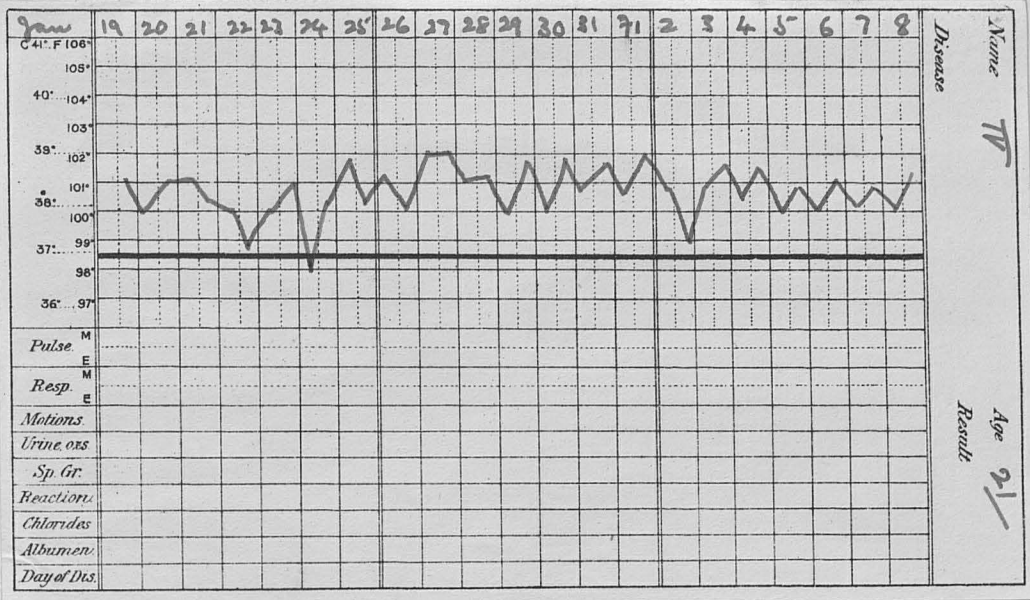
She said the swelling had only come on two days previously and that the sickness had existed for a week. Her temperature was 101 F. and as she was obviously seriously ill, she was straightway admitted as an Inpatient under the care of Mr A. H. Moxon. The notes of her case are as follows:-

History: Patient does not remember about her father; her mother is alive and healthy. She is the fourth of a family of six.

Her home surroundings are comfortable. Her food is good. She has three meals a day - tea twice and meat once. Her work is exhausting as she has to stand all day over a machine.

Previous Illnesses: Patient does not remember suffering from any of the diseases of childhood. She had anaemia for two months at the age of 16 and again for about a month when she was 18.

Present Illness: Began last Christmas, (a month before admission). Patient says she caught cold



and got so weak and breathless that she had to give up her work. She has not worked since.

She has been treated at home with brandy and beef-tea. About a week ago, she began to feel pains in her legs, worst near the ankles, and she also became troubled with headaches and suffered from sickness. She has frequently vomited immediately after meals. Two days before admission the hands and wrists became slightly swollen and painful and she felt distinctly feverish.

State on Admission: Patient is well developed. The muscles are soft, but there is no sign of emaciation.

There is marked pallor. The sclerotics are pearly white. The expression is anxious and frightened, and patient seems nervous and excitable.

Alimentary System: The lips are pale and dry with a slight coat of sordes. Gums anaemic. Teeth are clean and in good condition with the exception of the right, second, lower bicuspid and the 2nd, left, lower molar which are represented by carious stumps.

Tongue pale but fairly clean. Appetite poor. Patient complains of nausea and occasional sickness after food. The bowels only move about once in four days. There is no abdominal tenderness. The liver is not enlarged.

Haemopoietic System: There is no unusual enlargement of glands. The thyroid is not enlarged. The spleen seems enlarged on percussion and is vaguely palpable. A drop of fresh blood looks thin and watery and does not coagulate readily. Fibrin, however, is increased and plates are numerous. The red corpuscles number 840,000 per cmm. Haemoglobin is 20% and white cells number 6,250 per cmm.

The average size of the red cells is distinctly increased. There is great diversity in size and considerable alteration in the shape of many of the corpuscles. In stained films megaloblasts and normoblasts are present. The white cells are slightly diminished in number. There is no alteration of the normal ratio of leucocytes to lymphocytes. The eosinophiles are markedly diminished. (Plates VI. and VII).

Circulatory System: There is ^{no} giddiness or faintness, but patient is troubled with palpitation. There is marked dyspnoea. There is visible throbbing of the arteries in the neck and marked epigastric pulsation. The apex beat is between the 4th and 5th ribs and $\frac{1}{2}$ inch internal to the nipple line. The impulse ^{is} sharp and jerking, but can be felt over a wide area. On percussion the heart seems small.

A long, blowing, systolic murmur can be heard in all the areas. It is best heard in the pulmonary area. There is a loud bruit de diable in the neck. The pulse is 138 per minute, regular in time and force. The volume is rather small; tension is very low and not sustained. The vessel wall is not thickened.

Respiratory System: There is a slight, irritating cough not accompanied by expectoration. The alae nasi move with respiration. Respirations 30 per minute. The pleura and lungs on examination seem healthy.

Integumentary System: There is slight, puffy swelling about the wrists. There is marked oedema at both ankles. There are no indications of haemorrhage and no excessive perspiration.

Genito-Urinary System: Urine pale, sp.gr. 1010, acid, contains no abnormal constituents. Patient missed her last period.

Nervous System: Patient is very excitable and does not sleep well. She complains of tingling in the fingers when they are the least chilled. There is very slight ptosis of the left eye. Patient says this began during her first attack of anaemia when

she was 16. The pupils are dilated. They react well to accommodation and light. The fundus is healthy. The reflexes are unaltered.

Locomotory: Patient complains of pain in the legs and wrists and there is some tenderness over the tibiae.

Diagnosis, Treatment and Progress: When this case was first seen we had to deal with a patient, a young woman of 21, who complained of pain and swelling of the wrists, who looked pale, whose circulation was excited and whose temperature was 101 F.

The diagnosis then made was acute, rheumatic endocarditis.

She was put to bed, fed on milk diet and treated medicinally with grs. XV. of Salicylate of Soda every 4 hours. There was very little improvement. The temperature remained about 101 F. The skin became yellow and the colour became gradually deeper. Listlessness continued.

Nine days later, as a result of the blood examination, the salicylate was stopped and arsenic was administered in increasing doses.

Patient complained of pains along the gums and the two stumps already referred to were extracted. There was no indication of inflammation or abscess

in connection with them.

The yellow colour now rapidly disappeared and in a week (Feb. 4th) the red cells rose in number to 1,231,200.

By February 10th patient was taking M.X. of Liq. Arsenicalis three times daily, but on that day she vomited.

She was again sick on the 11th and complained of pains along the tibiae. Next day the temperature reached 104°F. Arsenic was stopped and Beta-Naphthol was given. On Feb. 15th the temperature was down to 98.6 F. Arsenic was resumed and the Beta-Naphthol continued.

On Feb. 18th, patient was much better and for the first time since her admission, took an interest in her toilet and had her hair curled.

On February 20th a faint rash appeared on the face, neck, chest and limbs. The eruption consisted of small, dark-brown scarlatina-form spots.

This disappeared on February 22nd and was followed by a slight desquamation on the face.

On March 5th a second rash appeared on the face. This eruption had the same brown colour as the former one, but it appeared in large, scaly-looking patches. Beta-Naphthol and arsenic were stopped and patient got no medicine for a week.

On March 18th, Blaud's Pill (gr.V) with Arsenious Acid (gr.1/40) was ordered. From this time patient made steady progress and on March 23rd left hospital.

By this time, the cardiac bruits had disappeared, the spleen still seemed a little enlarged and patient complained merely of being easily fatigued and of some dimness of vision. No change in the fundus or error of refraction could be found to account for the latter.

The last time patient was seen, her red corpuscles numbered 4,700,000 and Haemoglobin was 70%.

She has remained well, till last heard of in July 1900.

TABLE VII.

Date.	Red cells per cmm.	White cells per cmm.	Hb. %	Colour Index.
1900				
Jan. 28th	840,000	6,250	20	1.2
Feb. 4th	1,231,200	5,312	22	.9
" 11th	1,200,000	2,812	22	.9
" 18th	1,837,200	2,500	28	.7
" 25th	2,480,000	2,108	20	.4
Mar. 4th	1,937,200	945	20	.5
" 11th	1,832,000	2,500	20	.5
" 18th	2,900,000	1,250	25	.4
Apr. 8th	4,280,000	6,562	70	.8
" 28th	4,700,000	5,562	70	.7

TABLE VIII.

Date.	Polymorpho- nuclear.	Lympho- cytes.	Eosino- philes.	Normo- blasts.	Megalo- blasts.
Jan. 28th	75.4	24.6	0	16	4
Feb. 4th	78	18	3	1	0
" 11th	84	16	0		
" 18th	69	31	0		
" 25th	76	20	4		
Mar. 4th	56	32	12		
" 11th	80	16	4		
Apr. 8th	80	19	1		
" 28th	58	36	6		

This is a case of considerable interest. Although the pallor was marked when the girl presented herself the diagnosis of pernicious anaemia was not thought of. This may have been in part due to the fact that it was quite exceptional for a girl of her age who did not suffer from anaemia to appear at Yarmouth Hospital.

It may be of service in connection with both the Etiology and diagnosis of this case to mention some facts regarding the extraordinary prevalence of anaemia at Yarmouth.

Of 1150 (male and female) cases coming in ordinary course to the Outpatient Department of the Hospital, 115 were cases of anaemia. This number is exclusive of cases suffering from other conditions complicated by anaemia.

The patients were girls working in the curing-houses, silk factory or as servants. Their appearance and symptoms and the condition of the blood were monotonously similar. I have tabulated twelve consecutive cases.

TABLE IX.

No.	Occupation	Age.	Red Cells. per cmm.	White Cells. per cmm.	Hb%	Colour Index.
1	Servant	21	3,000,000	4,062	15	.25
2	Housework	21	3,582,400	3,125	30	.42
3	Beatster	17	4,270,000	4,887	45	.54
4	Servant	23	4,150,000	3,516	25	.3
5	Housework	15	3,800,000	3,125	15	.17
6	Servant	17	4,500,000	3,515	15	.17
7	Schoolgirl	14	3,880,000	2,148	35	.45
8	Staymaker	16	3,080,000	6,586	35	.57
9	Housework	15	2,938,000	5,312	30	.51
10	Housework	16	3,589,600	6,250	35	.49
11	Factoryhand	23	2,320,000	1-870	25	.54
12	Factoryhand	20	3,200,000	3,750	30	.46

The differential leucocyte of the first three is typical of the others. In a very few cases were normoblasts found, and they were in no case numerous.

TABLE X.

	Polymorpho- nuclear.	Lympho- cytes.	Eosino- philes.
1.	66	33	1)
2.	77	22	1) per cent.
3.	66	32	2)

As regards etiological factors, it is difficult to ascertain anything that does not exist to a similar or greater extent in larger towns.

Yarmouth cannot be regarded as an unhealthy town, and a visitor to the Outpatient Department of the Hospital would perhaps notice the comparative rarity of phthisis next to the prevalence of anaemia.

The level of the surface water is high. David Copperfield was right, when he thought "that if the land had been a little more separated from the sea. and the town and the tide had not been quite so much mixed up, like toast and water, it would have been nicer."

As regards the social conditions of the girls, their homes compare favourably with the homes of the

same class in Edinburgh. Their food is fairly good. They eat too many "sweets" and live mainly on bread, fish and pork. As regards personal habits and cleanliness, they compare very favourably with the factory girls of such towns as Dundee or Brechin.

Case IV. was one of this class and according to her own statement, she had on two occasions suffered from the prevailing anaemia, but there is no history of any cause of the later illness that was not common to all the others. Though she had two loose stumps, her teeth as a whole were unusually good. It is hardly conceivable that they should have been the source of her illness. That the case, however, was essentially different from the group just described, is apparent from a comparison of the tables shown.

While the lowest number of corpuscles in the chlorosis series is over 2,000,000, in Case IV. they numbered 840,000. Haemoglobin in Case IV. was 20%. In some of the Chlorosis Cases, it is below that figure. While in Case IV. the colour index on the first examination was 1.2, the highest colour index in the twelve chlorosis cases was .57 and the lowest .17.

The large size of the red cells, the absence of a central concavity, the presence of polychromatophilia and megaloblasts were other points in which the results of the blood examination differed from that of the chlorotic cases. Apart from the blood examination, the yellow colour, the high temperature, the attacks of sickness, the enlarged spleen, the great circulatory excitement and the nervous phenomena were amply sufficient to justify us in holding that the case was not chlorosis. But was the case one of pernicious anaemia?

Against the diagnosis of pernicious anaemia were the presence in the blood of an increased amount of fibrin, a large number of blood plates (though observers differ as regards the number of the plates in pernicious anaemia, vide infra) the small number of megaloblasts and the fact that poikilocytosis was not well marked.

These objections, however, are not serious and the list of symptoms enumerated above is almost exclusive. Ulcerative endocarditis might give rise to the same group of phenomena and the same degree (if not the same variety) of anaemia, but the excellent recovery (for the time being, at least) without any sign of cardiac lesion excludes that diagnosis. The fact of rapid recovery may be urged against the diagnosis of pernicious anaemia, but remissions more rapid are fairly common.



In one of Cabot's cases (Amer. Jour. Med. Sci. Aug. 1900) the red cells increased from 1,800,000 to 5,200,000 in 14 days.

It is possible that there was a slight rheumatic element in the case and this would account for the increase of fibrin.

The case must be considered as one of pernicious anaemia, but cannot be regarded as typical. Further observation may give us more definite knowledge.

Regarding the progress of the case, it is interesting to note that improvement followed a febrile attack. Whether the rapid fall in temperature after the administration of Beta-Naphthol was merely post hoc or propter hoc one cannot say. The skin eruptions were probably due to the Beta-Naphthol. The great and rapid improvement following the administration of iron after the colour index had become low, is worthy of note.

CASE V.

A boy, aged 11, born in Antrim and residing at Broxburn was admitted to the Royal Infirmary under the charge of Dr James on May 5th 1900.

He complained of weakness of 6 months duration.

His father and mother were alive and healthy.

There was no history of any family tendency towards

May	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21			
C 41° F 106°																				
105°																				
40° 104°																				
103°																				
39° 102°																				
101°																				
38° 100°																				
99°																				
98°																				
37° 97°																				
96°																				
97°																				
Pulse M	132	132	132	132	120	124	126	128	120	130	122	132	122	120	123	128	132			
E																				
Resp. M	32	28	24	28	28	32	32	32	30	28	28	30	30	30	32	32	32			
E																				
Motions	1	0	0	1	0	0	1	1	0	0	0	1	0	1	1	1				
Urine oxs																				
Sp. Gr.																				
Reaction																				
Chlorides																				
Albumen																				
Day of Dis.																				

Name **T**

Age

Disease

Result

disease, but three brothers had died in childhood. He had received good food.

His only previous illness had been measles when 9 years old. His illness was said to have dated from a kick on the abdomen sustained while he was playing football in September 1899. He had not been much affected at the time, but had begun to get pale and by December, he had become very weak and had occasionally complained of sickness.

On several occasions it was stated, he had vomited dark, altered blood. His parents had noticed frequent oozing of blood from his mouth.

The bleeding had never been profuse, but almost constant. He had been treated at home with some form of iron. At the New Year, he had passed a small quantity of red blood by the rectum. He had occasionally since passed blood by the rectum, but it always, latterly, had been dark in colour.

The pallor and weakness had gradually increased and a week before his admission, he had become unable to walk.

On admission, patient was found to be well developed, extremely anaemic, but not emaciated. There was no evidence of injury or disease. On the abdomen there were a few small naevi.

As regards the Alimentary System, the lips and gums were exceedingly pale. Blood could occasionally be seen oozing up around the teeth. The teeth were good. There was occasionally sickness after food. The bowels tended to be confined. The lower border of the liver in the nipple^{line} reached $1\frac{1}{2}$ inches below the costal margin.

Haemopoietic System: There were no enlarged glands. The spleen was not enlarged.

The blood was exceedingly pale. On puncturing the skin the drop that exuded looked like serum.

Fibrin was much diminished, coagulation slow and rouleaux formation practically absent. The red cells numbered 485,000 white 2,184 per cmm. Hb. was 8%. There was great diversity in the size of the red cells but there was not so much deformity as might have been expected. There were degenerative changes in the red cells and well-marked polychromatophilia. Several large, nucleated forms were present. Leucocytes were diminished. A few myelocytes were present (Plate VIII.).

Circulatory System: Patient complained of palpitation and dyspnoea. The apex beat was in the 5th interspace $\frac{1}{4}$ inch internal to the nipple line.

There was visible pulsation of the carotids and in the epigastrium. On auscultation, there was a long, soft, mitral systolic murmur, a systolic murmur heard in the pulmonary area and a tricuspid, systolic murmur. Both aortic sounds were accompanied by murmurs.

The pulse was 120, regular in time, rather irregular in force. The tension was very low, volume small. The respirations were quickened, otherwise the respiratory system seemed healthy.

As regards the Integumentary System, there was marked pallor, no yellow discolouration, and no haemorrhages. The urine was pale, acid in reaction, with sp.gr. of 1012 and showed no abnormal constituents.

As regards the nervous system, the boy was drowsy and at times restless. Voluntary motor power was very much diminished, but the reflexes were unaltered. The fundus showed no haemorrhages.

Treatment and Progress: The boy was put on milk diet and treated medicinally with Liq. Arsenicalis, in increasing doses and 3 minims of Tincture of Digitalis thrice daily. He did not improve. On May 15th, an injection of Brown-Séquard's bone marrow and spleen juice was given. Next day an injection

of antistreptococcus serum was tried. This was followed by a rise of the temperature to 101 F. Still there was no improvement. Bleeding from the gums continued at intervals. The injection was repeated three days later, but no reaction followed and next day, the boy died. A sectio was not allowed.

TABLE XI.

Date. 1900	Red Cells, per cmm.	White Cells, per cmm.	Hb. %	Colour Index.
May 5th	485,000	2,184	8	.8
" 15th	480,000	1,500	5	.5
" 20th	295,000	20,000	5	.8

TABLE XII.

per cent.

per white 1000 cells.

Date.	Polymorpho- nuclear.	Lympho- cytes.	Eosino- philis.	Myelo- cytes.	Megalo- blasts.	Norme- blasts.
May 15th	53	47	0	0	5	0
" 20th	25	73	.3	.2	4	25

Before discussing this case, I should like to give some notes of another fatal case of anaemia in a boy aged 11.

CASE VI.

A boy of 11 was seen on June 25th, 1900 at his home. His parents stated that he had suffered from measles when he was five, and that when he was seven

he had taken a fit. They further stated, that he had been ill for 10 weeks and that the first symptom had been an attack of epistaxis.

Subsequently, epistaxis had recurred on two occasions and a fortnight before he was seen, a rash had appeared. A week later, he had an attack of haematemesis.

The boy was found to be apathetic and drowsy and could not be got to answer questions.

He looked profoundly anaemic. He was well-developed, thin, but apparently not much emaciated.

His lips were coated with sordes. Teeth were dirty, but not carious. Tongue dry and furred. Bowels had been confined.

The upper border of the liver was found at the 3rd rib. Its lower border in the nipple line was palpable $\frac{1}{2}$ inch below the costal margin.

The submaxillary lymphatic glands were slightly enlarged. The spleen was not enlarged.

The apex beat could be felt in the 5th interspace internal to the nipple line.

There were haemic murmurs at all the areas and there was the gallòp rhythm. The pulse was 140 per minute, irregular in time and force of very low tension and small volume.

Respirations were 40 per minute, shallow and sighing.

There were numerous purpuric spots - petechiae and vibices - on the trunk and limbs. There was no oedema.

Urine was pale. Its sp.gr. was 1008, its reaction acid. It contained no abnormal constituent.

He was ordered milk and beef tea and a mixture containing digitalis and arsenic. Two days later he was admitted to Dr James' Ward in the Royal Infirmary, where an opportunity was afforded for examining the blood. The blood looked pale. Fibrin was diminished. Plates were scanty and coagulation was slow. Poikilocytosis was present, but not very marked. There was some difference in the size of the red cells. The red cells showed only slight degenerative changes and no polychromatophilia.

The only abnormal cells found were normoblasts (Plate IX.)

The boy died two days after his admission to Hospital.

TABLE XIII.

Date.	Red Cells.	White Cells.	Hb.	Colour Index.
Jan. 7th	875,400	increased	14%	.8

TABLE XIV.

Polymorpho-nuclear.	Lymphocytes.	Eosinophiles.	Normoblasts.
57%	42%	1%	7 per 1000 white cells.

CASES V. and VI., form an interesting contrast.

Both were boys aged 11. Both came from mining districts.

Their symptoms were remarkably similar and both seem to have died from sheer bloodlessness.

Case V., was pernicious anaemia; Case VI., haemorrhagic purpura.

In both cases the cause of illness was obscure. It is hardly likely that the blow on the abdomen of which there is a history in Case V., should have had any direct causal connection with symptoms which were not marked till three months afterwards.

The first symptom noticed in Case V. was pallor and then bleeding from the gums.

In Case VI. epistaxis was the first symptom.

In Case V. the bleeding was all from the alimentary canal, - gums, stomach, rectum.

In Case VI. the haemorrhage occurred as epistaxis and petechiae.

The effects on the Circulatory System were somewhat different in the two cases. In both cases, it was profoundly depressed, but in Case V. there seemed to be a certain amount of reaction. There was visible carotid pulsation and till near the end the pulse was regular, its rate about 120. The respirations were slightly quickened.

In Case VI., there was a gallop rhythm with an irregular pulse of 140 per minute, while the respirations were 40 per minute, shallow and sighing.

Mentally both cases were very drowsy, but while Case V. could be roused and got to answer questions intelligibly (while he had four hundred thousand red corpuscles), Case VI. (with 800,000) when roused, only displayed feeble signs of irritability.

Comparing the results of the blood examinations, we find in both cases, slow coagulation, scanty fibrin and few plates.

Case V. showed the more marked poikilocytosis and greater diversity in size.

In Case V. the red cells stained more darkly with eosine and were of a slightly larger average size than in Case VI., and there was polychromatophilia which was absent in Case VI.*

Case V. showed megaloblasts, normoblasts and myelocytes. Normoblasts were the only abnormal cells found in Case VI.

There was a higher percentage of lymphocytes in Case V.

The last counts in Tables XI. and XII. should, however, be omitted for purposes of comparison between the two cases as they are complicated by an

* Plate VIII. does not show all these points. The field was selected as it showed a megaloblast.

extreme terminal lymphocytosis.

The low colour index (for pernicious anaemia) in Case V. is accounted for by the haemorrhage.

CASE VII.

A man, aged 73 who had been a butler, was admitted to the Royal Infirmary under Dr James's charge on July 2nd, 1900.

He complained of weakness, constipation and epistaxis.

His family history was good and his circumstances had been comfortable.

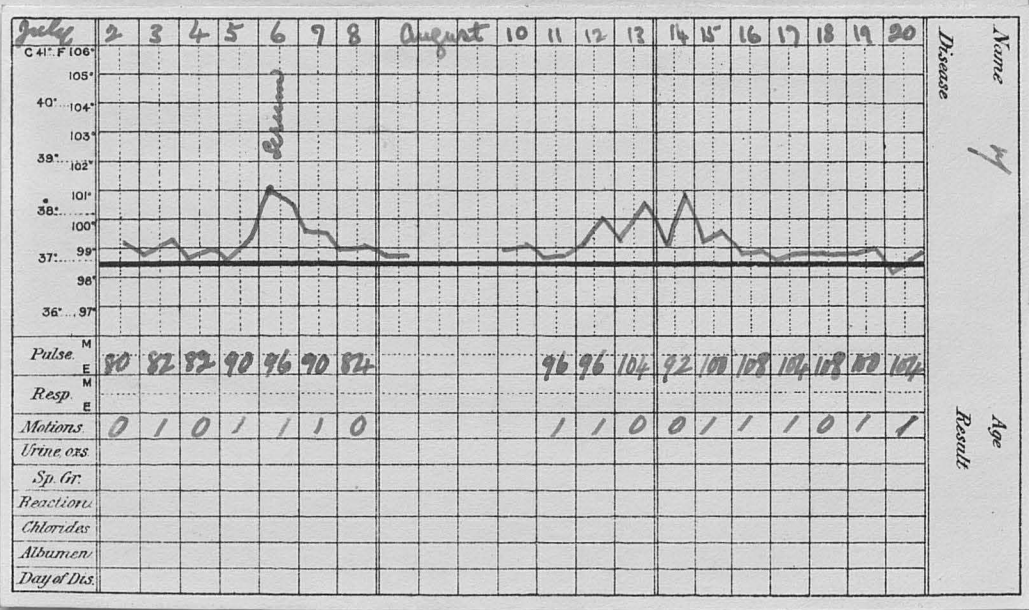
He had always enjoyed good health till three or four months before his admission, when it was noticed that he was getting weaker and he began to suffer from bleeding at the nose. The bleeding had never been in great amount but it occurred at pretty frequent intervals.

The weakness had greatly increased and for seven weeks before admission, he had been confined to bed.

On his admission, he was found to be well developed, but down in condition; his muscularity was poor.

There was marked pallor and the face showed a slight, lemon-yellow tint.

The conjunctivae were also slightly yellowish.



Albumen

W

Age
Result

Alimentary System: The lips and gums were pale. The tongue was dry, showed a slight coating of brown fur, and was indented by the teeth. The bowels were constipated.

The abdominal parietes were flaccid. The liver did not seem enlarged.

Haemopoietic System: There was no enlargement of lymphatic glands or of the spleen.

The blood was very pale in colour, and coagulated slowly. Fibrin was diminished and rouleaux formation was very slight.

There was well-marked, but not extreme poikilocytosis. The corpuscles showed great diversity in size, the average being much increased. Nucleated red cells were present. There were also a few myelocytes (Plate X.). The red cells numbered 800,000 per cmm. The haemoglobin was 24%.

Circulatory System: There was not much dyspnoea. Slight epigastric pulsation was noticeable. The apex beat was in the 5th interspace an inch internal to the nipple line. The heart did not seem enlarged. There was a long, soft murmur accompanying the mitral, systolic sound. The pulse was 80 per minute, regular in time and force. Tension low. Volume fair. The arterial wall was not thickened.

The Respiratory System: seemed healthy.

Integumentary System: There was slight yellow discolouration of the skin.

The urine was amber in colour, acid and its sp.gr. was 1015.

Chemical examination revealed no abnormal constituent, but the spectroscope showed the presence of urobilin.

Nervous System: Patient's mental powers were below par. Although he could answer questions concerning his symptoms, he was practically a dement. The sensory, reflex and motor functions were not markedly impaired. His sight was good, and the fundus oculi on each side looked healthy.

Treatment: Patient was treated with arsenic in increasing doses. On July 6th his temperature showed a slight rise and an injection of 1 cc. of antistreptococcus serum was given. No reaction followed.

During September salol was given in addition to the arsenic. Retinal haemorrhages were now noticed.

Patient got gradually weaker and died on September 25th 1900.

TABLE XV.

Date.	Red Cells.	White Cells.	Hb. %	Colour Index.
July 2nd	8000,000		24	1.5
" 14th	1,274,400	6,250	30	1.2
" 25th	1,360,000	3,125	30	1.1
Sep. 25th	937,500		20	1.0

TABLE XVI.

Date.	Per Cent					Per 1000 white cells			Mi
	Polymorpho- nuclear.	Lympho- cytes.	Eosino- philes.	Myelo- cytes.	Baso- philes.	Megalo- blasts.	Normo- blasts.	bla	bla
July 2nd	67	31	.8	.4	.1	4	3		
" 14th	62	35	2	.1	.2	14	11		
" 25th	56	40	3	.5	0	10	80		
ep. 25th	43	56	0	.5	0	205	120		28

On September 27th, a post-mortem examination was made by Dr Welsh.

The body showed great pallor with a slight yellow colour also seen on the conjunctivae. There was considerable emaciation. Rigidity marked.

There were five ounces of fluid in the pericardium and 25 in the left pleura. The left pleura was much thickened. The right was healthy and contained five ounces of fluid.

The epicardial fat was very oedematous. There was very little atheroma of the coronary arteries or aorta. There was thickening about the attached borders and Corpora Aurantii of the aortic segments. There was diffuse, fatty degeneration of the heart muscle with thickening of the endocardium, but the "thrush's breast" appearance was not present. The left lung was very oedematous; the right less so. The spleen was of a diffuse red colour. The Malpighian bodies were obscure. The liver was dark brown in colour and showed advanced fatty degeneration. There was a well marked iron reaction, especially at the periphery of the lobules.

The kidney cortex was atrophied. The papillae were pale. The capsule was not adherent. There were a few cysts.

The dura mater was greatly thickened and oedematous and firmly adherent to the skull. The internal carotids were much thickened.

The mucous membrane of the stomach and intestine showed no naked-eye change.

The bone marrow of the femur was of a diffuse crimson colour and the medullary cavity was enlarged. Microscopically, the bone marrow showed a very large number of nucleated red cells of various size.

Many of the red cells showed karyokinesis.

The main interest of this case lay in the question of diagnosis. Against the probability of the case being pernicious anaemia were the emaciation, the high percentage of polymorphonuclear cells and the fact that normoblasts appeared as numerous as megaloblasts in looking over only one or two films. Really "typical" megaloblasts were very scanty.

Cancer of the stomach was suggested, but careful examination failed to reveal any such condition.

On the other hand, the high colour index and the decreasing percentage of polymorphonuclear leucocytes were in favour of pernicious anaemia which diagnosis was made during life and confirmed by the autopsy.

The mental condition was fully accounted for at the "Sectio".

The great thickening of the dura was probably due to the combination of old age and anaemia.

CASE VIII.

This case is merely mentioned in order that it may be compared with the foregoing. The patient was a man over 50 who suffered from cancer of the stomach with some obstruction of the cardiac orifice. The blood was examined the day after a somewhat severe haematemesis.

The blood looked pale, but not streaky. Coagulation time about normal. Fibrin not diminished. Rouleaux formed readily. There was not much poikilocytosis or diversity in the size of the red corpuscles and they were pale and small. There was no polychromatophilia. Plates seemed diminished (Plate XIII).

It is interesting to note that while the total number of leucocytes is diminished, probably due to starvation, the percentage of polymorphonuclear leucocytes is high.

TABLE XVII.

Date.	Red Cells.	White Cells.	Hb. %	Colour Index.
Sep. 1st	2,000,000	5,937	22	.55

TABLE XVIII.

Date.	Polymorpho-nuclear.	Lympho-cytes.	Eosino-philes.	Myelo-cytes.	Normo-blasts.
Sept. 1st	88%	11%	0	1%	12 per 1000 white cells.

CASE IX.

This case is also mentioned for purposes of comparison.

A foreman boilermaker aged 40, residing in Leith, was seen on June 2nd 1900. He complained of weakness shortness of breath, and occasional pains in the bones. He had felt ill for about six weeks.

His father died of heart disease. His mother died young. Patient had been married twice. Up till three years ago, he had been in the habit of taking too much whisky.

Fifteen years ago, he became troubled with piles. These bleed on an average about every two months. Three years ago, he had a slight attack of delirium tremens. He has been teetotal since.

Present Illness: Six weeks ago, patient began to feel weak and lost his appetite. He got breathless, on slight exertion and once or twice has felt pains in his long bones.

Patient is of spare build but fairly muscular. He has a brownish complexion.

Alimentary System: Lips and gums pale. A few teeth are carious. Tongue furred. Appetite and digestion fairly good. Bowels tend to be constipated. Liver not enlarged.

Haemopoietic System: The lymphatic glands and spleen are not enlarged.

The blood looks a fairly good colour and coagulates readily. Rouleaux are not well formed; blood plates and fibrin are not diminished.

There is very marked poikilocytosis and diversity in the size of the red cells. Megalocytes are present, but small sizes preponderate. There is no poly-

chromatophilia and no nucleated red cells or myelocytes were found. (Plate XIV).

Circulatory System: Patient suffers from dyspnoea on slight exertion. He has occasional palpitation and giddiness. There is no enlargement of the heart. The first sound is rather faint, but there are no murmurs. The pulse is 75 per minute and regular. Its volume is fair, its tension low. The arterial wall seems slightly thickened.

Integumentary System: There is occasionally slight swelling of the ankles at night and puffiness of the eyelids in the mornings. The urine is of amber colour, acid, with a sp.gr. of 1014 and presents no abnormal constituent.

The nervous system seems healthy.

TABLE XIX.

Date	Red Cells.	White Cells.	Hb%.	Colour Index.
June 2nd	3,300,000	5000	45	.6

TABLE XX.

Polymorpho-nuclear.	Lymphocytes.	Eosinophiles.
60	38	2%

Meanwhile, at least, this case must be regarded as one of secondary anaemia.

There is a definite history of chronic haemorrhage as a cause. The colour index is low and the

percentage of polymorphonuclear white cells is not diminished. The history of pain in the bones and the great poikilocytosis are, however, suggestive of pernicious anaemia and that possibility must be borne in mind as the features of that disease in its early stages are not well known.

The next two are well marked cases of pernicious anaemia, in which I have had the opportunity of examining the blood, but have not the notes of the clinical details.

CASE X.

A man over 50: The blood was pale and unusually fluid. It coagulated slowly. Fibrin was diminished. Rouleaux formation was slight. Plates were diminished. The red cells showed great variation, but their average size was markedly enlarged. Poikilocytosis was well-marked.

In stained films, degenerative changes in the red cells were marked. Megaloblasts were numerous. (Plate XV).

TABLE XXI.

Date.	Red Cells.	White Cells.	Hb. %	Colour Index.
June 3rd	1,112,000	6,250	30	1.3
" 8th	1,020,000	6,800	35	1.7
" 22nd	924,000	6,406	33	1.8

TABLE XXII.Per Cent.Per 1000 white cells.

Date	Polymorpho- nuclear.	Lympho- cytes.	Eosino- philes.	Myelo- cytes.	Megalo- blasts.	Normo- blasts.	Micro- blasts.
June 3rd	37	58	4	1	8	0	
" 8th	34	65	.2		2		1
" 22nd	35	63	1	.5	2	10	

CASE XI.

A woman over 60. The temperature was 103°F. when the blood was examined. It was very pale and the corpuscles seemed almost at once to form a precipitate in the plasma.

Coagulation was slow. The red cells showed an increase in their average size, poikilocytosis and marked polychromatophilia and fissuring. There were numerous megaloblasts. (Plate XVI.).

TABLE XXIII.

Date	Red Cells.	White Cells.	Hb. %	Colour Index.
July 10th	680,000	5,625	32	1.1

TABLE XXIV.Per Cent.Per 1000 white cells.

Date.	Polymorpho- nuclear.	Lympho- cytes.	Eosino- philes.	Baso- philes.	Myelo- cytes.	Megalo- blasts.	Normo- blasts.	Micro- blasts.
July 10th	78	21	.2	.2	.6	10	2	2

CASE XII.

A married woman, aged 48, residing in Edinburgh was seen on September 4th, 1900.

She complained of breathlessness, weakness, yellow colour of the skin and a slight cough.

History: Patient's father and mother are alive and have celebrated their golden wedding. She is one of a family of seven, all alive and healthy. Her home surroundings are comfortable. She was married at the age of sixteen. She has two children, both healthy. Fourteen years ago she had an abortion followed by severe haemorrhage.

Previous Illnesses: She had small-pox 29 years ago.

On several occasions she has had illnesses similar to her present one. The first was ten years ago. At that time she was six months in bed. The second was six years ago and the third only five months ago. During the last attack, she became very

yellow and was treated with arsenic. She rapidly improved and did not continue taking her medicine although advised to do so.

Present Illness. About a fortnight ago, patient began to feel weak and breathless and her skin became yellow. She began taking stout to dinner, but found that it made her sick.

Present Condition: Patient is well developed. The muscles are soft, but adipose tissue is plentiful. There is a slight, lemon-yellow tinge on the skin and conjunctivae.

The temperature has never been found above 98.6.

Alimentary System: The lips and gums are pale. The teeth are very bad. In the upper jaw there is only one carious canine; in the lower jaw there are seven black and carious stumps.

The tongue is moist and clean.

Appetite is only fair. Patient says she has been troubled for nearly eight years by a sense of nausea in the morning which does not disappear till after breakfast. The bowels act regularly. The abdomen appears healthy. No hepatic enlargement can be detected.

Haemopoietic: The spleen is not enlarged. There are no enlarged glands.

The blood looks pale and streaky. Fibrin is diminished and coagulation is slow.

The red cells do not form rouleaux. There is well marked poikilocytosis and great diversity in size. The average size is considerably increased. There is slight polychromatophilia. Nucleated red cells and myelocytes are present. Red cells number 1,400,000. Haemoglobin is 28%. (Plate XVIII).

Circulatory System: There is great dyspnoea on slight exertion. No palpitation or giddiness.

There is slight epigastric pulsation. The apex beat can be felt just outside the nipple line. The left border of the heart at the level of the 5th rib is nearly an inch outside the nipple line.

A long, soft, blowing, systolic murmur can be heard at the mitral and pulmonary areas. There is a bruit in the neck.

The pulse is 110, regular, of low tension. Its volume is small. The arterial wall does not seem thickened.

Respiratory System: Patient complains of an irritating cough but no morbid condition can be detected on physical examination.

Integumentary System: There is slight swelling of the ankles at night.

Genito-Urinary System: Urine pale, sp.gr. 1020, acid, contains no abnormal constituent. About a year ago menstruation stopped for a period of six months. Five months there was a return on one occasion. Patient has seen nothing since.

TABLE XXV.

Date	Red Cells.	White Cells.	Hb.%	Colour Index.
Sept.4th	1,400,000	5937	28	1

TABLE XXVI.

Date.	Polymorpho- Nuclear.	Mympho- cytes.	Eosino- philes.	Myelo- cytes.	Megalo- blasts.	Normo- blasts.
Sep.4th	48.5	48.5	2	1	19	8

This case is a fairly typical one. The only points that may now be noticed are the unusually long history (ten years, according to the patient's story), the number of relapses, and the onset of the first attack four years after a large uterine haemorrhage.

CASE XIII.

A labourer aged 33, single, was admitted to Ward 31, Royal Infirmary on October 7th 1900.

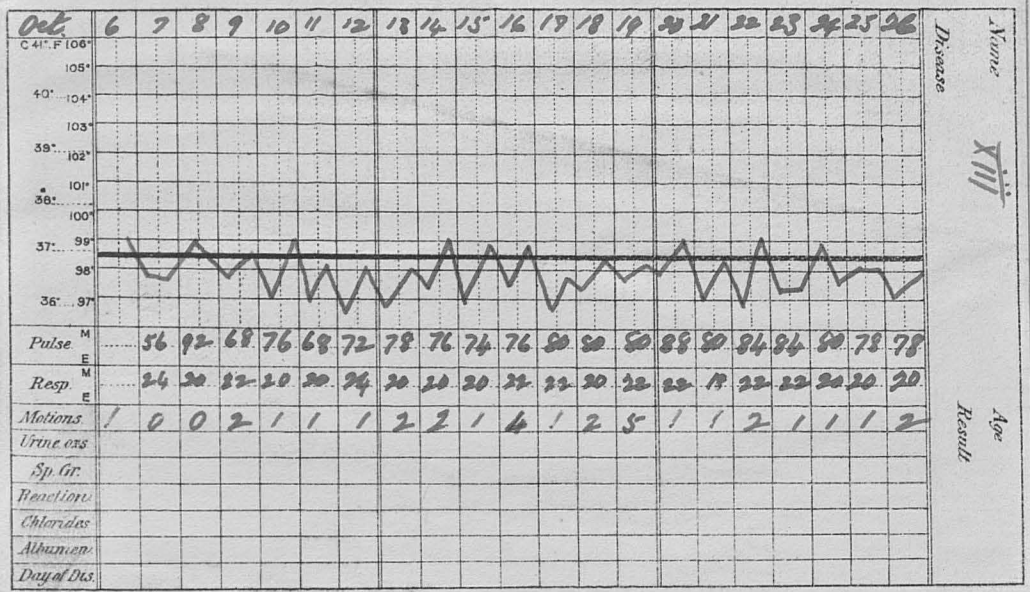
Complaint: "Weakness, shortness of breath and giddiness".

Duration: Two months.

Hisotry: Patient's family history is good. His home is fairly comfortable. He works for three hours before breakfast, which generally consists of ham or meat and tea. His mid-day meal is carried. At night, he has either fish, meat or porridge. He drinks on an average three pints of beer and one glass of whisky per diem. He smokes an ounce of black twist each week. At work he is exposed to all sorts of weather.

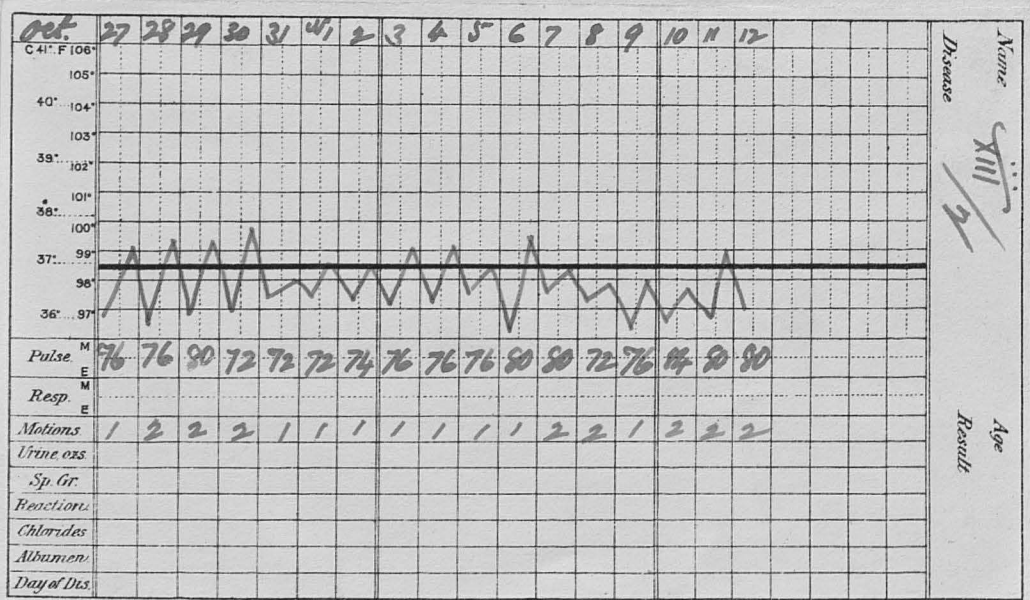
Previous Illnesses: Patient had scarlet fever in childhood. Fifteen years ago, while serving as a soldier in Natal, he contracted gonorrhoea. Three years later he had malaria. He came home nine years ago and says he has had recurrent attacks of malaria about every two years since. The last attack was about a year ago.

He states that he had an illness similar to his present one four years ago.



Name
Disease
XIII

Age
Result



Name
Disease
XIII
7/2

Age
Result

Present Illness: Patient was in his usual health and at work till two months ago. At that time a hammer fell on his head, while he was at work. As a result he had to keep his bed for a fortnight. When he got up he felt very weak and had very little appetite. He became breathless and giddy on even slight exertion. He therefore sought admission to hospital.

State on Admission: Height 5 ft. 8 in., Weight 12 st. 4 lbs. Development and muscularity good, but the muscles are flabby. There is obvious pallor and the skin has a very faint, lemon-yellow tinge.

Alimentary System: Lips and gums pale. Teeth bad. Several are missing and some are carious. The tongue is slightly furred. The mouth is dry, and patient complains of a bad taste in his mouth.

Appetite is poor. There has been occasional vomiting after food. Some flatulence. Bowels irregular. The abdomen looks healthy. The liver deep dulness begins at the 4th rib, superficial dulness at the 6th and the lower border is $\frac{1}{4}$ inch below the costal margin in the nipple line.

Haemopoietic System: The cervical glands are slightly enlarged. The spleen is not enlarged.

The blood looks pale and coagulates slowly.

Fibrin is diminished. Blood plates are fairly numerous. There is well-marked poikilocytosis but most of the corpuscles are normal in shape and size. Polychromatophilia is not marked. Several of the red cells have no central concavity. Red cells number 1,680,000. White cells 6,975 per cmm. Hb. 20%. Three normoblasts were seen in counting 1000 white cells. (Plate XXI).

Circulatory System: Patient complains of pain over the praecordia: dyspnoea, palpitation and giddiness on slight exertion. There is visible pulsation in the neck and suprasternal notch. The apex beat can be felt in the 5th interspace half an inch external to the nipple line. It is weak and diffuse. On percussion, the upper border in the parasternal line is at the 3rd rib.

The left border is $\frac{1}{2}$ inch external to the nipple line at the level of the 5th rib and the right border is $\frac{1}{2}$ inch to the right of the sternum at the 4th rib.

A somewhat rough, systolic murmur can be heard at the mitral area.

There is also a systolic murmur, softer in character, at the pulmonary area. The pulmonary second sound is accentuated. At the aortic area the second sound is loud and slapping. There is a bruit in the neck. The pulse is 88 per minute, slightly irregular, of small volume and loud tension. The arterial wall is slightly thickened.

Respiratory System: The reppirations are 20 per minute, costo-abdominal. There is a slight cough at times. There is no alteration of vocal fremitus and no percussion dulness. On auscultation, the sounds are vesicular. A few crepitations can be heard at the bases during respiration.

Integumentary System: The skin is moist and pale yellow in colour. There is no dropsy.

Urinary System: The urine is straw-coloured, acid in reaction. Its sp.gr. is 1008 and there is no abnormal constituent. The nervous system seems healthy.

Treatment and Progress. During patient's stay in hospital, he was treated at first with arsenic, subsequently with arsenic and iron.

His symptoms greatly improved, but improvement was not so marked in the blood condition. After a stay in hospital of just over five weeks, he went for three weeks to the Convalescent Home. At the end of that time, he felt stronger, but the number of red cells had somewhat diminished although many of the more serious qualitative changes were not so marked.

TABLE XXVII.

Date	Red Cells.	White Cells.	Hb. %	Colour Index.
Oct. 7th	1,680,000	6,875	20%	.59
" 9th	1,600,000	8,333	20%	.62
" 13th	1,540,000	5,000	18	.6
" 20th	1,472,000	2,500	22	.74
" 27th	2,060,400	2,500	27	.65
Nov. 3rd	1,807,200	4,375	28	.77
" 10th	1,920,000	5,000	20	.52
Dec. 4th	738,000	4,375	15	1.0

TABLE XXVIII.Per Cent.per 1000 white
cells.

Date.	Polymorpho- nuclear.	Lympho- cytes.	Eosino- philes.	Baso- philes.	Myelo- cytes.	Megalo- blasts.	Normo- blasts.
Oct. 7th	33	65.5	.6	.4	0	0	3
" 13th	32	66.5	1	.5	0	0	0
" 20th	36	62.6	1	0	.3	3	0
" 27th	40.5	57.5	2	.5	0	5	5
Nov. 3rd	35	64	.25	.25	.25	0	0
" 10th	50.6	48	1	.3	0	0	2
Dec. 4th	62.3	36.2	1.3	0	0	0	0

In this case we again find obscurity as regards etiology.

Attacks of malaria seem to have been the most important predisposing cause. It is curious that patient should attribute his illness to a blow on the head. Its only effect probably was to direct patient's attention to his symptoms.

The case may be regarded as a chronic one and resembles Case II in this respect as well as in some of its other features.

CASE XIV.

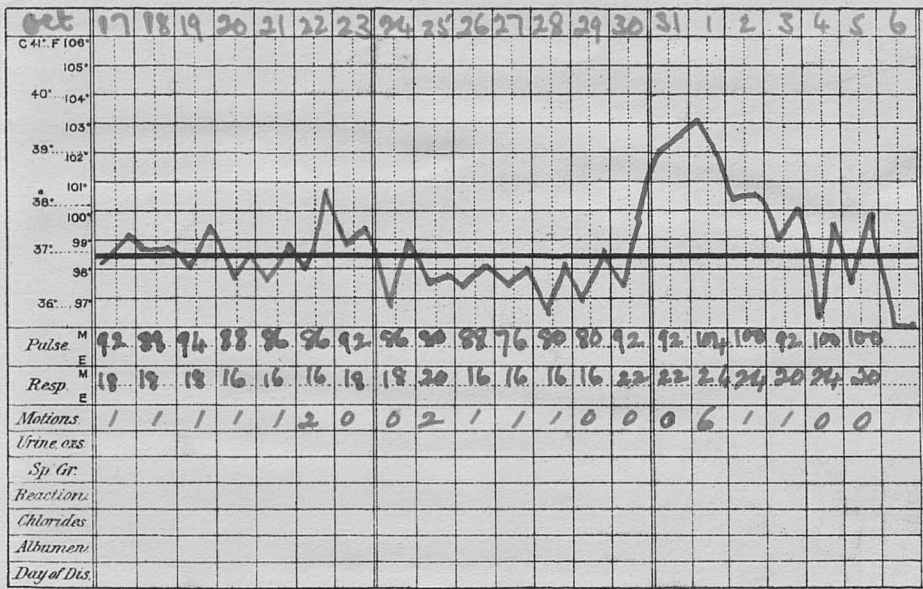
A brewery worker, aged 42 was admitted to Ward 31, Royal Infirmary, on October 16th 1900.

Complaint: "Weakness, breathlessness, swelling of the feet and cold hands."

Duration: 10 weeks.

History: Patient's family history is good. He is married and his home is comfortable. The only previous illness he can remember was an attack of bronchitis when he was 16.

Present Illness: Patient was at work six weeks ago. Ten weeks ago, he first noticed his face becoming yellow and he saw a doctor who prescribed blue pills. He continued at work for four weeks, but felt very



Name

XIV

Age

42

Result

weak. He says he could manage his work (washing barrels) when he got to it, but walking greatly fatigued him and he had eventually to give it up, because his "legs failed". He next began to find difficulty in keeping his hands warm and got breathless on slight exertion.

He went to the sea-side for a fortnight but did not improve. His feet began to swell at night.

On his return he sought admission to the Infirmary.

State on Admission: Patient is 5 ft. 4 in. He is well developed. His muscles are soft, but he has plenty of adipose tissue.

He is obviously anaemic and skin and conjunctivae show a slight yellow tinge. Temperature 99.4

The lips and gums are very pale. Several of the upper teeth are carious. In the lower jaw they are overcrowded, but in fairly good condition.

Appetite is poor. Bowels rather confined. Abdomen seems healthy. Liver is not enlarged.

Haemopoietic System: There are no enlarged glands. The spleen seems slightly enlarged, but is not palpable.

The blood looks streaky and coagulates slowly. Rouleaux formation is absent and fibrin very scanty.

There is marked diversity in the shape and size of the red cells. Many have no central concavity

and polychromatophilia and other degenerative changes are marked. Plates are diminished. Megaloblasts, microblasts and normoblasts are present. There are also a few myelocytes. (Plate 22).

Circulatory System: There is dyspnoea on slight exertion. Epigastric pulsation is visible. The heart does not seem enlarged.

There is a slight, systolic murmur at the mitral area. There is also a soft, systolic murmur at the pulmonary area. The aortic second sound is slapping in character and accentuated.

The pulse is 92 per minute, regular, of exceedingly low tension and small volume. The arterial wall is not thickened.

Respiratory System: There is a slight cough at times, accompanied by muco-purulent expectoration.

There is no alteration of vocal fremitus and no percussion dulness.

The inspiratory murmur at the bases is a little harsh and there are a few ronchi.

Integumentary System: The skin is slightly yellow. There is oedema of the ankles.

Urinary System: The urine is dark amber, and acid and its sp.gr. is 1010. Chemical examination reveals no abnormal constituent, but on spectroscopic examination there is a well-marked absorption band due to the presence of urobilin.

Nervous System: Patient is drowsy and sleeps a great deal through the day. There are numerous retinal haemorrhages in both eyes. The reflexes are unaltered. Patient is somewhat drowsy and his intelligence is not of a high order.

Treatment and Progress: For the first five days Liq. Arsenici Hydrochlorici and the Tincture of Perchloride of iron each in 5 minim doses were administered.

Patient showed no improvement and seemed so seriously ill that it was determined to try the effect of antistreptococcus serum.

On October 22nd therefore, the leucocytes were counted and an injection of 1 cc. of antistreptococcus serum was administered just before patient's dinner.

The leucocytes were again enumerated just before tea in order as far as possible to avoid the disturbing agency of digestive leucocytosis. After the serum was given a slight reaction occurred and the effects on the blood are shown in Table XXX.

TABLE XXIX.Reaction.

First Count) Serum given. (Time.	Temp.	Pulse.
	1.45	99	84
	2.45	98.8	90
	3.45	99.2	90
Second Count	4.45	100	100
	5.45	100	104
	6.45	100.2	112

The temperature remained about 100°F. till 10.45, then gradually fell and reached 99 at 2.45 a.m., and was down to 98.4 at 7.45.

TABLE XXX.

Total number of white cells before serum = 7812 per cmm.

Total " " " " after " = 10,312# "

Polymorpho- Lympho- Eosino- Myelo- Basino- Megalo- Normo- Micro-
nuclear. cytes. philes. cytes. philes. blasts. blasts. blasts.

Before	56.6	41.5	.5	1/	.5	12	8	7
After	69	30.2	.4	.4	0	15	18	1

Total Number of

	Polymorpho- nuclear.	Lympho- cytes per cmm.
Before Serum	4936	3501
After "	7198	3114

* Per Cent.

Per 1000 white cells.

No further medicinal treatment was adopted for a week as it was intended at the expiry of that time to repeat the injection of serum.

On October 29th, however, patient complained of a bad cold and cough which kept him from sleeping. Wheezing ronchi could be heard at both bases.

On October 31st, there was much muco-purulent expectoration and wheezing ronchi could be heard all over the chest.

Cultures were made from the sputum and two organisms were found. One was Frankel's pneumococcus and the other the bacillus pyocyaneus.

A mixture consisting of Potassium Iodide gr.5
 Aromatic Spirit of Ammonia M.5
 Tincture of Digitalis M.5
 and Water

was given every four hours.

Next day some patches of percussion dulness could be detected over both lungs posteriorly.

Although the temperature began to come down, patient did not improve. He continued to cough up a large quantity of frothy muco-purulent sputum. On November 4th, the iodide and ammonia were stopped and digitalis and arsenic were given. Patient died on November 6th.

TABLE XXXI.

Date	Red Cells	White Cells.	Hb. %	Colour Index.
Oct. 16th	800,000		20	1.2
" 19th	728,000	8,437	16	1.1
" 22nd		{ 7,812		
		{ 10,312		
" 26th	712,000	5,937	14	.98 7
Nov. 2nd	680,000	10,000	15	1.0
" 3rd	530,000	10,000	14	1.3
" 6th	524,960	9,375	14	1.3

TABLE XXXII.

Date.	Polymorpho- nuclear.	Lympho- cytes.	Eosino- philes.	Myelo- cytes.	Baso- philes.	Megalo- blasts.	Normo- blasts.	Micro- blasts.
Oct. 19th	57.4	41.6	.6	.4	0	32	16	2
" 22nd	{ 56.5	41.5	.5	1	.5	12	8	7
"	{ 69	30.2	.4	.4	0	15	18	1
" 26th	56.5	42	1.5	0	0	30	7	5
Nov. 2nd	68	30.8	0	1.2	0	24	10	2
" 3rd	68.2	31.4	.2	.2	0	50	16	2
" 6th	71.4	28	0	.6	0	33	16	6

On November 8th a post-mortem examination was conducted by Dr. R. A. Fleming.

The body was found to be anaemic and somewhat emaciated. The skin was of a deep yellow colour.

Lividity was slight. Rigidity was absent in the arms, marked in the legs. There were no adhesions in the left pleura. In the right there were a few scattered adhesions posteriorly and over the lower lobe of the lung anteriorly. The left pleura contained 8 ounces of slightly bile-stained fluid, the right five ounces. The pericardium contained an ounce of similar fluid.

Heart. Both ventricles were somewhat enlarged. The left was slightly and the right markedly flaccid. There was a milk spot near the apex of the left ventricle anteriorly.

The right ventricle was well covered with fat. There was a considerable amount of colourless and non-adherent clot in the pulmonary artery and aorta extending into the ventricles. There was a large amount of colourless non-adherent clot in the right auricle and appendix. The pulmonary artery showed slight fatty changes in the intima.

The aorta was fairly healthy. There were slight fatty changes near the cusps. The cusps are fairly healthy. The mitral and tricuspid valves were healthy. The heart muscle showed fatty degeneration and there was fatty infiltration of the wall of the right ventricle. The fat was of a bright canary yellow colour. The left lung showed recent pleurisy over

its whole surface, most marked over the lower lobe anteriorly.

The bronchial tubes were congested and contained much thick, yellow mucus. On section the lung showed marked oedema and on pressure pus exuded from the smaller tubes.

There was extensive lobular pneumonia over practically the whole of the left lower lobe.

The upper lobe showed well-marked oedema and near its root a few patches of catarrhal pneumonia. Near the anterior margin of the upper lobe were some well-marked areas of pneumonia and of collapse.

The right lung showed over its greater part thick, fibrinous, pleuritic exudation.

The lower lobe was congested and oedematous and there were a few patches of catarrhal pneumonia near the root. The upper and middle lobes were oedematous.

The spleen weighed 10 ounces, was slightly enlarged, its capsule was slightly thickened and there was a slight degree of acute congestion.

The liver weighed 3 lbs. 15 oz. It was dark brown in colour. It showed numerous haemorrhages in the central zone of the lobules as well as marked pigmentation in the same areas. There was fatty infiltration and a well marked free iron reaction.

The left kidney weighed nine ounces. It was pale. The capsule stripped easily. The deep cortex showed fatty changes.

The right kidney weighed six ounces. There were a few large, subcapsular cysts containing clear fluid. Otherwise it resembled the left kidney.

The bone marrow was bright red in colour and gelatinous-looking. The medullary cavity seemed slightly dilated.

On microscopic examination, numerous nucleated red cells were found.

The brain was slightly anaemic. The convolutions were slightly atrophied. There was some excess of cerebro-spinal fluid.

In the pons there were several minute haemorrhages dotted irregularly throughout its structure. There were a smaller number in the medulla and a few in the cerebellum. Throughout both hemispheres in the ependyma and lateral ventricles, there were a few scattered haemorrhages. The vessels at the base were healthy. The eyes showed numerous retinal haemorrhages.

This case was an unusually rapid one. There was no previous illness of any important bearing on the case and the patient was at work less than three months before he died.

The blood when first examined, indicated a serious prognosis. The only favourable point was the comparatively high percentage of polymorphonuclear leucocytes, but this may to a certain extent have been due to a slight leucocytosis accompanying chronic bronchitis.

The number of red cells slowly but steadily diminished.

A certain leucocytosis accompanied the pneumonia (for 10,000 cells must be considered a leucocytosis where the usual figure has been between 5,000 and 8,000), but it was so slight that for that reason alone one would have given a very grave prognosis apart from the underlying question of pernicious anaemia. In this case antistreptococcus serum seemed useless.

One injection of 1 cc. may not be considered quite a fair trial, but a definite reaction followed its use and there was a definite increase of leucocytes during the reaction, so that we must admit that the serum at least affected the blood, although that effect did not appear to lead to improvement.

SUMMARY OF CASES.

In the foregoing pages we have given the clinical records of nine cases of pernicious anaemia.

Though the number is small, a short summary of their main features may be of some value.

As regards sex, six were males and three females.

As regards age, the extremities were 11 and 73.

Of the other seven, three were under 40 - 21, 27 and 33. The remaining four were between forty and fifty.

As regards Etiology, there is no definite history of a causal agent in any of the cases.

Two of the patients, however, ascribed their illness to accidents and one to excessive cycling.

In three of the cases, there was no history of previous depressing conditions of any kind, while the others narrated a variety of antecedent conditions more or less connected with the onset of their illness.

Symptoms, etc. All the patients complained of weakness and in seven of the cases it was the first symptom noticed. It is interesting to note that in a recently published series of 110 cases, Cabot

(American Journal of the Medical Sciences, August 1900) found muscular weakness to be the earliest and the most frequent symptom.

Since Hunter (Lancet Jan. 27th, Feb. 3rd and 10th 1900) has put forward the view that dental caries may be an important factor in the causation of the disease, it is interesting to note the condition of the teeth.

In four cases they were good; in one much neglected, but not carious; in the remaining four they were both decayed and dirty.

Five of the cases at some time were troubled with sickness. Four had diarrhoea.

In four of the cases, the spleen was enlarged, but in none of the cases was the enlargement marked.

Cardiac murmurs could be heard in every case. The most constant murmur was a systolic mitral.

In five cases cough was complained of. In two there were physical signs of pulmonary conditions to account for it, but in the other three, the result of physical examination was entirely negative. In these three cases the cough was short and irritating, was not accompanied by expectoration and occasionally kept the patient from sleeping.

The specific gravity of the urine was rather low in all the cases. In four urobilin was present at times. In one of these it was found on every occasion

on which the urine was examined. Symptoms referable to the nervous system were present in five of the cases.

One of these was Case VII, an old man of 73 who had senile dementia.

The other four cases complained of tingling and numbness of the fingers and one in addition complained of difficulty of vision, though no change in the fundus and no error of refraction could be detected.

Tenderness over the long bones was found in three cases, but in no case was it elicited without a leading question.

As regards results, five cases died. Of the remaining four, only one so far recovered that the blood films would not be looked upon with suspicion. The other three passed from immediate observation with red cells numbering 1,460,400, 1,400,000 and 738,000, respectively.

In spite of the vast accumulation of literature regarding pernicious anaemia, very little is to be found regarding the bearing of the different symptoms on prognosis.

This is perhaps due to the belief that the result is practically always fatal, but since the duration varies so greatly it is of importance to have some indication of how any individual case is going.

Information on this point is more readily obtained from the blood examinations as we shall subsequently endeavour to show, but detailed examination of the blood is not always obtainable and in any case, it should be supplemented in every way possible.

The age of the patient does not appear to affect prognosis.

The incidence of such symptoms as sickness or diarrhoea, yellow colour of the skin or oedema does not appear to affect prognosis.

Patients may and frequently do improve after a feverish attack, but on the other hand they may get rapidly worse.

Haemorrhages seem to be of grave prognostic omen. Four of our series showed this symptom and all died.

James (International Clinics III, October 1897) mentions 24 cases of which 12 died. Haemorrhages occurred in five of the fatal cases and not in any of the others.

F. W. Mott (London Medical Record, December 20th 1899) reports retinal haemorrhages in all of five fatal cases.

Bramwell (Anaemia, etc., 1899 p.98) regards haemorrhages other than retinal haemorrhage as of grave prognostic omen, but does not consider the latter so serious.

Complications involving the respiratory system appear to be of grave significance.

We may also note that urobilin occurred in the urine in four of the five fatal cases and in none of the others.

THE BLOOD IN PERNICIOUS ANAEMIA.

The blood in pernicious anaemia presents a series of changes which may be tabulated as follows:-

I. Gross Changes in

1. Colour
2. Fluidity
3. Coagulation time
4. Specific gravity.

II. Changes seen in fresh specimens in

1. ~~The~~ The number of cells and plates,
2. Rouleaux formation
3. The amount of fibrin
4. The size of the red cells
5. The shape of the red cells
6. The amount of haemoglobin.

III. Changes seen in stained specimens in

1. The staining reactions of the red cells
2. The presence of nucleated red cells
3. The relative proportion of the white cells
4. The staining properties of the white cells
5. The presence of abnormal white cells.

(NOTE:-

The blood in anaemia due to intestinal parasites e.g., ankylostoma duodenale closely resembles that of Pernicious Anaemia. I have no personal experience of the condition, and leave it out of account in the following description.)

I. Gross Changes.

1. Changes in Colour.

When the anaemia is not marked, slight pallor may be the only noticeable feature.

In more marked cases the blood may be pale and yellowish and often looks streaky as if the corpuscles were not evenly distributed in the plasma. In extreme anaemia, precipitation of the corpuscles as the blood exudes seems actually to occur. Usually the precipitated corpuscles are red, but Coles ("The Diseases of the Blood", 1898) has described an appearance like coffee grounds. This I can confirm, but have only noted it in moribund cases and in these not constantly.

Observations on the sp.gr. of the plasma in these cases are required. Grawitz, however, states that the plasma in pernicious anaemia has a relatively larger amount of solids than in secondary anaemia in which this precipitation of the corpuscles is not seen.

2. Changes in the fluidity.

The blood in pernicious anaemia is more fluid than usual and has a lower surface tension. The increased fluidity is generally proportionate to the degree of anaemia. It is not generally marked when the corpuscles are over 2,500,000.

3. Coagulation Time. (Changes in)

Coagulation time is delayed and this change may persist after improvement in other respects.

4. Changes in Specific Gravity.

Sp.gr. is always diminished and the diminution is roughly proportionate to the diminution of haemoglobin.

II. Changes seen in fresh specimens.

1. Changes in the number of cells and plates.

Diminution in the number of red cells is generally marked. The average number in our eleven cases at the first examination was 1,049,090.

Cabot ("Clinical Examination of the Blood", 1900) gives the average number when the patient first came under observation as 1,200,000. In a more recent paper (American Journal of the Medical Sciences, August 1900) he gives the following figures.

500,000 - 1,000,000	in 27 cases	
1,000,000 - 1,500,000	in 45	"
1,500,000 - 2,000,000	in 34	"
Total cases under 2,000,000		- 106
2,000,000 - 2,500,000		
Total		<u><u>110</u></u> ⁴

The numbers may fall very low indeed. Our lowest count was in the case of a boy (Case V.) with haemorrhage from the gums, 295,000.

The lowest count on record is 143,000 (Quincke).

The number of the corpuscles alone is of importance from a diagnostic point of view. F. P. Henry

(American Journal of Medical Sciences, August 1900), writes as follows:-

"According to my experience there is no disease except pernicious anaemia in which the number of the red corpuscles is at any time reduced below 20 per cent. of the normal, i.e., below 1,000,000 per cmm."

With a reservation in favour of disease complicated by haemorrhage, I am disposed to agree entirely with this statement.

The number of red cells has a prognostic significance. The lowest count after which a remission has followed in our series is 840,000 per cmm. Another case improved and remained well for a year after the red cells had fallen to 872,000. James (International Clinics III, October 1897) states that diminution to 500,000 with 10 per cent. haemoglobin is only met with in fatal cases. Cabot (American Journal of the Medical Sciences, August 1900) on the other hand states that remissions may occur even after the red cells have fallen as low as a half million per cmm.

I know of no instance of remission when the red cells had fallen below that figure.

A few weeks' observation of the number of the red cells gives a pretty certain indication of how a given case will go on. Thus a case whose corpuscles are well under 1,000,000, say 800,000, rarely con-

tinues long at that stage. If the corpuscles have shown a distinct tendency to fall in about a fortnight, we may predict a fairly early termination.

On the other hand, if the tendency of the corpuscles is to rise, we generally find that our case will fall into one of two groups.

- (a) If the symptoms are well marked we may expect a fairly satisfactory remission.
- (b) If symptoms are not marked - dyspnoea, yellow colour and fever absent or slight, the case will probably run a somewhat chronic course. The corpuscles will reach to between one and two million and remain at that point, it may be, for years.

The number of white cells is always diminished. Leucocytosis in adults is always due to a complication. The average number in our cases at the first examination was 5,687. This figure is considerably higher than that usually stated. This diminution is of some diagnostic value as in many cases of secondary anaemia, there is a marked leucocytosis.

Opinion varies as regards the numbers of the blood plates. Stengel, V. Limbeck and Coles, are among those who hold that they are increased while Hayem, Muir and Gulland maintain that they are diminished. In only one of our cases, and that not quite typical, were they increased at the first examination. In all the others they were diminished. They may be numerous in the blood during remissions.

2. Changes in Rouleaux Formation.

Rouleaux formation is very slight in marked cases and the red corpuscles are seen in separate groups of four or five. This condition seems to depend, in part, at least, on two factors:-

- (a) The paucity of corpuscles in a given amount of plasma, and
- (b) ~~the~~ poikilocytosis and diversity of size.

The latter point can be demonstrated by mixing a drop of healthy blood with a drop of blood from a case of pernicious anaemia. The healthy corpuscles seem not only to form rouleaux with one another, but also with some of the normal cells from the anaemic blood, while the megalocytes and poikilocytes are left solitary or in small groups.

3. Changes in the amount of fibrin.

Fibrin is always diminished and this diminution persists even after the red cells have risen to above 3,000,000.

In one of our cases (IV.), it was increased, but the increase was probably due to complication by rheumatism.

4. Changes in the size of the red cells.

This is always a marked feature in pernicious anaemia, and in no other condition do we find such diversity or such extremes of size.

While all sizes may be present, the average is considerably increased and this is one of the charact-

eristic features of the disease. It is one of the last features to disappear during a remission.

5. Changes in the shape of the red cells, Poikilocytosis.

In the great majority of cases many of the red cells are deformed. Perhaps the commonest variety is the oval cell. Now and again, we meet with a case in which deformity is very slight. It has been stated that the amount of poikilocytosis depends on the degree rather than on the type of the anaemia. The statement is only partly true.

Occasionally we may find poikilocytosis less marked in a severe case of pernicious anaemia than in a mild one, but on the whole, poikilocytosis is generally much more marked in cases of pernicious anaemia than in cases of anaemia corresponding in degree but of another nature.

6. Changes in the amount of Haemoglobin.

The amount of haemoglobin is always reduced, but when the case is marked the reduction is not proportionate to the reduction in the number of corpuscles. Hunter (Practitioner, September 1889) considers this the only characteristic feature presented by the blood in pernicious anaemia.

Von Limbeck (Pathologie des Blutes, 1896) considers it a feature of all severe anaemias, but his view is not borne out by other observers.

The relatively high percentage of haemoglobin is due as Henry (American Journal of the Medical Sciences, August 1900) points out to three factors:-

1. The large size of the corpuscles.
2. The presence of microcytes which are often not seen when counting the red cells and in any case are not counted.
3. The highly coloured plasma during exacerbations.

Erben (Zeitschrift fur Klin. Med., Band XLl, page 226) states that he has found the iron in the blood lessened on the whole though the serum contains it, and the red cells show an excess. He suggests that in pernicious anaemia, either the haemoglobin is richer in iron than normal, or the red cells contain iron in some other form.

In all our cases, whose corpuscles were under one million the colour index was one or over one except in a fatal case (V.) with haemorrhages.

The colour index tends to be higher throughout in pernicious anaemia than in other anaemias, but the colour index is not above one nearly so constantly as the text books would indicate. As the case improves, the colour index tends to fall. A high colour index is generally a serious indication.

III. Changes seen in stained specimens.

8. Changes in the staining properties of the red cells.

In any marked case of pernicious anaemia, the majority of the red cells seem spherical and show no central concavity. Others, however, may be represented by mere rings.

Streaks and fissures as first noticed by Maragliano and Hayem are common.

The red cells take up basic dyes more readily than in health and this character is more marked in pernicious than in any other form of anaemia except malarial.

The change is sufficiently marked in even moderately severe cases to be easily distinguishable without the aid of a microscope.

If a film of healthy blood and a film of blood from a case of pernicious anaemia be made on different parts of the same cover slip, to ensure exactly the same technique in staining, the difference is striking.

When eosine and methylene blue are used the healthy film looks a bright red. The pernicious anaemia film is dark purple.

The change is not so well seen with the naked eye when Ehrlich's triple stain is used but with the

microscope, while the healthy red corpuscles appear bright orange, the red cells in pernicious anaemia appear dark brown or even greyish. The change is often exceedingly well marked in the megaloblasts.

Granular degeneration of the red cells is frequently seen. When methylene blue or haematoxylin is used, either with or without an acid counterstain, the affected cells show numerous, very fine, dark, blue points. (See Plate XXIII.).

The change is not one which will much help in the diagnosis of pernicious anaemia. Of its prognostic significance I am ignorant except that I have only seen it in the gravest conditions.

2. The presence of nucleated red cells.

Nucleated red cells occur in pernicious anaemia in three varieties, megaloblasts, normoblasts and microblasts. A few cases have been recorded - a recent one by Sir Dyce Duckworth (B.M.J., November 10th 1900) - in which they were not found, but their presence is of great diagnostic importance. Indeed, when megaloblasts are more numerous than normoblasts, the case is almost certainly pernicious anaemia.

We do not, however, invariably find megaloblasts the more numerous. Bramwell notes this in quoting Cabot's statement of the blood conditions.

(Anaemia and disease of the blood forming organs and ductless glands 1899, p.68). As a case improves, megaloblasts are apt to be outnumbered by the normoblasts and may disappear while normoblasts persist. It is exceedingly rare to find megaloblasts in any condition simulating pernicious anaemia and in no other condition are they numerous or as numerous as the normoblasts.

Microblasts are more rare, but have the same diagnostic and prognostic bearing as the megaloblasts and their numbers may be taken together to compare with the number of normoblasts.

The type of megaloblasts seems to give some information as regards prognosis.

Thus the megaloblast with a large nucleus with obvious chromatin seems to be of more serious import than the megaloblast which looks like a large normoblast or the type with a small dark nucleus.

Von Noorden first called attention to sudden outpourings of nucleated red cells which have been termed "blood crises". These have generally been found in the blood during recovery from haemorrhage. Curiously, the only two instances in which I have met with the phenomenon in pernicious anaemia have been in cases (V. and VII.) shortly before death.

In one case (V.) normoblasts were mostly found. In the other (VII.) all forms had greatly increased but the most numerous were megaloblasts of a normoblastic type.) See Plate XII).

3. Changes in the relative proportion of the white cells.

As we have already seen, the total leucocyte count is diminished and the usual condition is that the polymorphonuclear cells are diminished, consequently the relative number of lymphocytes is high.

The usual condition is that the percentage of lymphocytes is just under 50 or slightly higher. Usually as the case gets worse, the percentage of lymphocytes rises.

Ewing, however, has noted a rise of the percentage of polymorphonuclear cells as death approached although no complication could be discovered.

Observations on the percentage of the white cells week by week have led me to believe that a connection exists between the temperature and the percentage of the polymorphonuclear cells, although in other febrile conditions no such connection can be observed.

The temperature may rise owing to a complication and cause leucocytosis. Obviously in this case the percentage of the polymorphonuclear cells will be increased.

On the other hand the temperature may rise either as the result of a complication or as an intrinsic feature of the disease and either no increase or an actual diminution of the total number of white cells occur. Even in this case the percentage of polymorphonuclear cells will be found to be increased.

The conclusion we therefore arrive at is that a rise in temperature causes a diminution in the total number of lymphocytes, which may or may not be accompanied by a slight corresponding rise in the total number of polymorphonuclear cells.

In other words, a rise in temperature causes an increased percentage of polymorphonuclear cells at the expense of the lymphocytes.

The following tabular statement from cases where the data are sufficient and uncomplicated bears out this view.

Case.	Date.	Temp.	Total Leuco- cyte Count.	Percentage of Polymorphonuclear	Remarks.
I.	July 28th	100	2,500	67.26	872,000 red cells
	Aug. 3rd	99.5	4,375	53.46	1,182,000 " "
	" 31st	98.6	4,650	49.46	2,000,000 " "
II.	May 22nd	98.6	2,500	43.56	Lymphos. 1400 per cmm.
	after serum	103.6	3,125	59.40	1250 " "
	June 15th	103	2,812	64.34	
	July 30th	98.6	2,500	54.38	
IV.	Jan. 28th	101	6,250	75.24	840,000 red cells
	Feb. 11th	104	2,812	84.16	1,200,000 " "
	Apr. 28th	98.4	6,562	58.36	4,700,000 " "
XI.	July 1st	103	5,625	78.28	680,000 } " " moribund. }
XIV.	Oct. 22nd	99	7,812	56.41	Lymphos. 3501 per cmm.
	after serum	100	10,313	69.30	" 3114 " "
	Nov. 2nd	100.5	10,000	68.30	

It may be noted in this connection (see Tables I and II.) that in Case I with a falling temperature the percentage of polymorphonuclear cells steadily fell although the case was improving.

In Case XIV. with a rising temperature the percentage of polymorphonuclear cells steadily rose although the case was becoming worse.

We may further note that on each occasion on which a leucocytosis was induced by antistreptococcus serum, it was accompanied by an actual fall in the total number of lymphocytes. The rule that the percentage of lymphocytes rises as the case gets worse holds good only in the absence of fever.

Other factors, too, are of greater importance in determining prognosis than the relative numbers of the white cells, for the percentage of lymphocytes is apt to be persistently high in a group of chronic cases who do not improve but whose course is generally very protracted. In moribund cases, there may be a terminal lymphocytosis. This is almost peculiar to pernicious anaemia. (It occasionally occurs in Leucocythaemia). An extreme example was noted in Case V.

Though late in the day, it may be of value in clinching a diagnosis before the case is seen by the omniscient pathologist.

The percentage of eosinophiles is sometimes increased, more commonly diminished. I agree with Cabot's statement that no prognostic significance can be attached to their numbers.

4. Changes in the staining properties of the White Cells.

Nothing of clinical importance has yet been ascertained in connection with the arrangement of the nucleus and the granules.

The iodine reaction described by Goldberger and Weiss occurs occasionally in severe cases of pernicious anaemia, but as a clinical test of the condition it is of little value. A good account of the technique and significance of the reaction is given by Theodore Dunham in the "Annals of Surgery" for June 1900.

5. The presence of abnormal white cells.

A percentage of myelocytes may be found in pernicious anaemia. Cabot's average of 52 cases is 2%. When it is remembered that the total number of leucocytes is diminished their actual numbers must be very small. Their presence is in no way distinctive of pernicious anaemia. They are probably more numerous in the more serious cases.

VALUE OF THE BLOOD EXAMINATION

in

DIFFERENTIAL DIAGNOSIS.

In a well-marked case the blood presents features easily distinguishable from those of any other condition except the parasitic anaemia not likely to be met with in this country.*

The differences between the blood in pernicious anaemia and chlorosis need hardly be discussed outside a class-room.

Much has been written about the difficulty of diagnosing pernicious anaemia from gastric cancer. I cannot help thinking that this difficulty has been exaggerated and that if in doubtful cases a careful differential count of 1000 white cells were made and at the same time the numbers and character of the nucleated red cells noted less would be heard of it.

Cabot and Henry have done good service in dealing with this point in papers published simultaneously in the American Journal of the Medical Sciences for August 1900.

Cabot writes:- "It is true that in two cases of typical pernicious anaemia diagnosed as such by Ehrlich himself, a cancerous nodule the size of a walnut was found in the stomach post-mortem, but

* See note Page 97.

in such cases I see no sufficient reason for believing that the cancer was the cause of the anaemia. Cancerous growths are not usually accompanied by any considerable degree of anaemia until they have reached a considerable size. It seems to me more reasonable to suppose that in Ehrlich's cases the cancerous nodules occurred as a complication and not as the cause of the anaemia. Latent cancerous growths complicating other diseases have been repeatedly found and no one would consider a case of nephritis or phthisis due to cancer of the stomach because such a growth was found in the stomach post-mortem."

Again, Henry writes:- "I admit the possibility of a reduction of the number of the red corpuscles in gastric cancer to 40 or even to 30 per cent. of the normal, i.e., to figures characteristic of pernicious anaemia although I have never met with such a condition. Supposing such a case to exist I would regard it as one of pernicious anaemia complicated with gastric cancer or as one of gastric cancer complicated with pernicious anaemia, for the figures last mentioned are characteristic of pernicious anaemia and not of gastric cancer."

The following points as regards the blood condition serve to distinguish the two diseases.

1. The reduction of red cells is greater in pernicious anaemia than in cancer.
2. The reduction of haemoglobin relative to corpuscles is not so great in pernicious anaemia as in cancer.
3. The average size of the red cells is greater and polychromatophilia is marked in pernicious anaemia.
In cancer the cells are small and may show fissures, but not so marked polychromatophilia.
4. Megaloblasts are present generally in greater number than normoblasts in pernicious anaemia.
Their mere presence is of great importance as, although normoblasts are common, megaloblasts occur with very great rarity in cancer.
5. In the absence of complication, there is no leucocytosis and in the absence of fever there is ^{relative} lymphocytosis in pernicious anaemia. In cancer leucocytosis is the rule. Lymphocytosis does not occur.

There are times in the course of pernicious anaemia cases, when it is impossible to diagnose it with certainty from the blood examination alone. This is especially found in chronic cases and in cases during a remission whose red cells number between one and two or even three million and whose colour index is low. The blood cannot be distinguished from that of secondary anaemia though the real nature of the case may be suspected from the high percentage of lymphocytes. Clinically, the absence of any definite history of a cause and the

lack of improvement add to our suspicions till an attack of fever, dyspepsia or yellow discolouration brings us nearer certainty. Sooner or later, however, the blood examination will furnish data to warrant a definite diagnosis.

VALUE OF THE BLOOD EXAMINATION IN PROGNOSIS.

The prognostic value of the different features of the blood has already been discussed.

It is now generally recognised that the disease is fatal and six years is given as the limit of life after the case comes under observation. Taking into account the patient's history, however, many cases must last longer.

It is of importance for us to know what course a given case is likely to run.

Four groups of cases may be distinguished and in each group the blood characteristics have something in common.

I. Acute favourable cases.

This group is represented by Case IV.

1. The symptoms are marked.
2. Red cells are much diminished, but show a tendency to rise.
3. Megaloblasts are atypical and not numerous.
4. Normoblasts are numerous.
5. The colour index is high but tends to fall.
6. Polychromatophilia is not marked.
7. The percentage of polymorphonuclear cells is high.
8. Myelocytes are absent or scanty.

Course:-

A remission to a fairly normal condition which may be maintained for years.

II. Chronic Cases. This group is represented by Cases II., XII., and XIII.

1. Symptoms are not well-marked.
2. Red cells tend to remain about one or two millions.
3. Megaloblasts are absent or scanty.
4. Normoblasts are absent or scanty.
5. The colour index is generally below one.
6. Polychromatophilia is slight.
7. The percentage of lymphocytes is high.
8. Myelocytes are scanty.

Course:-

Apt to be chronic. Patients can work though they feel weak, and though febrile attacks, etc., may occur they have little bad effect. Improvement seldom occurs but the duration may be for several years.

III. Subacute Cases. This group is represented by Cases I., III., and X.

1. Symptoms are fairly well-marked.
2. Red cells about one million showing slow and irregular tendency to rise.
3. Megaloblasts are numerous.
4. Normoblasts are less numerous than megaloblasts.
5. The colour index is high.
6. Polychromatophilia is distinct.
7. The percentage of lymphocytes is high in the absence of fever.
8. Myelocytes are fairly numerous.

Course:-

Symptoms improve and the blood improves to a certain extent. The duration is about two years, but complications may cut it short.

IV. Acute Unfavourable Cases. This group represented by Cases VII., XI., and XIV. (Case V. also belongs to this group, but is complicated by excessive haemorrhage).

1. Symptoms are marked and there may be haemorrhages.
2. Red cells are about 1,000,000 and tend to remain or go lower.
3. Megaloblasts are typical and numerous.
4. Normoblasts are less numerous than megaloblasts.
5. The colour index is high.
6. Polychromatophilia is marked.
7. Percentage of lymphocytes is high in the absence of fever.
8. Myelocytes may be numerous.

Course:-

A fatal termination in a few months.

Treatment.

The treatment of pernicious anaemia is unsatisfactory. Many different measures have been tried and benefit has followed some of them. Unfortunately,

results are generally published long before it is known whether ^{the} improvement noted has been permanent or the case has merely undergone a remission.

Striking improvement has followed the indirect transfusion of blood as described by Brakenridge (Ed. M.J., Nov. 1892).

Affleck (B.M.J., 1892) and Gibson (E.M.J., Oct., 1892) have also published cases in which marked improvement followed.

Of this method of treatment Gulland (Encyclopaedia Med. I. p. 171) states that when a case is going down it does harm, when a case is improving and there is a demand for fluid, it does good.

Again, improvement has followed the use of red bone marrow either fresh or as a glycerine extract.

Cases are recorded by Dixon Mann, (Lancet March 10th, 1894.) ; the first successful case by Fraser, (B.M.J., June 1894.); Drummond (B.M.J., May 1895.), Duckworth, (B.M.J., Nov. 1900) and many others. Von Ziemsson recommended hypodermic injections of defibrinated blood - 25 cc. into each thigh.

For the different symptoms a host of different measures have been recommended.

Milk diet, artificially digested food, full diet and wine have been recommended.

Hydrochloric acid, Salicylate of Bismuth, Salol and Beta-Naphthol and the various nostrums of chemical houses have all their advocates. Recently Cabot (American Journal, August 1900) has suggested the use of purgatives in the hope of preventing the absorption of pernicious substances from the alimentary canal.

On the ground of Hunter's view of the pathology, antistreptococcus serum has recently been employed. So far as I know the only published result* is Elder's case (Lancet April 21st, 1900). Striking benefit certainly followed, but again we are left in doubt as to the permanency of the improvement. Eighteen injections, each of them consisting of about 10 cc. of serum were given and it is stated that the patient "had no constitutional symptoms after them."

In every instance of the administration of serum in our cases a definite reaction followed in about three hours with doses of only 1 cc. No good effect could be demonstrated. We must conclude that either Dr Elder's case or serum was different from those in our experience.

It will be noticed that there is no common rationale for any line of treatment. Even arsenic, perhaps the most widely used remedy, is given for a

* Since this was written Hunter has communicated a case to the Royal Medical Society of London (B.M.J. March 30th 1901.)

variety of reasons according to the belief of the physician. Bramwell first introduced it judging from its beneficial action in fatty heart that it should benefit a disease in which fatty changes are so marked.

Stephen Mackenzie (Lancet, Feb. 7th 1891) classes it as an anti-haemolytic.

Stockman and many others hold that it stimulates haemogenesis.

Hunter suggests that it acts locally on the mucous membrane of the stomach and intestines.

Copeman holds that it lessens the vulnerability of the corpuscles.

Whatever be its action, it is probably the most useful remedy in pernicious anaemia, we possess.

Whatever view of the pathology we adopt, our main efforts as regards treatment must be directed to stimulating haemogenesis. Even then, we are, as it were, merely flogging a tired horse, but we must try to keep the horse going.

I would venture to plead that our treatment should be based on our knowledge of the symptoms and the information to be gained by the blood examination rather than on our belief in any one of the various views of the pathology of the disease.

Thus when alimentary disturbances are present intestinal antiseptics should be given and if severe, the stomach may be washed out, but the mere theory of

intestinal absorption of toxins should not lead us to take these measures indiscriminately and in the absence of suggestive symptoms.

Where a case resists ordinary means and is rapidly getting worse any one of the measures referred to which seems most appropriate should be tried, but in ordinary cases we might sum up the treatment as follows:-

In bad cases rest in bed is essential. Care must be exercised with regard to the diet, but as soon as possible it should be as rich as the patient's digestion will allow. It will, at least, do no harm to see that the teeth are attended to.

If gastro-intestinal symptoms arise, milk diet and the administration of antiseptics such as Beta-Naphthol should be employed.

Haemogenesis should be stimulated.

- (a) When the colour index is high, say above .8 arsenic alone should be employed in very gradually increasing doses. Iron will probably do harm.
- (b) When the colour index is lower than .8 iron and arsenic should be given together. If the least sign of gastro-intestinal irritation should occur, these drugs should be stopped for a week unless the patient's condition is urgent from excessive bloodlessness.

Plate I.

Case I. Red Cells 872,000 per. Cmm.

Note. Changes in the red cells,
a large normoblast,
a Polymorphonuclear leucocyte
a large lymphocyte.

X 650

Eosine, Methylene Blue.

Plate II.

Case I.

Note. Changes in the red cells.
a megaloblast - rare form with two nuclei.

X 1100

Haematein, Eosine.

Plate III.

Case I. Red Cells 1000000 per. Cmm.

Note. The red cells are less irregular
and many show central concavity.
An eosinophile leucocyte. X 650.
Eosine, Methylene Blue

(The periphery of the field is not shown)



5. 4

H.

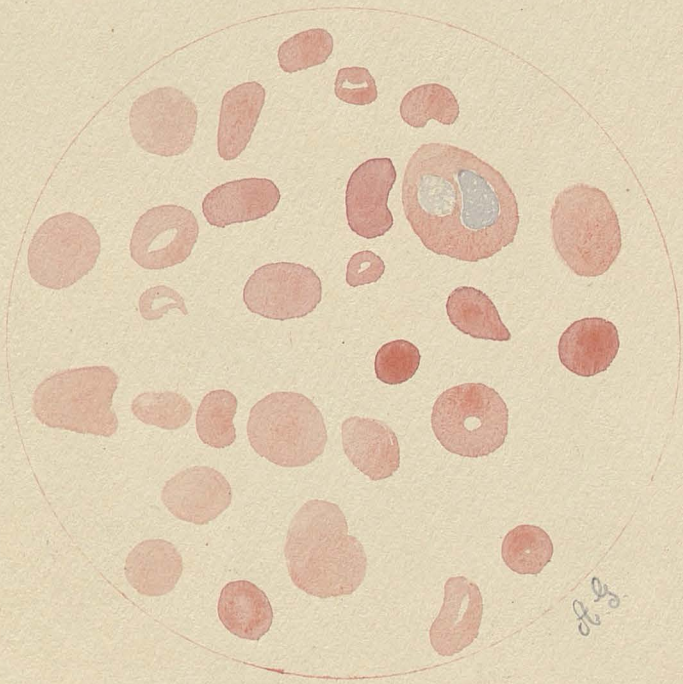
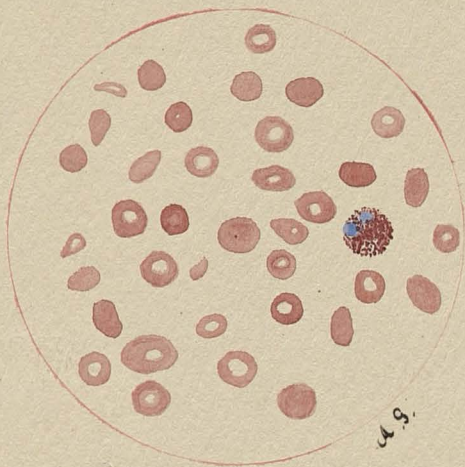


Fig.



82

III.

Plate IV.

Case ii. Red Cells 2,066,400 per. Cmm.

Note

A megablast showing marked polychromatophilia and fissures.

Ehrlich's triple stain. X about 1000.

Plate V

Case iii Red Cells 2,000,000 per. Cmm.

Note.

Toxiculocytosis etc.

A large and a small lymphocyte.

A polymorphonuclear leucocyte whose granules do not appear with this stain.

Haematein, Eosine

X 1100.



69.

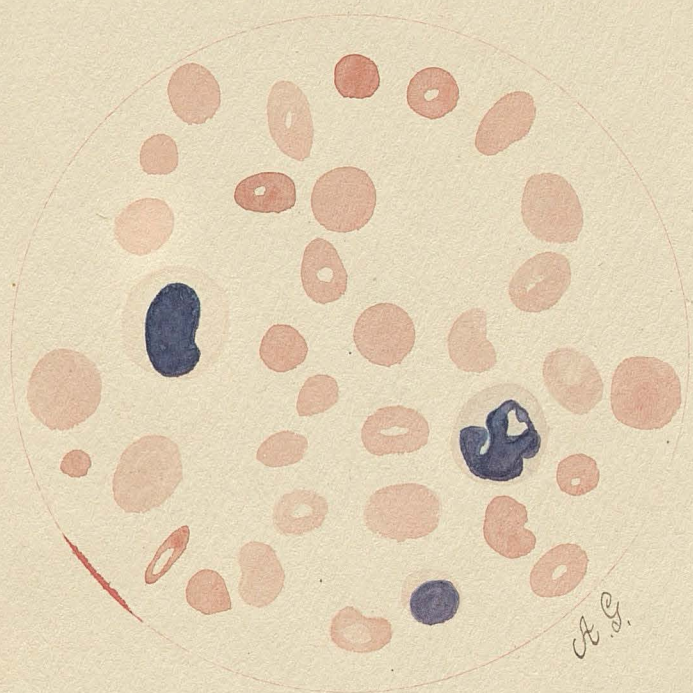


Fig. 2

Plate VI.

Case IV. Red Cells 840,000.

Note. Diversity in size but not so much
in the shape of the red cells.

A large fissured megaloblast.

A polymorphic leucocyte.

A lymphocyte.

Numerous plates.

Eosin, Methylene Blue X850

Plate VII

Case IV. Red Cells 1,200,000

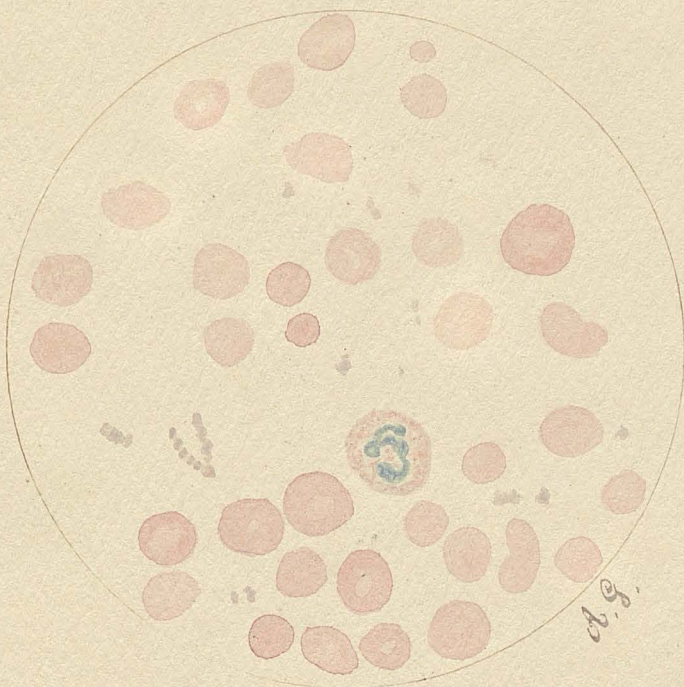
Note.

Changes in red cells less marked.

A polymorphic leucocyte

Numerous plates.





8.2

Plate VIII.

Case V Red Cells 485000 per Cmm.

Note. Polychromatophilia etc.
a megaloblast
a myelocyte
Two lymphocytes

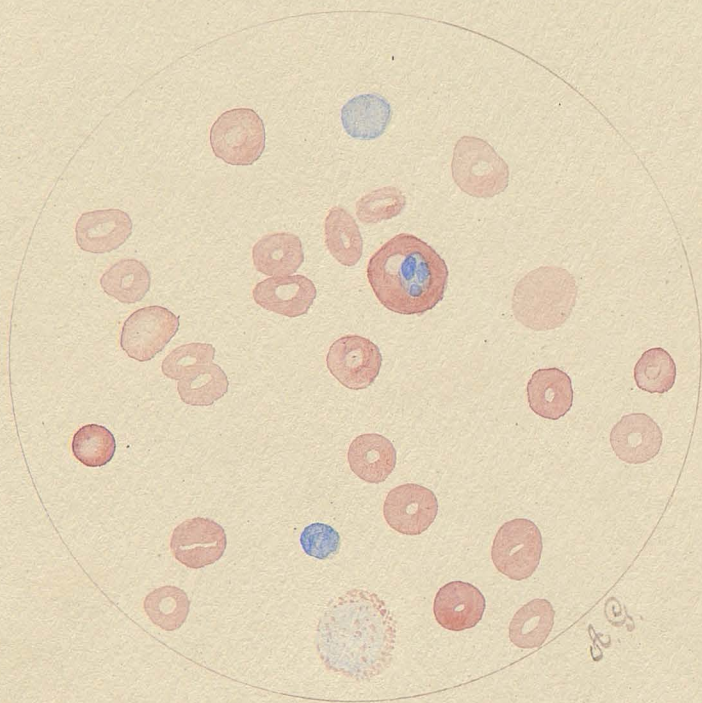
Plate IX.

Case VI. Red Cells 875000 per. Cmm.

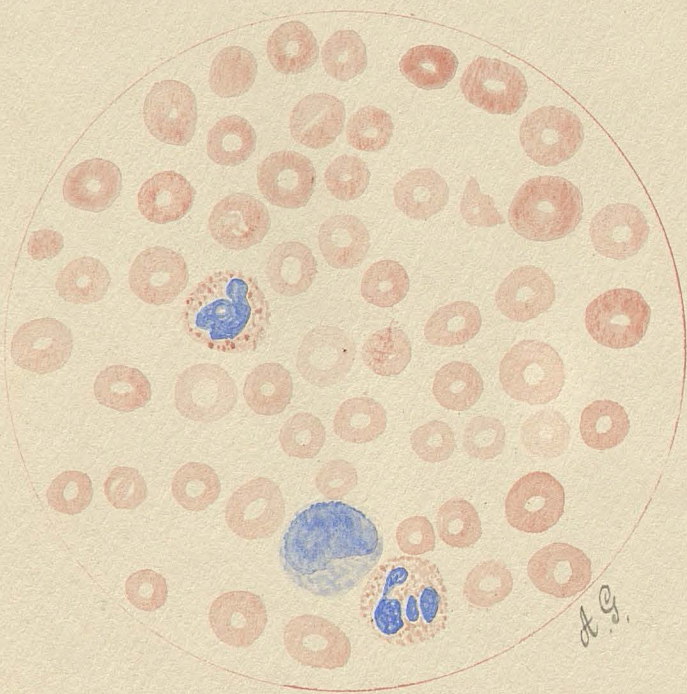
(Case of purpura)

Note. The comparative regularity of the
red cells.
Two polymorphonuclear leucocytes.
a large lymphocyte.

Eosine, Methylene Blue + 1100



8.20



A.G.

Plate X.

Case VII. Red Cells 1,274,400. per C.M.M.

Note The red cells are comparatively small
a megaloblast
Two polymorphonuclear leucocytes.

Eosin, Methylene Blue X 850

Plate XI.

Case VII A collection of cells from one film.

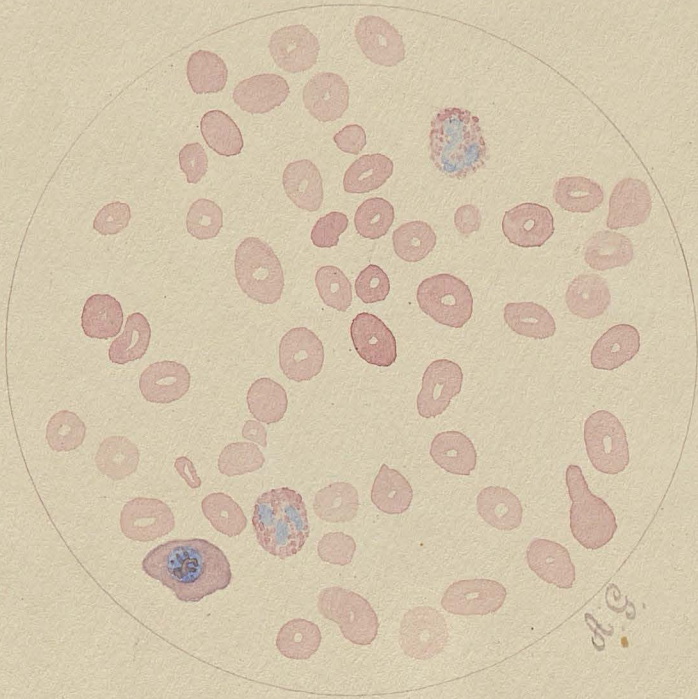
Note (a) a normoblast
(d) a megaloblast
(b) An intermediate form (megaloblast)
(c) A large lymphocyte
(e) Poikilocytes
(f) An eosinophile
(g) a small lymphocyte.

Eosin, Methylene Blue X 1100.

Plate XII.

Case VII.

Note - A collection of nucleated red cells from one film during a "blood crisis" on the day patient died.



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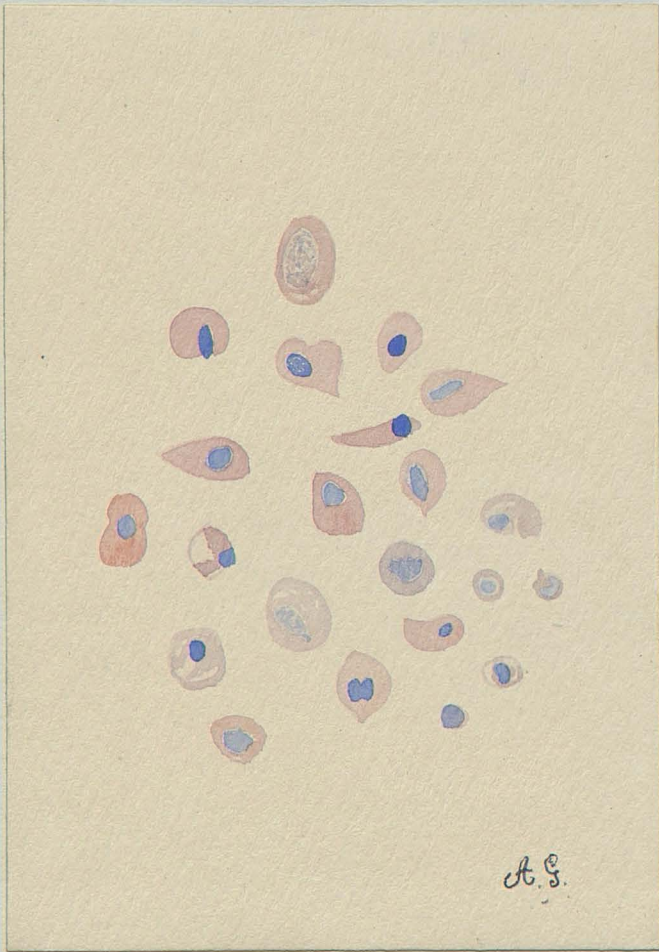


Plate XIII.

Case VIII. Red Cells 2000000

(Gastric Cancer after haematemesis.)

Note

The pallor of the red cells.

A myelocyte

A large lymphocyte

Two polymorphonuclear leucocytes.

(From another field)

A normoblast

Two lymphocytes.

Eosine, Methylene Blue X1100

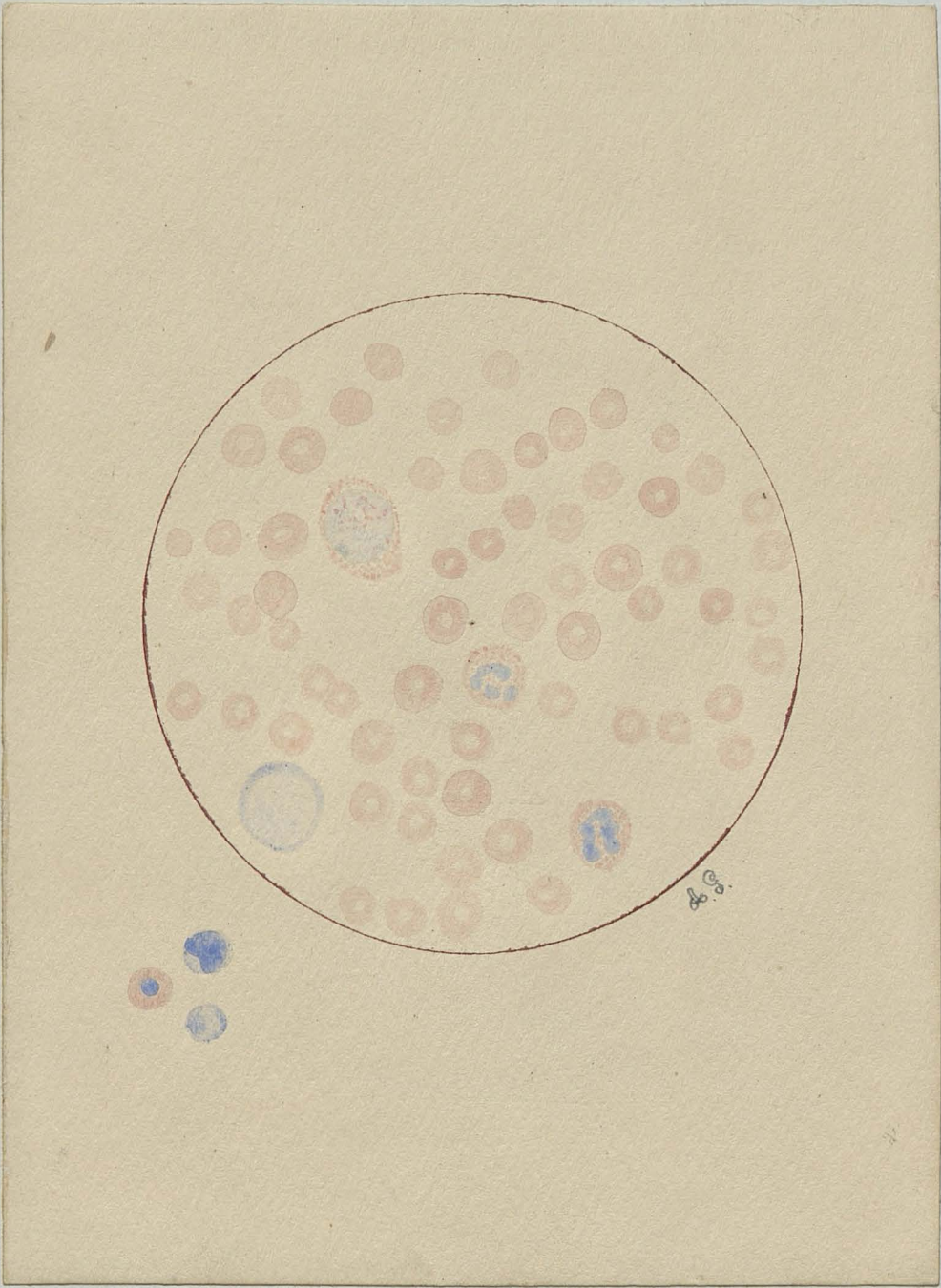
Plate XIV.

Case IX Red Cells 3,300,000.

(Secondary anaemia from haemorrhoids.)

Note - The extraordinary poikilocytosis.
A large lymphocyte.

Eosine, Methylene Blue X1100.



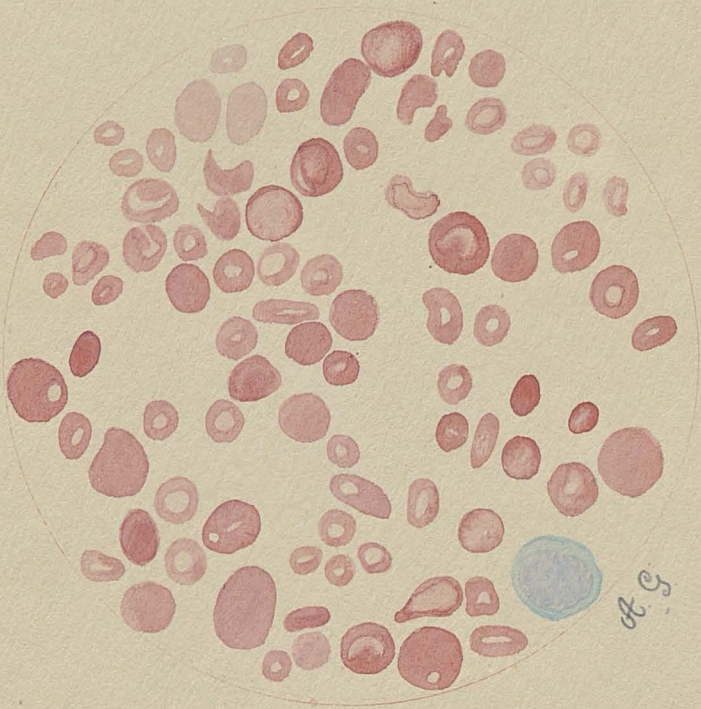


Plate XV.

Case X. Red Cells 1020000 per. Cmm.

Note

Degenerative changes in the red cells

Poikilocytosis etc.

a polymorphic leucocyte.

a myelocyte.

Eosine, Methylene Blue X 1100

Plate XVI.

Case XI. Red Cells 680000 per. Cmm.

Note

a megaloblast showing polychromatophilia

Two polymorphonuclear leucocytes.

E. M.B. X 1100.

Plate XVII

Case XII Red Cells 680000 per. Cmm.

Another film showing smaller
cells and a megaloblast.

E. M.B. X about 1000.

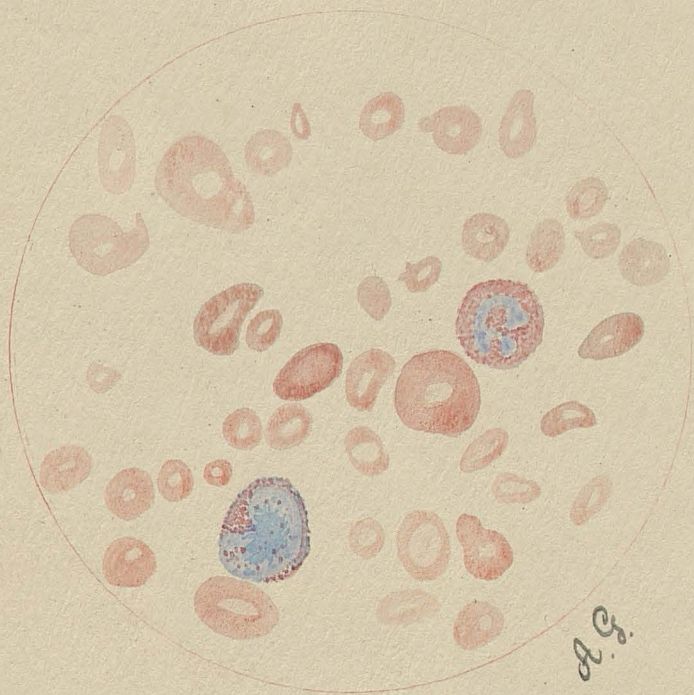
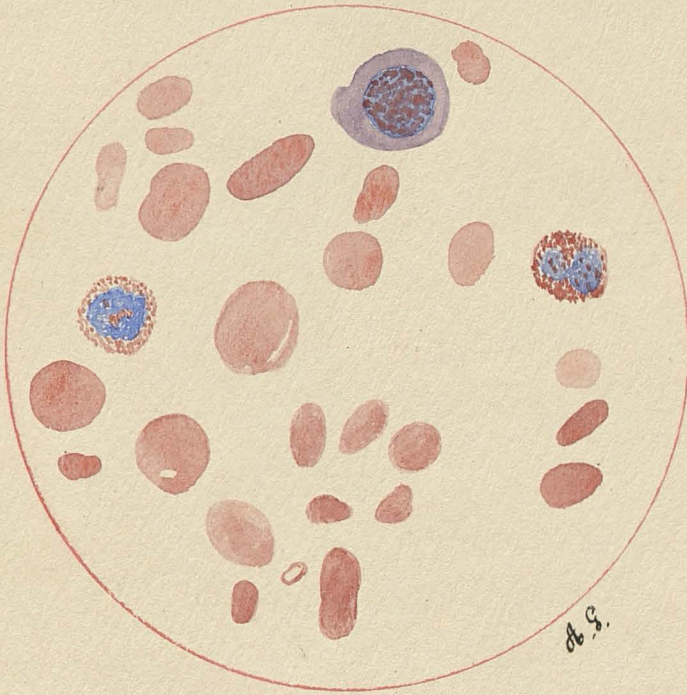
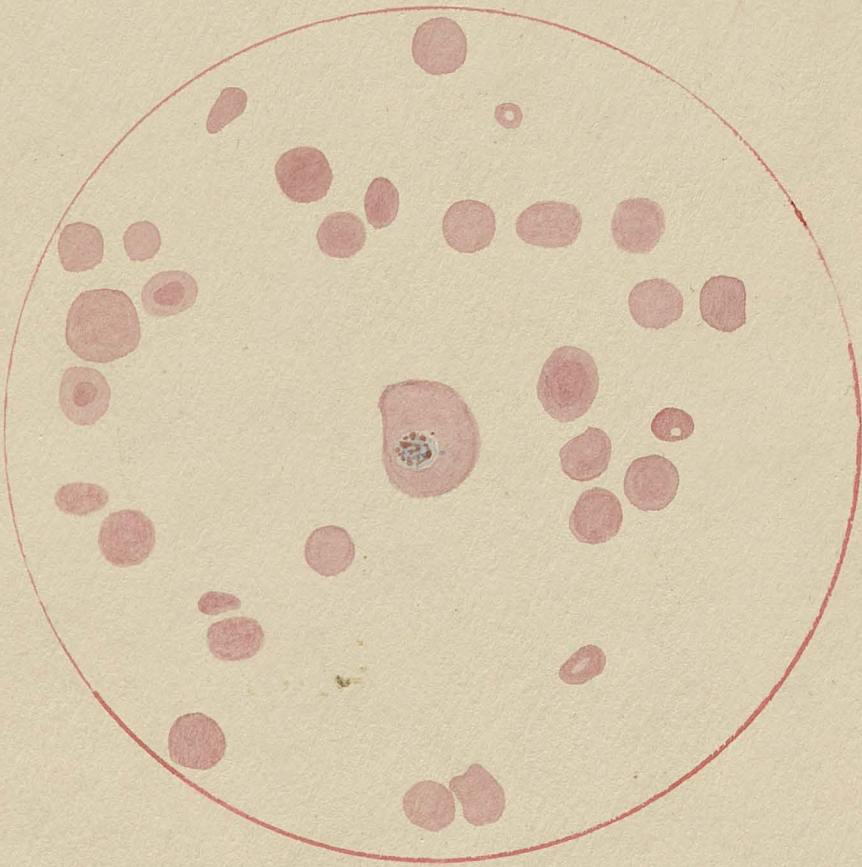


Fig.



89.



A. G.

Plate XVIII.

Case XII. Red Cells 1400000 per Cmm.

Note - Diversity in size and shape of the red cells.

A degenerated poikiloblast.

Eosin, Methylene Blue X1100.

Plate XIX

Case XII A Collection of Cells.

Note (a) A polymorphonuclear leucocyte.

(d) " " "

(b) A normoblast

(g) " "

(c) An eosinophile.

(e) An erythrocyte

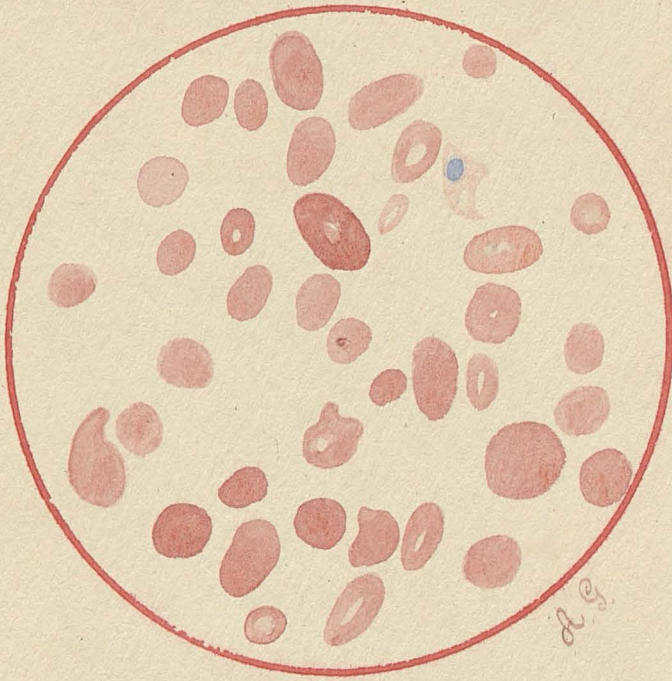
(f) A microcyte.

Ehrlich's triple stain X1100.

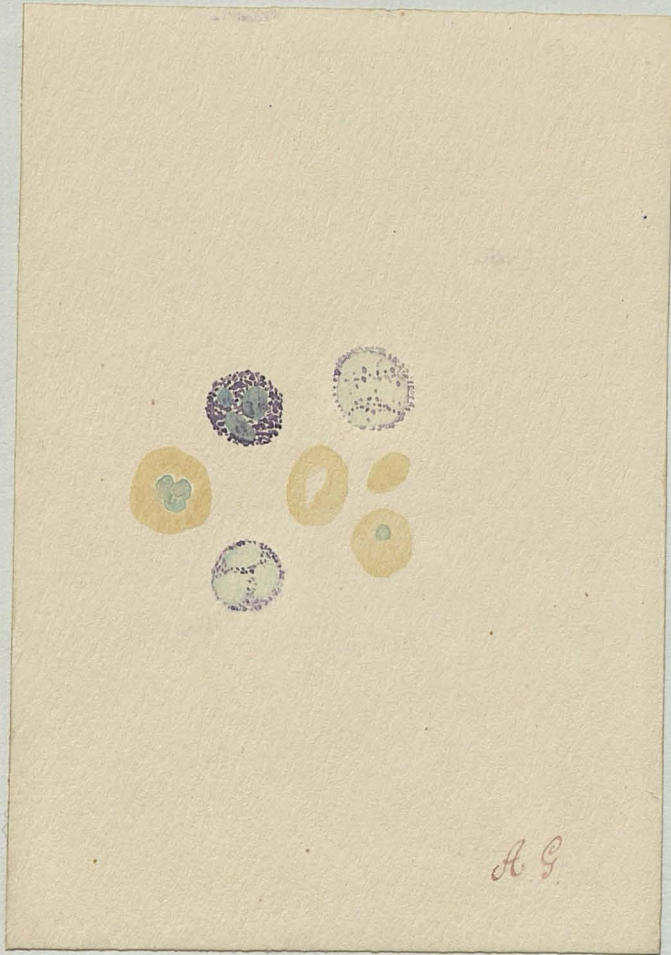
Plate XX.

Case XII A collection of poikilocytes and a lymphocyte from one film.

E. M.B. X1100

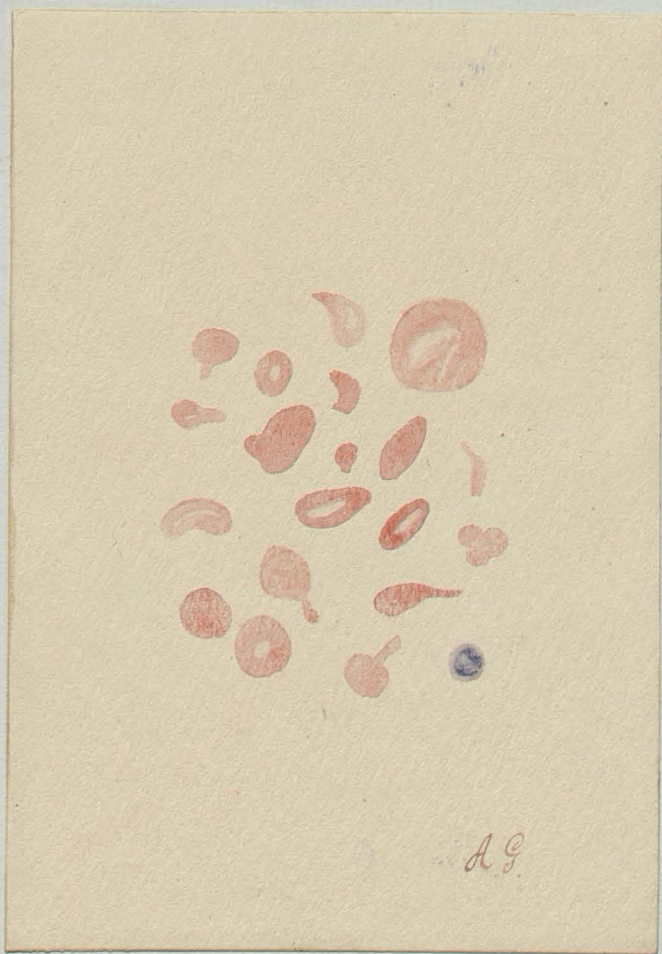


c
b
a



d
b
f
g

A. G.



A.G.

Plate XXI.

Case XIII. Red Cells 1680 000 per. Cmm.

Note Poikilocytosis.
a basophile leucocyte ("mast cell")
a lymphocyte.

Eosine Methylene Blue X1100

Plate XXII.

Case XIV. Red Cells 680 000 per. Cmm.

Note. Poikilocytosis.
Polychromatophilia
Two megaloblasts.

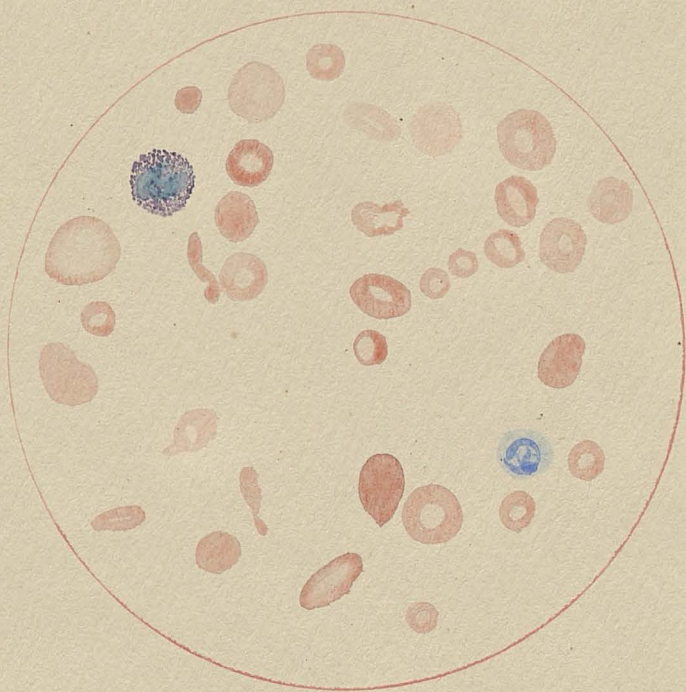
E. M.B. X1100

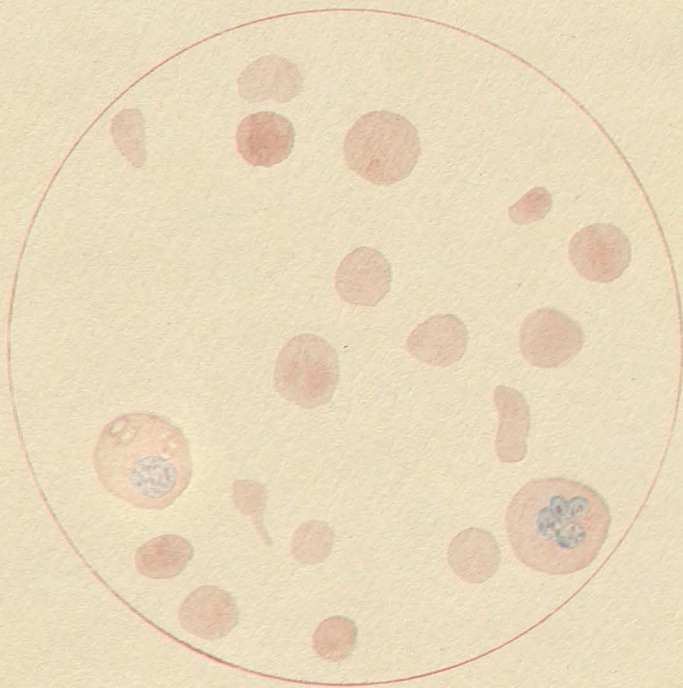
Plate XXIII.

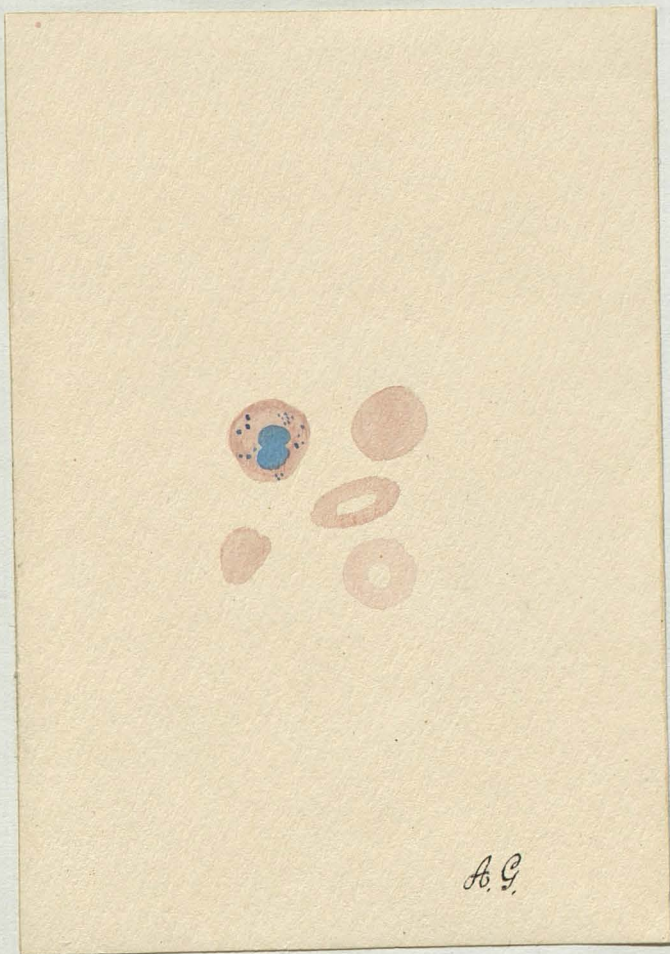
Case XIV.

Note A megaloblast showing
"granular degeneration."

E. M.B. X1100.







A. G.