University of Edinburgh

Thesis
presented for the Degree of M. D.
by
David Ferrier M. B. Ch. B.
27 Somervile Place
Dundee

Subject
Pernicious Anaemia
with Cases.
Table of Contents

Name and Definition ------- Pages 1 to 9

Nervous Anatomy ------- Pages 10 to 31

Etiology ------- Pages 32 to 41

Symptoms and Signs ------- Pages 42 to 85

Pathology ------- Page 86 to 98

Diagnosis ------- Pages 99 to 101

Prognosis ------- Pages 102 to 104

Treatment ------- Pages 105 to 112

Cases ------- Pages 114 to 169
Name and Definition

The name and definition of this condition of anaemia first prominently drawn attention to in 1855 by Addison and termed by him Micopathic Anaemia (On the constitutional and local effects of disease of the spleen in infancy—Collected works of the New Sydenham Society) will largely depend on the views held as to its nature and pathology. Whether or not they believe that there is a distinct pathological entity characterized by the symptoms and signs generally described how under Pernicious Anaemia, nearly all observers are agreed, that there is certain a clinical condition which without having an adequate ascertainable cause is characterized by so profound an anaemia, so progressive in its nature and so resistant to treatment, that it is justifiable to use a special term to denote it. There have many names been given to this clinical condition, some, based on the fact that no adequate cause has as yet been discovered and others based on apparent causes.
Names that have been applied:—

Idiopathic Anaemia, Essential Anaemia,
Hypogenic Anaemia, Progressive
Pernicious Anaemia, Gangliconic Anaemia
Anaematosis.

None of the above names can be
considered satisfactory. Owing to our
advance in the knowledge of general
pathology such terms as, idiopathic,
and essential are probably quite
inadmissible.

Our knowledge of the pathology of
the disease itself shows that
terms like hypogenic, gangliconic
and anaematosic are also inapplicable.

The term Pernicious Anaemia or
Progressive Pernicious Anaemia first used
by Réka in 1871 appears to me to be
that most suitable at the present time.
This does not commit one to any
pathological opinion and yet describes
the essential feature of the condition
well enough and considering our still
In sufficient knowledge of the pathology of the disease I do not think we are entitled to use any term connected therewith.

While most recognise the condition as a clinical entity, there are great differences of opinion as to whether it is a specific disease i.e. a morbid entity or merely an extreme form of anaemia which may be secondary to any of the ordinary causes of anaemia.

Thus in one of the earliest references to the disease, Dr. J. S. D'Orby (Proc. of the Medico Chir. Soc. 1824 p. 144) says, "If any train of symptoms may be allowed to constitute anaemia a generic disease the following may be considered an example of it in its most idiopathic form," and goes on to describe a case presenting all the features of the disease now known as Pernicious Anaemia.
Immermann (Deut. Archiv. f. Phis. Med. 1844 p. 209) holds it to be a disease sui
generic owing to its comparative rarity, the extreme anaemia present, the
absence of emaciation and practically
non-effect of treatment.

Immermann again in (Klemm's Handb. d. spez. path. u. therap. 1875) holds that
it is an independent disease and when
it occurs following chlorosis and
secondary anaemias, it is a complication.

Tézene (Roma Mensecles de Méd. 1877)
thinks the condition follows generally
on causes recognised as predisposing
to anaemia but is of opinion that
there is added some individual
debility in the blood forming power
and therefore to a certain extent it is
a specific disease.

On the other hand, Fichte (Dockmann's
Sammlung f. klin. Med. 1876, p. 100) considers it
a secondary anaemia the result of very
different processes and that it represents the highest type of the anaemic condition.

Biermer (Correspondence Schweiz. Arch. 1872) considers it a profound anaemia secondary to many causes such as gastrointestinal trouble, poor food, haemorrhage, pregnancy etc.

Muller (Die progressive perniöse Anämie 1872) also considers it a secondary anaemia.

Andrew (Medical Times and Gazette 1874, p. 471)

Bristowe (B.M.J. 1883: 1 : p. 1148)

Sydney Coupland (Kancer 1881: 1)

all consider the condition not a disease in itself but secondary to many causes which however we may or may not always be able to find.

Flechtiert (Die progressive perniöse Anämie 1893) takes the view that some cases are primary or essential, the disease beginning in the blood and that others are secondary to pregnancy, haemorrhage
and other exhausting conditions.

Henry (Anaemia 1887 and Medical News 0th 5th and 12th 1889) holds the view that Pernicious Anaemia is the final stage of several forms of symptomatic anaemia and chlorosis.

At the present time I think the consensus of opinion is in favour of it being a disease sui generis, one of the ablest supporters of this view being William Hunter Thomson, who has done so much to elucidate the pathology of the disease and whose work strongly supports the view that Pernicious Anaemia is a morbid entity.

If Pernicious Anaemia were merely an extreme degree of secondary anaemia, i.e. Anaemia due to such causes as cancer, parasites, haemorrhage etc. it would be very frequently met with and yet how seldom.
speaking do we find the changes clinical and post-mortem in secondary anaemia which are so characteristic of pernicious anaemia.

In a majority of the cases no adequate cause is present and no definite predisposing cause. In only one of my 9 cases, namely case 4, I noted the condition be called secondary where there was the history of an abortion followed by haemorrhage, immediately preceding the disease and a history of gastric ulcer with haematemesis 16 years before.

Cobbt (Ames Jour. Med. Sc. 1896 vol. 120) in an analysis of 110 cases states that in only 4 did the condition begin immediately after parturition or during the previous pregnancy. In all the others no cause was found.

In 20 cases reported by Billings (Ames Jour. Med. Sc. 1900) no definite cause or predisposing cause was found except in two where there were alimentary
symptoms for a year or two, one of those having diarrhoea for two years and the other exophthalmic goitre for several years.

In these cases where the signs of Pernicious Anaemia are present and in which there is apparently a definite cause as cancer or in which the signs have followed a secondary anaemia as from haemorrhage, I think we are forced to the conclusion that the presence of this apparent cause and its secondary anaemic condition is merely a coincidence. At least its action is probably only a predisposing cause and not the specific disease. Pernicious Anaemia has been acquired in addition.
Definition

In formulating a definition I consider it is desirable to, at present omit any reference to it to the pathology of the disease since this still remains so uncertain.

Therefore I do not think we are justified in going further than to say that Pneumococcal Anaemia is an extreme and increasing anaemia without loss of flesh, not secondary to any, so yet discoverable adequate cause. Characterised especially by marked diminution in the number and changes in the form of the red blood corpuscles, with a similar but generally less marked diminution in the Haemoglobin, and nearly always terminating in death.
Morbid Anatomy

In many of the reports of post-mortem examinations in cases of Pernicious Anaemia, changes are noted, such as atrophy of glands in the alimentary tract, degeneration in the intestinal plexuses of nerves and abdominal ganglia, which seem to occur very rarely and it is difficult to say whether these changes have had any direct connection with the disease either as cause or consequence. By some observers several of these changes have been looked upon as causes of the disease.

Opposed to this, however, as Hunter has shown (Hanset 1881 vol. ii) are the facts:—

1. Similar anatomical changes sometimes more marked are constantly to be met with in cases presenting none of the features of Pernicious Anaemia.

2. Cases of Pernicious Anaemia are constantly met with in which no such gross anatomical changes are to be found.
General Facts

The body is rarely emaciated and I think we may say never emaciated if associated diseases are excluded. Skin is as a rule lemon tinted.

The subcutaneous fat is well preserved and is usually of a deep yellow colour. The skin may show haemorrhages.

The blood serum may have a yellowish tinge from admixture with haemoglobin and even it has been reported in some cases stain the hands of the pathologist.

Frequently there is fluid in the peritoneal cavity and other serous cavities.

Total degeneration is one of the most constant and most marked features of the disease. It is usually well marked in the heart, liver and small vessels all over the body and in the latter is probably the cause of the numerous subcutaneous haemorrhages which are so common in all the serous membranes.
Heart is usually large as a result of dilatation and flabbly. Its muscular substance is pale yellow in colour and shows marked fatty degeneration. In fact in no other condition does fatty degeneration of the organ seem to be so constant and so marked. However it cannot be considered as an absolutely characteristic lesion since it occurs in other diseases although perhaps not to so marked a degree and again, does not seem to be always present even in Pernicious Anaemia. Thus Forel (Sciences 1881 vol. 1 p. 689) in an analysis of 16 cases found that in 6 cases the heart was stated to be healthy.

Lungs. As a rule show nothing special. Engorgement at the bases is often present probably from the weakened state of the circulation.

Stomach. Usually shows marked pallor of the surface of the mucous membrane. Occasionally atrophy of the glands and thickening of the submucosa is found but this these are important lesions in
neglected by the fact that they have rarely been reported and may be merely associated lesions or in some cases possibly the result of the extreme anaemia or long-continued cachexia which some of these cases have shown.

Herwick (Transact 1891 Vol II pages 39, 77) describes cases of apparently Pernicious Anaemia - no blood examination is given - in which atrophy of the gastric mucous membrane was found post-mortem and where the Pernicious Anaemia had seemingly followed on this. His symptoms of the atrophy had long preceded the development of the Pernicious Anaemia. From this he advances the view that atrophy of the gastric glands may be the primary lesion.

Babazon (13, M. J. 1878 Vol II p. 134)

Henry and Ader (Med. Jour. of Med Sci. 1886 vol II p. 498) also describe cases of Pernicious Anaemia in which atrophy of the gastric mucous membrane was found and in which the P.A. followed the symptoms of this condition.

Stengel (Hansp. Gazelle 1894 p. 378) also describes
a case where the patient developed Pernicious Anaemia after suffering for 15 years from gastric trouble and at the autopsy carried by the stomach was found with almost complete destruction of the gastric glands. Against this view are the facts:
1. No emaciation occurs in most cases of Pernicious Anaemia as one would expect if they were due to the above lesion.
2. Many cases of undoubted Pernicious Anaemia show no such atrophy.
3. Atrophy occurs in other conditions, as cancer of the stomach or of other parts of the body without Pernicious Anaemia being present.

I see no reason therefore why we should not adopt this view — in fact we are almost forced to do so — that in these cases of Pernicious Anaemia in which atrophy of the gastric mucous membrane is found it is an independent condition or at most a predisposing cause or a consequence of the disease P.A. itself. The same may be said of cases reported as due to Sarcoma and Carcinosarcoma of the
Liver

This organ is usually somewhat enlarged and shows fatty degeneration. It may however be normal in size and colour (Principles of Medicine 1875 p. 228) states that it was not enlarged in most of his autopsies although usually fatty.

The important feature connected with the liver however is the large excess of iron pigment which it contains in practically every case, and since Flinders first drew attention to this fact much importance has always been attached to it and a great deal of work done in connection with it.

The presence of the Fe pigment is readily shown both to the naked eye and microscopically by dipping a section of the liver in a solution of Potassium Ferrocyanide and then in a solution of Hydrochloric Acid when a deep blue colour is developed owing to the chemical reaction which takes place.

Ammonium Sulphide gives a brown to black
Colour depending on the amount of Fe present.

Peloppius (Practitioner 1898 vol. 45) says that Fe pigment is found constantly present in the liver cells and also in some of the endothelial cells of the hilobular capillaries and giving the usual reactions. He advances what he calls the Ferrogenic Function of the liver. By this he means:

A. Separation of Fe from effete iron-containing pigment
B. Storage of the Fe in the form of a more compound

This Fe, he says, may be particular in precipitated or it may be diffused throughout the cell in a state of solution. By special tests this pigment can be made to react and he got the most intense reaction eight to twelve hours after meals. Minimum reaction immediately after meals. He finds that after the destruction of red blood corpuscles in various parts of the body a stable albumino ferrogenic compound is formed which does not give the reaction of free iron. This comparatively stable compound is decomposed by the liver cells and Fe is then shown by some tests, not by the ordinary tests. This precipitated and
insoluble albuminous ferruginous compound accumulates in the liver while the elaborated bile is excreted, and is redissolved and passed back into the vessels when the secretion of bile has stopped.

William Hunter, who has devoted much time to this part of the subject was of opinion that he is rarely if ever to be detected in the liver in heaeth. Hunter was the first to show that the pigment found in the livers in Pernicious Anaemia, and which has been called Haemosiderin, was in the form of fine granules and had a characteristic distribution being chiefly in the hepatic cells of the outer and middle thirds of the hepatic tubules. Hunter has found that in no other disease is there such an excess of Fe deposited in the liver and with this distribution, and he considers this the most characteristic feature of the disease post-mortem. He also considers the importance of the fact that the percentage of Fe in the liver is always much greater than that found in the spleen, this being
a feature distinguishing Pernicious Anæmia from other diseases when there is found a deposit of Fe in the tissues for in such the pigment in the spleen is always in excess that found in the liver.

He gives (Honecker 1883 vol ii p 610) of an average percentage of Fe found by various observers, in the liver as against 0.078 and 0.12 in other diseases.

Most workers support the observations of Jundke and Hunker as regards this excess of Fe in the liver and its peculiar distribution and also the difference in the percentage of Fe contained respectively in the liver and spleen.

Dels (Principles of Medicine 1875 p 728) says that A. J. Scott examined the liver in 45 autopsies without finding except in Pernicious Anæmia the special distribution of the pigment.


1. In 17 cases including acute and chronic diseases, as Pneumonia, Scarlet Fever, Carcinoma,
no fe reaction was got

2. In 24 cases, including especially all forms
of wasting disease no reaction was obtained
in the liver and only slight in the
spleen and bone marrow.

3. In 33 cases, including 4 of granular
kidney; 4 in which the liver showed changes
of the nature of congestion; 3 of chronic lung
disease; 12 of interstitial cataract in
children and the remainder partly tubercular,
partly disease of the blood as purpura,
Pernicious Anaemia etc. Some reaction was
found in the liver, spleen and bone marrow.
In most the reaction was very slight. In
Pernicious Anaemia the reaction was very
marked especially in the liver.

Russell (13. M. 9. 1889 died Jan. 12) tested 44 cases,
taken without selection from the post-mortem room,
for the fe reaction with 9% 14% 11% 10%.
He found, in 11 a marked reaction
in 14 a slight reaction
in 20 no reaction.

The 4 giving marked reaction included:
1. Turbicci kidney with hypertrophied heart.
2. Ovarian Jaundice with Carcinomatous Kidney and Fatty Heart.
3. Carcinoma of Liver, Tumors and Infections with Carcinomatous Kidneys.
4. Malignant Obstruction of the Cardiac End of the Heart.
5. Malignant Thickening of the Stomach and Large Intestine with Acute Peritonitis.

6. Jaundice due to Cancer of the Head of the Pancreas and also Cancer of the Liver.
7. Chronic Hepatic Nephrosis Hepatitis.

6 of the spleens from the above cases gave a marked reaction.
4 of the spleens of the 20 in which there was no liver reaction gave a marked reaction.

J. Verree Poston (Jour. of Path. and Bact. 1898 p. 376.)

Has shown that there is a deposit of Fe pigment in the cells and capillaries of the liver in malaria to the extent of in one case 1.208% and in the other 4.4%. In the spleens there was also an excess of pigment to the extent of 1.135% and 1.325%. Although therefore the percentage of Fe in malaria may be high, the distinguishing feature between the disease and Pernicious Anemia is that in malaria the spleen contains a higher percentage than the liver, while in Pernicious
Anaemia the opposite seems always to be the case.

In the above two cases of malaria the distribution of the Fe was very similar to that in Peronospora Anaemia being contained in the Hepatic cells and capillaries of the liver. But not so distinctly localized to the outer \( \frac{2}{3} \) of the Lobule and was most abundant in the capillaries of the Liver.

In purpura haemorrhagica Fe pigment has been found in excess in the Liver but here it is scattered in large masses irregularly throughout the Liver and not in the cells of the outer \( \frac{2}{3} \) of the Lobule.

In blood extravasated into the Liver as in cirrhosis the pigment is found in irregular masses in the parenchyma tissue, i.e. in the site of the extravasation (Hunger, Lancet 1888 Vol. ii).

In large extravasations of blood in the body and in which the blood is absorbed there may be found excess of Fe pigment in the Liver, but there again the spleen contains no much larger a percentage than the Liver. This condition is also differentiated. Besides, the

Thus new excess of Fe demonstrable by the ordinary tests can hardly be looked upon as absolutely characteristic of the disease, since it occurs in so many other diseases. The distribution of the pigment of the pigment seems certain, the characteristic but even this may be closely approached as in malaria.

1. However the percentage weight of Fe is estimated in the liver and spleen, decided differences are brought out between Pernicious Anaemia and other diseases and so far seem to be almost sufficient to differentiate Pernicious Anaemia from other diseases.

Hence the percentage of Fe in other diseases showing deficiency of Fe in the liver is usually not higher than .1%. The cases by Burton are exceptionally high and even in these the percentage was only .4% while in Pernicious Anaemia it seems to average .7%.

2. The percentage weight of Fe in the liver is always greater than that in the spleen in Pernicious Anaemia and in no other disease in which there is a defect of Fe has this been shown to be the case, the decrease being the condition observed.
Spleen: Shows no marked changes as a rule. In some cases it is larger than normal, but in others smaller than normal. It is interesting to note Hunter's view regarding the variation in size. He believed that during an exacerbation of the disease, the spleen plays a large part in the haemolytic process, and if death takes place at this time it will be found large, whereas if death takes place between the exacerbations it will be found small. The spleen usually contains an excess of pigment.

Kidneys: Are usually pale and show the pigment granules in the cells of the cortical tubules, which give the blue reaction with Pl. Fe by 6 + HCl.

Pancreas and Suprarenals show no change.

Intestinal Pleures of nerves and Abdominal Ganglia may show degenerative changes.
Nervous System

Brain is usually pale and edematous and may show petechial haemorrhages on the surface and in the substance.

Spinal Cord Track of sclerosis in the cord appears to be not uncommon, especially in the posterior columns and slightly in the lateral and anterior columns.

Tieckert in 1887 reported some cases (3) in sclerosis chiefly in the posterior columns. His pupil Minnick (Zeitschrift fur Path. Med. 1892) reported a careful examination of 6 cases—3 previously reported by Tieckert and 3 of his own—which presented symptoms of cord affection during life. The autopsy in every case showed degeneration in the posterior columns, especially Goll's but also in posterior external tracts. Posterior roots and Hiss's tract were unaffected.

In 4 the lateral columns were affected especially in the outer and posterior parts. In 3 of these there were some changes in the anterior columns chiefly in the invasion of the direct pyramidal tracts. He noted that there was no shrinking
in the posterior columns as in tabes and suggested that this was probably because the lesion was a subacute process rather than a chronic scrofula.

Eisenthr (Deut. Medizin. Wochenschr. 1892) reported one case in which there was degeneration in the posterior columns and scattered foci in the corticospinal columns.

Forte (Arch. f. Psychiatr. 28, 1893) reported two cases in which most marked changes were found in the posterior columns especially in Holl's tract which presented the appearance usually found in ascending degenerations in the upper dorsal and cervical regions.

Posterior external column showed various degrees of change but everywhere the zone bordering the inner aspect of the posterior columns, the posterior nerve roots and Tisserand's tract was unaffected. Some degeneration was present in the direct cerebellar and crossed pyramidal tracts and slight in the direct pyramidal tract.

H. M. Bowman (Brain 1894, Dec. 17) reported a case in which post-mortem degenerative changes were
found in all three columns, being chiefly in the lateral and anterior columns below and in the posterior columns above. The posterior column was not affected anywhere and there was always a clear area between this and the degenerated parts. All over, there were parts showing the medullary sheath first affected — swelling and multiplication of nuclei etc. and in the dense parts some sclerosis. He considered that the parts showing densest degeneration were secondary, descending, in the crossed pyramidal tracts below and ascending, in Helli's column above. He found that the early changes were present in all parts of the cord and considered these as the change a primary one and more of a subacute parenchymatous myelitis than a chronic sclerosis.

The lesions found therefore in the spinal cord are not constant and cannot be considered specific since very similar changes are found in combined sclerosis apart from anaemia as in that described by Lorren as Ataxic Paraplegia.
Various views have been held regarding the relation between the disease Perenicious Anaemia and the nervous lesions found.

Minick doubted if the anaemia caused the change and in Norrie's second case the symptoms seem to have preceded the symptoms of anaemia. Minick suggested that both the Perenicious Anaemia and the nervous lesions were due to some primary toxic cause. He found in five cords out of twelve examined, 8 patients who had suffered from Perenicious Anaemia but showing no nervous symptoms, change in the cord bearing a general relation to his 6 previous cases.

In favour of the anaemia causing the change is the fact that sometimes, nervous symptoms are noted in Chlorosis and anaemia from Haemorrhage - as of the nervous and motor weakness - and following the onset of the anaemia. In many of these when the anaemia has improved the nervous symptoms have cleared up.

Gowers (Disease of the Nervous System) reports marked motor weakness in Chlorosis and secondary Anaemia from Haemorrhage.
Considering the tendency to petechial haemorrhages in P. A some observers have advanced the view that the lesions in the nervous system may be due to such haemorrhages.

The only conclusion at which we can arrive at the present concerning the patholgy of these changes in the spinal cord is,

1. Anaemia associated with haemorrhage acts in some cases probably.

2. There is probably a toxic cause in others because of the early onset of the symptoms, the bilateral symmetry of the lesions and the way in which certain facts are picked out.

Bone Marrow

In the majority of cases of Pernicious Anaemia the marrow of the long bone shows well-marked changes, but since all the cases do not show these and as similar changes have been noted in other diseases, such as anaemia from haemorrhage, they cannot be considered a constant and characteristic feature of the disease but must be looked upon
Rather as secondary.

Normally the marrow in the shafts of the long bones is of a light yellow colour and microscopically shows the following structure.

A. A delicate connective tissue stroma in the meshes of which are three distinct varieties of cells.

2. Smaller reddish nucleated cells (blasts) from which normal red blood corpuscles are formed. The nuclei disappearing.
3. Marrow cells proper—roughly speaking, like white blood corpuscles, but larger.

There are several varieties of these:

a. Cells containing granules and a regular round nucleus—such are found in the blood in myelogenous leukaemia.

b. More numerous cells with irregular and notched nucleus, some of which contain granules taking on eosine stain while others do not stain at all or take up basic stains.

c. A variable amount of fat.

In Pernicious Anaemia the marrow usually presents to the naked eye a dark red appearance—in some
Cases even a violet colour.

Microscopically hardly any fat cells can be detected the tissue being made up of large numbers of nucleated red corpuscles, both hemoblasts and megaloblasts as well as marrow cells.

Numerous non-nucleated red blood corpuscles are also seen presenting a great variety in size and shape. Sometimes long crypts containing parts of red cells within them, as seen.

There is also in most cases a deposit of fat pigment recognized by the ordinary tests. The long trabeculae in some cases have been reported as showing evidences of absorption. The marrow in fact seems to revert to the embryonic type.

Muir (Jour. Path and Bact. 1896 vol vii) reports the examination of the marrow in the long bones from five cases of Pernicious Anaemia and says that the changes found are not found in other diseases. He found:—1. In all, a marked red colour of the marrow with absorption of the long trabeculae.
8. Height in some, marked in others
2. Large number of hemosblasts and a few megablasts in all. In two the megablasts were fairly abundant.
3. Pigment in the marrow is considerable quantity except in one where practically none was found.
The changes were chiefly in the centre of the bone, fading off towards the ends where the condition was almost normal.

Lymph Glands in some cases have been reported to be of a deep red colour.

In only one of the two cases of my series which died while under observation, was a post-mortem examination obtained (case 3). It showed typical post-mortem lesions.

The subcutaneous fat was darker in colour than normal but fairly well preserved.
The serous membrane of the heart and abdomen showed numerous petechial haemorrhages.
Heart was slightly enlarged owing to dilatation of
of the left ventricle. It weighed 8 oz.
The muscle showed marked fatty degeneration
Lungs pale and showed slight congestion
in lower part — otherwise normal.
Liver not enlarged. Weighed 30 oz.
Showed some fatty degeneration and gave
marked + reaction with 7% Fe CPy + HCl.
Microscopic examination showed distribution of
pigment to be chiefly in outer and middle
parts of hepatic lobule.
Gonad. Mucous vessels pale — not
examined microscopically.
Spleen slightly enlarged. Weighed 9 oz.
Did not give distinct + reaction.
Kidneys showed slight but distinct +
reaction with usual reagents.
Bone marrow. In specimens of Dr. arm
was altered in colour, being red.
Spinal cord not examined.
Etiology

The etiology of Pernicious Anaemia is still very obscure. In fact, many insist that it is the absence of any cause or predisposing cause that is one of the most characteristic features of the disease. Thus, Addison, in one of the earliest references (in the Enquiries and Causation of Disease of the Suprarenal Cages, 1855), refers to the disease as "a general anaemia occurring without any discoverable cause whatever, cases in which there had been no previous loss of blood, no exhausting diarrhoea, no cholera, no purpura, no renal, splenic, mesenteric, glandular, strumous or malignant disease.

We constantly see cases, however, of true Pernicious Anaemia in which the symptoms, signs and post-mortem appearances have followed on exhausting conditions (especially exhausting to the blood-forming tissues) such as anaemia from haemorrhage, gastric trouble, etc., and I think we must consider such conditions as at least predisposing.
Predisposing and Anaemia-producing causes

(a) Pregnancy and Parturition

Some seem to occur during pregnancy, as in Fickl's case quoted by Osler (Principles of Medicine 1895: p. 727) where 19 out of 29 occurred during pregnancy.

The condition may be post-partum as in 5 out of 24 reported by Osler (Principles of Medicine 1885).

(b) Gastro-intestinal Disturbance

In connection with this, which is so frequent a symptom in Pernicious Anaemia arises the question whether the symptoms are an evidence of the disease or a predisposing cause.

Oliver's view of the pathology of the disease is correct, that it is a disease localized to the alimentary tract, then gastrointestinal symptoms, when they exist previous to the onset of Pernicious Anaemia are probably an important predisposing cause in many cases.

That this is not certain, a constant predisposing cause is shown by the fact that some cases have not shown any gastro-intestinal disturbance until the onset of well-marked symptoms.
9. the anaemia

9. Atrophy of the Stomach has been advocated as a cause by Fenwick, Babayan, Henry and others. — See previous reference to this under section of Morbid Anatomy.

(c) Parasites as Bothriochasmus Latum and Antiglotostomum Duodenale.

Some cases of anaemia associated with these parasites in the intestine have shown all the clinical characters and post-mortem changes characteristic of Pernicious Anaemia but that they act as more than a predisposing cause is very doubtful. In the case of Bothriochasmus Latum it has been shown that these worms are often present in considerable numbers without even causing Anaemia.

Antiglotostomum probably predisposes to the condition by causing a secondary anaemia.

Of course it must be admitted as possible that these parasites may lay the production of some substance which is absorbed from the alimentary canal actually be the cause of true P.A. and support is clear to this view by the fact that cases have been described closely resembling Pernicious Anaemia in which
after the death of the parasite by anthelminthics the symptoms have cleared up. The reports of many such cases however do not by any means show all the clinical features of Permain Anaemia and at the present time would not be diagnosed as such but merely cases of secondary anaemia which when the direct cause was removed recovered. If however the parasite be not removed it may produce a progressive form of anaemia ending in death, but not always showing the characteristic features of Permain Anaemia.

Rundberg (Deut. Archiv. F. Trop. Med. 1884 p. 304) reports that out of 19 cases of tape-worm anaemia treated with anthelminthics only one died whereas before, all his cases died when treated with arsenic, iron etc.

J. B. Trotter (Griffith's Cyclopedia of Diseases 1890 Vol. 15) expresses the opinion that the anaemia closely simulating Permain Anaemia which is produced by BOTHROPHILUS LATUS is toxic and the result of chemical matter absorbed into the blood, and cites cases by Schapiro, Regel, and Rundberg.
(d.) Repeated Haemorrhages

Hae Hemorrhage (Med. Jour. and Gyneka 1846) reports case following attack of erysipelas.

Finni (B.M.J. 1890 vol ii p. 43) reports a case following hemorrhage.

Greenhow (B.M.J. 1871 vol ii p. 163) reports a case following hemorrhage.

Stockman (A.M.J. 1895 vol i) reports case following hemorrhage.

Case 4 of my own series seems to have followed hemorrhages.

Haemorrhage I think however can only be

sustained upon a predisposing.

A case reported fully by Alfred Edgecombe,

Harrington (B.M.J May 4 1901) supports this view in my opinion.

Here then had been ordinary anaemia for

12 years before patient seen i 1899, thought a

and kept going on repeated small haemorrhages

and discharges of small quantities of pus from

the nose. During this time up to two years

before being seen by Edgecombe the anaemia

which showed no resemblance to Persuasive Anaemia

yielded readily to treatment with iron.
During these last two years, however, the attacks although improved by the former seem to have yielded very slowly to it and in addition they had become attacks of diarrhoea. When seen by Edgecombe in 1899, the case presented some features of well-marked Pernicious Anaemia. Now it is reasonable to think that there is secondary anaemia capable of passing into Pernicious Anaemia without the addition of some specific cause. This case would have done so long before being seen by Edgecombe for the anaemia produced from time to time during the first ten years of the illness was sometimes very severe. The onset of attacks of diarrhoea which continued afterwards and which had never been present before point to some distinct change in the course of the illness and not to have been dependent merely on extreme anaemia.

Other predisposing causes of less frequent occurrence have been reported:

Syphilis (Mcllwain—Challis Annae, 1839 (Vol. 10), 253)
(Tarby—Die Anämie 1883)

Yellow Fever (Branwell—Edin. Med. Jour. 1877 Vol. xii)
Mental Stricken (Mackenzie—Lancet 1878 Vol. 2)
Tuberculosis (9 cases by Mueller, Progr. Pernix, Wiener. Archiv 1877) and one case each by Marshall Hall (Henry's Practice of Medicine 1877) and Courpeland (Tannet 1881 vol. i).


However, after considering all these there remains a large number of cases where no cause or predisposing cause can be found. Thus in 18 out of 24 cases reported by Adler (Medicin & Medicine 1895) no cause was discovered.

In 20 cases by Billings (Amer. Jour. Med. Sci. 1900) no definite cause or predisposing cause was found except in two, where one had had chronic diarrhoea for two years and the other ophthalmic goitre for several years.

In 160 cases by Talbot (Amer. Jour. Med. Sci. 1896 vol. 120) no cause was found except perhaps in four where the condition began immediately after parturition or during the previous pregnancy.
In 110 cases collected by Coupland (_thames 1881 vol. i_ ) in 40 the cause attributed.
In the others the alleged cause was too remote or too slight to have influenced the case at all.

In my own cases only one (case 4) showed any adequate predisposing cause, namely, haemorrhage after premature labour.

It may be said that the known etiological factors of _pernicious anaemia_ are those of simple anaemia which rarely if ever shows symptoms of true _pernicious anaemia._

See _Most statistics agree in showing its predominance in males to a slight extent._

Thus _Wales (Practitioner of Medicine 1895)_ reports that 9 of his 24 cases 10 were in female and 14 in male.

Of 110 cases by Coupland (thames 1881 vol. i p. 571) 56 were males and 54 female.

_Samuel (Diseases of the Blood 1899)_ says that in his 45 cases 29 were in male and 16 in female.
Pyne Smith (Guy's Hospital Reports) 1883 vol. xvi p. 264 reports that of 107 collected cases 48 were in males and 59 in females.

Of my own cases, 6 were in women and 3 in men.

Ziemland also gives statistics by Professor Brehmer from Die Prognose Anämie Kurz 1874 in which out of 44 cases, 9 only were in males and 35 in females.

The discrepancy in these statistics is largely accounted for by the fact that many observers include under Pernicious Anæmia only those cases presenting the characters of the disease, in which no adequate cause is found. If this be done the so-called idiopathic cases certainly seem to predominate in men.

If those cases are included in which all the characters of the disease have supervened on a secondary anaemia, and I do not see why they should not, statistics show the cases to be about equally affected or perhaps the disease to be of more frequent occurrence in females.
Age. By far the majority occur between the ages of twenty and forty-four.
In Coupland’s cases, 59% of the men were between 40 and 60 years of age, and 63% of the women between 20 and 40 years of age.
My own cases were between 30 and 66 years of age. Four were above 45.
In Bramwell’s 45 cases, 24 cases were between 35 and 64 years of age, 8 occurred below 35, and 10 above 54.
Symptoms and Signs

One of the marked features of Petrucois, Anaemia is the slow and insidious onset and in most cases the patients have difficulty in fixing exactly when they first began to feel really ill. As a rule the first thing noticed is slight symptoms of anaemia such as shortness of breath and palpitation on exertion. Pallor of the skin soon becomes evident and the symptoms of the anaemia become marked until eventually in usually a few months all the symptoms and signs of the disease are well marked.

Some cases have gastric and intestinal symptoms before the onset of the symptoms of anaemia and as yet it is difficult to say whether this is an evidence of the disease or not. According to Hunter's view that the disease is one localised to the alimentary tract these symptoms would be considered an evidence of the disease.

In 8 of my cases the first symptoms complained of were those of anaemia. In only one (the 9th) was there any disturbance of the gastric-intestinal
Tract preceding the symptoms of anaemia and there had been attacks of diarrhoea for some months but no vomiting. All my cases were interrogated specially with a view to finding out whether there had been any gastro-intestinal symptoms preceding these anaemia.

In the following consideration of the clinical features special attention is devoted to those illustrated in my own series of cases.

**Haemorrhagic Septum**

**The Blood**

In all my cases the blood for examination was taken between meals, from the Coe of the ear, after a good-sized puncture had been made with a Grecio's knife. I seldom had difficulty in obtaining a good supply of blood and in cases where the flow was slow, gentle rubbing of the surface of the punctured part caused free emission of blood.

The corpuscle counting was done by means of the Thoma and Hæmoglobinometer. The Haemoglobin was estimated by Fowkes'
Haemoglobinometer
Films were dried in the air, fixed for about 5 minutes in a 10% vol. of formalin in absolute alcohol and stained some with eosine and methylene blue, others with eosine and haematoxylin.

The blood in some cases appeared pale and watery while in others it was dark in colour and appeared even of a deeper colour than normal. This is probably accounted for by the fact that in some cases as shown by Topham (St. Thomas' Hospital Rep. Vol. XXI p. 155) the haemoglobin separates from the red blood corpuscles with abnormal readiness and colours the Typh. Sanguinio. It usually separates from films easily owing to the small number of cells present.

Red Blood Corpuscles
One of the most marked and constant features of Thrombocytopenia is the decrease in the number of red cells. These are usually reduced at
One stage, below 2,000,000 per cubic millimetre and in one case reported by Lusinche were as low as 143,000 per c.mm.

There is no other disease which shows such a marked diminution of red blood cells. Talbot (Am. Jour. Med. Sci. 1895) considers this reduction of diagnostic importance as in no case of anaemia due to wasting diseases, such as cancer, did he find the red cells reduced below 2,000,000.

The lowest count of my own cases at the time when first brought under observation was 900,000 and the highest 1,650,000.

Microscopic examination of a fresh specimen of the blood shows as a rule the following abnormalities in the red blood corpuscles:

1. Defective rouleaux formation. This was present in all my cases.

2. Absence of the echinoccele depression in many of the red corpuscles - present in all my cases.

3. Irregularities in shape or Poikilocytosis.
As termed by Funcke, Poikilocytosis at one time thought characteristic of the disease may occur in any severe anaemia. It has been shown that they can be produced from normal blood by careful heating and this is taken as an indication that they are products of fragmentation of red blood corpuscles. Poikilocytes are probably paradoxic, as no evidences of degeneration are seen in them and they would increase the respiratory surface Poikilocytosis was present in all my cases.

4. Irregularities in size

Special attention has been devoted to very large forms, measuring from 10 to 15 micromillimeters in diameter. They show a pale centre and have been termed macrocytes or megalocytes. Importance has also been attached to very small red blood cells called microcytes or Dickhout corpuscles, Dickhout being one of the first to describe them. These are of very small size often not exceeding 1/4 of a normal R. B. C. They are perfectly spherical and of a uniformly deep
yellow colour.

Each of these forms has been at one time
looked upon as pathognomonic of the disease
but it has been shown that they do not
occur — at least the microcytes — in all cases
of Pernicious Anaemia and they have been
found in cases of anaemia distinct from P.A.

Some observers hold that microcytes when
they are seen are almost pathognomonic and
state that although very scarce forms of red
blood corpuscles are found in other anaemias,
they differ from leucothotic corpuscles in not
being perfectly spherical but in being irregular
in shape — drawn out, pointed etc.

Microcytes were found in some time in 6 of my
cases. No. 1, 2, and 9 did not show them.

Megalo- and were present in all my cases.

Besides the above, one marked feature shown
in stained films of practically all cases of
Pernicious Anaemia is polychromatophilic degeneration
of certain of the red cells. This is shown by
the protoplasm of the corpuscles affected taking
on a bluish tint with methylene blue instead
of being bright red like healthy surrounding
corpuscles. This was present in all my cases.
Ehrlich has suggested that this points to a gradual death of the red blood corpuscles leading to a coagulation necrosis of the discopen - the cells taking up the protoids of the blood and so staining with a nuclear stain.

Some say that corpuscles showing polychromatophilic degeneration are not dying forms but young forms. This seems to be supported by the fact that in the early stages of certain anaemias the nucleated red cells show this polychromatophilic

Grounds for believing polychromatophilic cell degeneration
(Histology of the Blood, Thiele & Lazarus, by A. G. G. James, Cambridge University Press)


2. In experimental anemia they can be produced in large numbers in the blood, e.g., in conditions where there is least question of fresh production of red blood corpuscles.

3. In acute losses of blood in man these staining conditions can be observed in 24 hours while
In this time no nucleated reds are found.

4. This staining condition is frequently observed in nucleated reds particularly in megaloblasts. Normoblasts which are typical of normal regeneration rarely show this condition.

Nucleated red corpuscles

Three forms may be seen:

2. Normoblasts — Nucleated red corpuscles of size of normal red cells. Nucleus is sharply defined and lies generally in the centre and comprises the greater part of the cell and is characterized by its intense colour with nuclear stains. The cell often has an irregular outline and an eaten-away appearance. They were present at some time in all my cases.

6. Megaloblasts 2 to 4 times larger than normal red blood corpuscles. Normoblast often shows degenerative change of an anaemic character. Nucleus is larger than that of a normoblast as a rule but does not form 2/3 of large fraction of the cell. Nucleus is
of a rounded shape. Its often is not sharply defined. It has a weaker affinity for nucleic stains and does not stain so deeply as that of a normoblast. Outline of cell usually sharp. Present in all my cases.

e. Microblasts are only occasionally present. They are stated to be more frequently found in traumatic anemias than in any other forms. They were not seen in any of my cases.

Dot-like granules are occasionally seen in the protoplasms of nucleated red corpuscles, staining with methylene blue, especially in the megaloblasts. It has been suggested that these are products of nuclear degeneration. They were well marked in cases 8 and 9 of my series.

Significance of the change in the red blood corpuscles.

In all anemias of a severe type all the above abnormalities in the red blood cells with the exception perhaps of the megaloblasts, can be seen and are probably to be explained by
increased haemogenesis of the blood forming tissues especially the bone marrow, owing to the great demand for new red blood corpuscles, which the excessive destruction has brought about. Many of the leucocytes however may be the result of partial destruction of normal red corpuscles in consequence of a haemolytic process or may be due to fragmenting of the red blood cells in order to give a large respiratory surface. I have seen megaloblasts in almost all severe anaemias, the result of haemorrhage, infection and organic disease. They are usually however scanty.

Tajani and Ehler's (Histology of the Blood 1901) have shown that megaloblasts are never found in haemorrhagic anaemias and in chronic anaemias of the severe type as in the cases e.g. of old syphilis, carcinoma of stomach etc. it is almost impossible to find them. On the contrary they say in Pernicious Anaemia almost without exception megaloblasts are found. In the later stages they may be rather scanty. I have examined several cases of chronic anaemia from carcinoma of the stomach and haemorrhage and did not find megaloblasts.
Present at any time although holoblasts are often found. Holoblasts are normally present in adult bone marrow and almost certainly are the precursors of normal non-nucleated red blood cells. Megaloblasts are never present in the bone marrow of adults under normal circumstances, and are only seen in the embryo and in the first few years of extrauterine life.

While therefore in secondary anaemia the blood tends to produce small forms in ischaemic anaemia there is a tendency in the opposite direction.

The appearance of megaloblasts and megalocytes may be taken as indicating that the regeneration of the blood is not proceeding in a normal manner but in a manner which approximates to the embryonic type. Megaloblastic formation is probably not a useless formation because:

1. Since from formation of red blood corpuscles by means of megaloblasts is clearly much slower.
2. Since megalocytes, which are formed from megaloblasts probably (Shelcut & other)
process in proportion to their volume, a relatively smaller respiratory surface and so constitute a type disadvantageous for anemic conditions. This is still more evident when the fact is considered that the formation of reticulocytes is probably a serviceable function (histology of blood, 1901 — Uyens). Bichat and Lagars also hold that megaloblastic degeneration is probably due to chemical influences which act on the bone marrow and alter the type of degeneration in a disadvantageous manner.

The presence of megaloblasts in the blood in any considerable numbers is, I consider of very great importance and would I think be found in every case during some stage of the progress of a fatal condition were made. When they are present in considerable numbers and in greater proportion than the normoblasts it is almost pathognomonic.

Toldt (Clin. Exam. of the Blood) says that in pernicious anemia megaloblasts are always more
humorous than normal. And he has never yet seen this in secondary anaemia. In a report of 140 cases (Am. Jour. Med. Sci. 1895, vol. 120) he found megaloblasts in 104. They were not found in 3 but in these only one examination was made.

Frank Belling (Am. Jour. Med. Sci. 1902, November, p. 304) gives analysis of blood in 20 cases. He found normoblasts and megaloblasts in everyone at some stage or other, in all when the blood loss and condition was improving.

Megaloblasts outnumbered normoblasts at some stage in 14.

Gilles (B. M. J. 1900, vol. 2, p. 703) found in two cases of Pernicious anaemia with examinations frequent that megaloblasts outnumbered normoblasts in almost every count.

In cases 5, 6, 7, 8, 9 of my series which were the only cases thus counted the megaloblasts highly outnumbered the normoblasts when the blood first examined.
Haemoglobin. This is absolutely diminished but not in the same proportion as the red blood corpuscles. Thus, the individual richness in Haemoglobin of each corpuscle is nearly always in many cases. The colour index, obtained by dividing the percentage of Haemoglobin by the percentage of corpuscles, is therefore in Pernicious Anaemia often plus sometimes unity and seldom slightly below unity. There is no other disease which shows so constantly as Pernicious Anaemia this high colour index and this fact alone is of great importance in the diagnosis, especially in distinguishing the disease from chlorosis and secondary anaemias to which the colour index is always minus. This relatively high percentage of haemoglobin has had various explanations but probably depends on the facts:

1. Increased average size of the red corpuscles each containing more than the usual amount of haemoglobin.
2. Many microcytes present which are often not counted or at least not all counted.
In they may be so small as not to be seen in the diluted blood used for the count.

3. The hemoglobin may be estimated during an exacerbation of hemolysis and the more highly coloured plasma contribute to its elevation.

Frank Billings (Amer. Journ. Med. Sci. Nov. 1907, p. 554) in an analysis of 20 cases states that in only 3 cases was the colour index below and then only slightly so while in all the others it was unity or above.

In 5 of my cases, namely 1, 6, 7, 8 and 9 the colour index was above one when blood examined for the first time. In cases 9 and 4 it was 1.

In only two cases was it below namely 2 and 5 where it was 0.9 and 0.95 respectively.

Leucocytes. Most observers state that the leucocytes are absolutely diminished.

Billings (see previous reference page) found a diminution in 14 of his 20 cases taking 7000
In the normal

Talbot (Am. Jour. Med. Sci. 1895 Vol. 120) found in 96 out of 110 cases the leucocytes diminished below 4000.

Blamire (Disease of the Blood 1899 p. 67) says that in uncomplicated cases of Pernicous Anaemia the white blood corpuscles are almost always diminished, sometimes markedly so.

In my own cases the leucocytes were reduced below 4000 except in Case 3 when they numbered 7000.

With regard to the relative proportions of the leucocytes there is not much definite knowledge yet.

Ogles (Medicine 1895 page 430) states that in the grave cases a marked increase in the small mononuclear forms with a diminution in the polymuclear leucocytes is often noted.

Talbot (Q. M. J. Vol. I 1900 p. 408) found in two cases in which a careful count of the leucocytes was made that the average proportion was

\[
\text{Multinucleated : Lymphocytes : Large Mononucleated : Smallest} = 4:6 : 45 : 3.5: 4
\]
In 5 of my own cases in which a differential count of the leucocytes was made, I found the lymphocytes always relatively increased, taking as the normal the following:

- Leucocytes with multiparticulate nuclei and very fine cytoplasmic granules, 60-70%
- " Round branched " " Coarse " " 2-4%"
- Small Leucocytes with round nuclei and no granules, 20-30%
- Large Leucocytes with round nuclei, " 6%

(Hutchison and Rainy 1954 pags. 202-203)

<table>
<thead>
<tr>
<th>Case</th>
<th>Multinucleated</th>
<th>Lymphocytes</th>
<th>Large Mononucleated</th>
<th>Eosinophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 5</td>
<td>46</td>
<td>45-</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Case 6</td>
<td>39</td>
<td>54</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Case 7</td>
<td>47</td>
<td>40</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Case 8</td>
<td>26</td>
<td>62</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Case 9</td>
<td>40</td>
<td>51</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

While the lymphocytes were in these 5 cases relatively increased the large mononucleated and the eosinophils remained in about the normal proportion. Case 8 in which there was such a marked relative increase of the lymphocytes and diminution of the multinucleated was one of the greatest of the cases and recorded very low counts thus agreeing
With Osler's statement


In discussing the significance of the eosinophile cells states that he found in several anaemias such as Pernicious Anaemia which were recovering, the eosinophile cells increased markedly beyond that in health and in cases going down hill they markedly diminished.

In the only case of my series which died and in which a differential count was made I did not find that the eosinophile diminished. They remained in the proportion of between 3% and 4% all the time.

In some of my cases which were recovering films showed apparently a relative increase beyond that of health but an exact count was not made of the leucocytes in these stages.
Haemorrhages in Pernicious Anaemia

Haemorrhage may occur spontaneously or as a result of trauma and is probably due to the fatty degeneration of the blood vessels which it has been shown occurs extensively.

Haemorrhage has been reported as having occurred in almost every part of the body. While probably all cases have at some time or other concealed haemorrhages either localised or present only a certain number show external haemorrhages.

Tabor (Am. Jour. Med. Sci. 1896, vol. 120) reports that out of 210 cases which he had had under observation, external haemorrhage played a part in the symptomatology of only 39.

In my series, case 2, had a history of attacks of haemorrhage from the bowel for two months during the course of her illness and no causes for this could be found. Case 8 had a history of repeated attacks of epistaxis throughout the whole course of his illness and sometimes of a very profuse nature.

Case 5 showed well the tendency to haemorrhage as a result of trauma. While under observation.
this case had the central and extemal incision of the lower jaw removed, because of a cario-
 necrotic condition. Rather suppose haemorrhage followed this. Next day a very marked ecchymosis of the chin was present. Whether this was due to the penetration of blood through the subcutaneous tissues from the bleeding gum or to the firm pressure applied to the chin by the hand of the dentist is difficult to say but from its rapid appearance probably the latter was the explanation.
Alimentary System

Since Hunter advanced the view that Pernicious Anaemia is a disease affecting primarily the alimentary tract and localized to it a great deal of attention has been devoted to this system.

Hunter emphasizes the fact that in many cases the primary infection may be through the mouth, either directly, or by setting up an infective catarrh of the stomach and intestines, and so predisposing this part to infection, and in such cases there is a history of attacks of gastritis with usually a cario-necrotic condition of the teeth for years. That these parts cannot always be the first local site of the infection is shown by the fact that in a large number of cases no history of sore mouth is obtained and the teeth are in a good condition, while in some no history is obtained of gastro-intestinal symptoms until the anaemia has been well developed, which anaemia has been due presumably although not necessarily to the specific disease Pernicious Anaemia.
Hunter in a recent analysis of 200 cases only found a reference to stomatitis in 18. Of course no investigation may have been made as to a history of "toothache," but surely if this symptom had been prominent we would expect it to be mentioned by the patient in a larger number of cases without special interrogation.

Following stomatitis and glossitis there has been observed a smooth, white, polished appearance of the tongue and this is undoubtedly not infrequently seen in cases of pernicious anemia. It was present and well marked in cases 1, 7, and 8 of my series but in these there had been no previous history of stomatitis or glossitis on particular questioning, so that this appearance of the tongue can certainly exist apart from any previous inflammatory condition of the mouth.

Some of Hunter's cases are remarkable in having shown a previous well marked history of stomatitis or a long continued cario-kerotic condition of the teeth with distinct gastro-intestinal symptoms, for a considerable time before the onset of the anemia. Thus in the case of 1900 Jan. 27.
The reports 4 cases showing a cario-keratotic condition of the teeth or an inflammatory affection of the mouth with following infective gastritis or enteritis. As a result of his observations Hunter believes that the disease is a specific infection of the digestive tract especially of the mouth and stomach and probably although to a less degree of the intestine. The chief source of infection is the ways through the mouth from long continued and neglected cario-keratotic conditions of the teeth and sometimes possibly from stomatitis arising from other causes. The usual effect of this infection is a chronic infective catarrh of the mouth or stomach which may in time lead to deeper seated changes e.g. ulcers of the mouth and tongue and chronic gastritis with atrophy of the gastric glands.

That the history of many cases as well as the successful treatment of them by extraction of the cario-keratotic teeth and antiseptic attention to the mouth and alimentary tract supports such a theory is admired by almost all observers. But that this is the explanation in all cases cannot be granted for in many
Cases of undoubted Pernicious Anaemia to such conditions have been observed.

In my first 4 cases no special note was made regarding any history of "colic month". No detailed examination was made of the feet in these cases.

Case I Age 44. 3 years duration.
No inflammatory condition of the mouth while under observation.
Attacks of diarrhoea and vomiting throughout 1st year only. For last two years constipation had been the rule and very little vomiting had occurred.

Case II Age 44. Duration about four years.
No inflammatory condition of mouth while under observation.
No history of diarrhoea or vomiting until a few weeks before coming under observation although symptoms of anaemia were well marked all along.

Case III Age 30. No history obtained.

Case IV Age 35. Duration 3 years.
Attacks of diarrhoea from time to time.
No vomiting throughout whole illness.
Case V  Age 37. Duration, 6 months.
Bad teeth since age of 22. 
Teeth very carious all over.
Anaemia, attacks of vomiting and diarrhoea were noticed about the same time and had continued.

Case VI  Age 62. Duration, 8 months.
Attacks of vomiting and diarrhoea during last 5 months of illness only. 
Teeth were very good for her age. No marked caries — only one small stump.

Case VII  Age 58. Duration, 4 years.
Teeth had not been bad until last year of illness and patient blamed medicine for this. Medicine used to block his teeth. Examination showed one or two carious teeth in both upper and lower jaws.

Case VIII  Age 31. Duration, nearly 2 years.
Teeth very carious.
Severe diarrhoea for some months before onset of symptoms of anaemia. Diarrhoea and vomiting off and on all through illness.

Case IX  Age 66. Duration, 2 years.
Vomiting and diarrhoea since onset of symptoms of anaemia.
Teeth all extracted when 24 years of age for neuralgia.
In the last 8 cases there was no history of any inflammatory condition of the mouth and there was none ever present while cases under observation.

Regarding gastro-intestinal conditions therefore we can only say that in some cases they seem to be predisposing causes, in others probably they are an evidence of the disease and that although in some the infection may be through ceco-necrotic teeth, this certainly is not the case in all.

Liver may be enlarged. It was so in cases 2, 4, 5, 9, 10 of my series.

Spleen may be enlarged. It was in cases 3, 4, 5, and 8 of my series.
Circulatory System
In all my cases this system showed the usual symptoms and signs of extreme anaemia, there being nothing special to distinguish the disease from any other severe anaemia.

Respiratory System
Nothing characteristic of the disease has been noted in this system.

Integumentary System
One almost constant feature which the skin in Pernicious Anaemia presents is the marked pallor, associated with a yellowish or lemon colour, and much importance has been attached to this appearance by many observers, who consider it a point assisting in diagnosis. Very rarely has this peculiar appearance been observed apart from Pernicious Anaemia.
9 cases. Two of the other 8 cases showed a peculiar pigmentation to be described later and the third simply showed extreme pallor without the yellowish tint.

Sometimes distinct jaundice has been observed and this has been looked upon by some as hepatogenous in character and an indication of increased haemolysis. In only case 8 of my series was there slight jaundice while the patient was under observation and cases 6 and 8 gave a history of recurrent attacks of well-marked jaundice.

Pigmentation of the Skin

Little reference is made in the literature of the disease to pigmentation of the skin apart from that probably produced by arsenic.

Compland (Galtonian Lectures Lancet Vol 5 1881 p. 569) reports a case of a woman aged 29 who suffering from Plurimicros Acidaemia presented a tawny colour of the skin of the neck, axillae and
Back. Areolas of breasts hot pigmented and no pigmentation at root of hairs. P. M. showed suprarenals and semilunar ganglia to be quite healthy.

(Bremwell in (Anæmia and Diseases of the Blood 1890 p 122 at sq.) records 4 cases of Pernicious Anæmia in which there was marked pigmentation of the skin but never of the mucous membranes and in which there was difficulty in deciding whether or not the cases were combinations of Pernicious Anæmia and Addison's Disease.

Cases 5 and 9 of my series showed a well-marked pigmentation of the skin when first thought under observation. This pigmentation had come on in each case some time after the anaemia had developed and during the course of the illness had gradually become more marked. No cause such as arsenic could be discovered in either case.

Case 8 showed distinct bony pigmentation around the eyes, on the forehead and temples. There was also pigmentation of the neck, front of the chest especially over the sternum.
Nipples and areolas, flexures of arms, back of hands and wrists, were all deeply pigmented. There was marked pigmentation about the knee-joints. No pigmentation in the mouth.

This patient has never been under treatment before coming under present observation.

Face showed dark rings around the eyes. Neck, upper part of chest and back and lower part of abdomen were all deeply pigmented. Axillae and flexures of elbows much pigmented as also were the groins and upper part of the thighs. Very slight pigmentation was present of the hands, forearms, feet and legs. No pigmentation was found in the mouth.

Although this patient had been under treatment before coming under observation he had never been treated with arsenic according to the report received from the doctors who had always attended her.

Note the pigmentation in these cases which
was evidently not due to arsenic, was due to any effect of the disease Pellicinous Anæmia to. However, very unlikely since hardly any similar cases seem to have been observed notwithstanding the large number of cases of Pellicinous Anæmia now reported.

Possibly they were cases of combined P.A. and Addison's Disease although the absence of any segmentation in the mouth on the first careful examination, is against this. Against this too, is the fact that post-mortem examinations on somewhat similar cases have shown the presence of the bodies was found postmortem.

Subcutaneous Tissue

Although cases of Pellicinous Anæmia may and generally do lose weight through wasting of the muscles, the subcutaneous fat is as a rule well preserved and often increased giving an appearance of good nutrition.
In my cases the subcutaneous fat was well preserved in all except 6 and 9, those which showed the curious pigmentation.

In connection with this increase of fat an interesting condition may often be noticed, namely, a well-marked deposit of fat beneath the conjunctiva, either on both sides of each eye or occasionally only on one side of each eye.

Cases 1, 2, 4, 7 and 8 showed a well-marked deposit on both sides of each eye while case 6 showed it only on the outer aspect. Cases 3, 5 and 9 showed no deposit.
Nervous System

This system may present a large number of symptoms, some depending probably on cerebral anaemia, such as loss of memory, insomnia, delirium and violent mental excitement, others, such as convulsions, coma and paraplegia probably depend on haemorrhages.

Spinal symptoms which occur not infrequently may in some cases where they eventually clear up depend simply on the anaemic condition of the cord. In others, where there have been found pronounced changes in the cord probably a toxic action is responsible. In others again the symptoms may be due to haemorrhage into the cord.

These spinal symptoms seem to be by no means constant but usually they consist in progressive muscular weakness with slight ataxia and sometimes spasticity; various disorders of sensation and towards the end loss of control over the sphincters.
Mannich (Zeitschrift fur klin. Med. 1892, xx) reports 6 cases in which there was progressive muscular weakness and subjective disturbances of sensation in the extremities. Some of the cases suggested tabes, others disseminated sclerosis. Ataxia was noted in 3 but loss of knee-jerk only in one. Involuntary muscular spasms in two.

More (Archiv. fur Psychiatrie, 1893) reports 2 cases. In the first there was numbness and weakness in the lower extremities; definite ataxia in all limbs and occasionally gait sensations and muscular spasms. There was also slight sensory anesthesia and later, loss of control over the sphincters. Knee-jerks at first were diminished then lost and later again were obtained. The 2nd case had practically similar symptoms which developed to a certain extent before the onset of the symptoms of the anemia.

H. M. Bowman (Brain, 1894, vol. 17) reports a case in which there was weakness and inability
to stand; blunting of sensation to light tactile and painful stimuli in finger tips and slight tactile anaesthesia in the legs below the knees. There was anaesthesia in the toes. There were three-jerks were brisk & wrist-jerk was obtained. No clonus. There was a marked improvement in the nervous system under arsenic and almost all the above phenomena disappeared. Eight months afterwards the patient returned much better. There was now great motor weakness and impaired sensation to touch, pain and temperature in the legs and partly in the hands. Localisation was incorrect and appreciation of pressure much affected. Ataxy came on in the arms. Patient eventually died, incontinence of urine and faeces being present before death.

In all the above cases there was found a well marked lesion of the cord (see section on Mortid Anatomy.)

Ryco Dickworth (B. 11th. 1905 Nov. 10th.)
Reports a case in which there was found a softening of the lower part of the cord which had produced anaesthesia and weakness of the muscles with increased
Tense-jésko, extensor plantar reflex and bladder and bowel symptoms.

In only one of my cases did the nervous symptoms show to any marked extent. This occurred in case 8. Patient came under observation in the Edinburgh Royal Infirmary on July 19, 1900 and although put on gradually increased doses of Hyos. Arsphenamin steadily grew worse. On August 9 he complained of pains all over the body and of numb feeling in the legs. These symptoms continued during the next two days and at night patient wandered a little. On the night of Aug. 9 patient became wildly delirious, and although hypodermics of all kinds were tried the almost maniacal delirium continued and he had to be removed from the ward. He continued rather delirious all the next day but then gradually became quieter and on August 19 was able to be readmitted to the ward. Examination of the nervous system now showed that there was marked motor weakness, especially in the legs so that he could not stand alone and could walk difficulty draw then up in bed.
The muscles of the legs were thin and soft. Knee-jerks and ankle Achilles' jerks were absent. There was flexor response of the toes on testing the plantar reflex which was very feeble. There was blunting of sensation to touch and pain below the knees. Arms showed no impairment of sensation and there was no interference with sensation to temperature anywhere. There was no affection of the bladder or bowels. After this he was put on salol and gradually began to improve and with the improvement in the blood the nervous symptoms gradually disappeared until on Sept 29, there was considerable improvement patient being able to stand alone. There were slight knee jerks and practically no sensory disturbance was present.

It is difficult to explain the signs and their disappearance in this case unless they were due to the extreme anaemia of the nervous tissues without any definite lesion having been produced and on the anaemia becoming less marked they slowly improved.
Affections of the fundus of the eye might be included under this system.

Ophic neuritis has been reported but seems to be rare.

Haemorrhages (Retinal) are frequent and are always important as a point showing the extreme anaemia.

Retinal haemorrhages were present in Cases 1, 2 and 8 of my series and not present in any of the others at any time during observation.
Urinary System

Considerable attention has recently been directed to the urine in Perihepatic Anemia, especially with reference to the question as to whether there is constantly or even in a majority of the cases, an increase of pigment either normal or pathological.

The origin of the urinary pigments is still obscure but it seems probable that part at least is derived from the Haemoglobin of the Red Blood Corpuscles. Some observers, for instance Hunter, have noticed in a majority of cases that the urine is darker in colour than normal and believe that this is due to a pigment not giving the spectrum of normal urobilin, and to which the provisional name, "pathological urobilin," has been applied. Hunter holds that this high pigmentation of the urine is evidence of an increased haemolysis and it has been noticed in many cases that it is more marked after a rise of temperature and fall in the number of
red blood cells when presumably an increased haemolysis has taken place. This is however not a constant feature and in many cases have been reported without the dark colour of the urine accompanying it.

Some observers deny that there is anything of the nature of pathological urobilin ever present in the urine of pernicious anaemia and prominent among these is G. Rowland Hopkins who made most careful observations in five cases and gave the results in Guy's Hospital Reports 1894 vol.

**Summary of the results**

1. The hand-yielding pigment in pernicious anaemia is normal urobilin.

2. Occasionally small quantities of haematochrome may cause the urobilin extracts to show a three banded spectrum.

3. That "pathological urobilin" described
in other forms of disease is probably of this kind.

4. That the amount of urobilin in the urine of
Philhocris Anaemia, though in excess, is not
greater than that found in concentrated
normal urine which in the fresh state exhibits
the absorption band at 4. The presence of
this band would therefore seem to depend on
the condition of the pigment as well as on its
quantity.

5. Urea and sulphates are increased in

amount.

6. Unoxidised thiochrome compounds
are decreased.

7. The urine acid ratio is not affected
in any constant manner.

8. The excretion of iron by the kidneys
is intermittent.

In my cases cases 1, 5, 6, 7, 8,
and 9 showed frequently while under
observation a dark colour of the urine
with a deposit of uric acid.

Some urines show traces of albumin
and even sometimes casts but it is
difficult to tell the significance of
these abnormalities especially whether they
have any direct connection with the
disease.

Cases 2, 4, 6, 7, 8 and 9 showed
occasionally a faint trace of albumin
in the urine. But never any casts,
except Case 4, in the urine of which
occasionally a few hyaline casts were
found.

It cannot be said I think that
there is, as yet discovered, any
constant characteristic change in the
urine of Pernicious Anaemia.
Irregular attacks of pyrexia seem to be characteristic of the disease. This has been advanced as an evidence of some toxæmic process and it has been noticed in some cases that during these attacks the number of corpuscles diminished while the urine became deeply pigmented and the skin jaundiced, suggesting a temporary increase of the haemolytic process.

In cases 1, 4, 6, 7, 8 and 9 of my series, attacks of pyrexia occurred generally lasting for from 5 to 7 days, the highest recorded temperature being 102.8°F in case 8. In all the other cases the temperature never rose above 101°F. In cases 2 and 3 there was never any fever. In case 4 and 8 the attacks of pyrexia were very frequent and in these the number of corpuscles showed a steady decline during the time under observation. In the others no diminution in the red blood corpuscles was noticed during the pyrexia and the urine was not deeply dark. In case 8 only was jaundice noticed during an attack of pyrexia and that only once.
Pathology

The pathology of Pernicious Anaemia is still, in spite of the numerous investigations that have been made, very obscure. Many theories have been advanced but none satisfactorily explain all the phenomena that have been observed in connection with the disease.

From these varied theories there stand out I think three, each of which has received strong support.

1. Defective Hæmogenesis. as a result of which the red blood corpuscles are abnormally vulnerable and therefore are too easily broken down in the circulation. That a certain degree of Hæmalysis does occur normally is I consider proved. and in Pernicious Anaemia according to this theory the normal Hæmolytic process is simply excited on abnormally weak red blood corpuscles, resulting in an excessive Hæmalysis and an extreme anaemia. What causes this defective Hæmogenesis is not certain.
This theory has been supported by numerous able observers such as Henry, Stephen Mackenzie, Pindfleisch, and Brakenridge. The latter in the Edinburgh Medical Journal 1892 Vol. 38 says that the condition is due to the blood forming organs having lost their power to form leucocytic corpuscles and to a consequent tendency to their early death in the blood destroying organs. The chief fact supporting this theory seems to be the changes found in the blood forming organs especially in the bone marrow. (described under Morbid Anatomy)

The fact that the haemoglobin seems to separate from the corpuscles in Pernicious Anaemia with abnormal readiness cannot be taken — as it sometimes is — as evidence of defective haemogenesis since this has been known to occur characteristically in the first year of extrauterine life. Other facts are cited in support of this theory such as the beneficial effect of
Transfusion of healthy blood (Brakenridge, see previous reference)

Against this theory is the strong argument that in some cases of undoubted pernicious anaemia no change has been found in the most important of the blood forming organs, namely the bone marrow.

In other conditions such as cancer, haemorrhage, Bright's disease, etc., where the nutrition of all parts of the body seems to be affected and where therefore one would expect a defective haemogenesis and consequently a breaking down of corpuscles, no evidence of excessive haemolysis occurs.

The changes in the marrow when they are present would rather seem to indicate an increased activity of haemogenesis, for the haemopoietic tissue is much increased and red corpuscles of all kinds are produced and for the most part rich in haemoglobin. I think that we must look upon the alteration
in the bone marrow is chiefly secondary to the anaemia and as compensatory to it.

Moff (Practitioner 1890 vol. xiv p. 93) says that the pathology of Pernicious Anaemia so far, resolves itself into this that an excessive process of a progressive and remittent character occurs for no known ascertainable reason, leading to an attempt on the part of the hematopoetic tissues to repair the excessive waste and often eventually determining a return to the embryonic type of blood formation in the marrow and spleen.

Muir (Jour. Path. and Bact. 1894 Vol. iv) says that the first change in the bone marrow in Pernicious Anaemia is similar to that which occurs after Leucorhage and the 2nd is characterised by the presence of large numbers of nucleated reds peculiar to Pernicious Anaemia and suggestive of a return to the embryonic type. Both should be considered secondary to the anaemic state.

The only facts which in my opinion are opposed
to the bone marrow changes being wholly secondary and compensatory to the anaemia are the production of megalocytes and megaloblasts which are not useful (for reasons given under section of blood) and the presence of haemoglobin in the marrow. These might be explained however by accepting a toxic cause for the disease and supposing that the toxic process produced an interference with haemogenesis as well as a haemolysis.
2. Theory advanced by Stockman

Stockman holds that all are cases of secondary anaemia, even so called idiopathic Pernicious Anaemia, initially thought about by various causes and subsequently perpetuated and rendered “pernicious” by repeated minute haemorrhages into the tissues as a result of the anaemic state having produced a fatty degeneration of the vessels. In the idiopathic cases the haemorrhages are internal and clinically invisible. In the obviously secondary cases the haemorrhages are primarily external and visible, with the subsequent development in the later stages of the former condition.

This view has been strongly and only advocated by R. Stockman (B. M. J. 1895 Vol. I May 4th, 11th, and 18th)

Against this view are the following facts:

1. A large number of cases of pernicious anaemia show no previous adequate cause for anaemia and it is almost impossible to believe that multiple capillary haemorrhages could produce the marked oligohaematemia present.
2. Internal bleeding may never be present
or any evidence of capillary haemorrhage such
as retinal haemorrhages.

3. Continued bleedings, as in purpura,
haemophilia and metrorrhagia may go on
for a long time without producing the
symptoms or signs of Pernicious Anaemia, or
a want of response to the treatment which
is so characteristic of the disease.
In Pernicious Anaemia, the symptoms and
signs may come on quickly in a previously
healthy individual.

4. Various conditions may produce an
anaemic state and probably a fatty change
in the small blood vessels (such as cancer,
pregnancy, chronic anaemia, typhoid)
without producing Pernicious Anaemia.

5. Post-mortem, in most cases, there is
no evidence of so many haemorrhages as
to have caused the condition.
Stockman to account for this says that
the haemorrhages being so small and the
Blood showing an indisposition to clot readily the extravasations may be so quickly absorbed as to leave no trace.

Hunter has shown (P.M.J. 1896 Vol. 5) that in extravasation of blood even if the blood were absorbed quickly it would leave some trace in the lymphatic glands in the form of excess of the pigment, if the bleedings were so numerous as they must be to cause the intense anaemia, and this has not been found to be the case in Pernicious Anaemia.

6. After haemorrhage of various kinds as in phrenic, haemophilia, fracture of the pelvis, abundance of Fe has been found in the liver and spleen but not in the liver to such an extent and not showing the relation between the amount in the liver and spleen, as in Pernicious Anaemia, nor does it show in the liver the peculiar distribution seen in Pernicious Anaemia.

Hunter (P.M.J. 1896 Vol. 5 p. 328) describes experiments in which he produced a condition resembling extravasation by the injection of
Large quantities of blood from one rabbit into the peritoneal cavity of another rabbit.
In no case did the changes found post mortem resemble the changes found in the liver, spleen, and kidneys in Pernicious Anaemia.
Thus in the liver the pigment was hardly increased at all; in some cases no increase was found, while the spleen contained a large excess of pigment — the opposite of what occurs in Pernicious Anaemia.

1. In haemorrhage from the intestine caused by Bandic督查或Lata or Antilostomum duodenal, the intense anaemia produced by the worm, according to Stockman, marked fatty degeneration of the capillaries, and so capillary haemorrhages, which ought to go on and keep up the anaemia even after the expulsion of the worm, whereas in the cases recorded of a condition closely resembling Pernicious Anaemia, produced by these parasites, the anaemia quickly cleared up and the patient rapidly got well on removal of the cause.
3. **Hunters View**

Definition of the disease as given by Hunter (Cancer Vol 1 1900 p.374).

A chronic infective disease localised to the alimentary tract; caused by a definite infection of certain parts of the mucosa of the alimentary tract, chiefly of the stomach, occasionally also of the mouth and intestine.

It is characterised by:

1. Intermittent destruction of blood and increasing anaemia (and the pathological and clinical changes consequent to these) as the result of the absorption of poison into the blood.

2. Periodic disturbance of the alimentary tract as local effects of the injection.

3. Occasional toxicemic attacks.

Characterised by fever, sweating, nervous symptoms, not infrequently by effects denoting deeper nervous changes.

This view has been strongly advocated by Hunter and is very supported by numerous observations, clinical, experimental
and pathological. It is probably although
not in its full enunciation, that in
most favour at the present time.
Most observers if they do not accept
in full Hunter’s definition, agree that the
oligochaemia is due to a haemolytic process.

The more important proofs of haemogia are:

1. Condition of the blood which shows
dissociating corpuscles, macrocytes,
proteines, haemoglobin crystals etc.

2. Presence of excess of the pigment in the
liver, spleen and kidneys, being in the
form of iron, loosely combined in the cells.
Also occasional excess of pigment, either
pathological (according to Hunter) or mixture
of haemoglobin and urobilin (Broward Hopkins).

3. Yellow, yellow colour of the skin and
attacks of jaundice.

Hunter holds that the haemolysis takes
place in the portal circulation (probably
mainly in the spleen) and not in the systemic.
circulation. He supports this by demonstrating the large excess of the pigment in the cells of the liver and by the absence of jaunmoglobinuria. This latter he showed to occur when haemolysis took place in the systemic circulation as in paroxysmal jaunmoglobinuria, injection of glycerin and distilled water, pyrogallol and, whereas in Pernicious Anaemia or in haemolysis produced by bolusdiuricin (which appears to cause haemolysis only in the portal circulation) the iron is excreted by the kidney appears in the granules in the tubules of the kidney or as pathological uric acid in mixture of haemoporphyrin and uric acid (Handel 1888 Vol. ii).

While probably therefore, a haemolysis does occur and possibly for the main part in the portal circulation, the cause of the haemolysis is still a much debated question and a large number of objections can be urged against Hunter's view that the disease is a specific infection of the alimentary tract leading to the formation of toxins.
Which are absorbed into the portal circulation and then cause the haemolysis.

The main objections are:

1. All cases do not show gastrointestinal symptoms or at any rate preceding the apparent onset of the disease i.e. in some cases these symptoms appear to be secondary.

2. These symptoms may, even if they do precede the onset of the disease be operating on predisposing causes just like pregnancy, prolonged lactation and haemorrhage i.e. causes of exhaustion and its acting through the effects of microorganisms.

3. No specific organism has yet been found.

4. Ankylostoma duodenale and Bothriocephalus Hares may produce symptoms and signs clinically indistinguishable from Pernicious Anaemia, which after the worms are expelled...
clear up.
Diagnosis

It may be said that clinically, there is no one feature absolutely pathognomonic of the disease but there are certain distinctive features which when taken together warrant a diagnosis.

1. Slow insidious onset without a definite adequate cause.

2. Preservation as a rule of the subcutaneous fat with a lemon yellow colour of the skin.

3. Paroxysmal attacks of vomiting and diarrhea without relation to diet or treatment.

4. Tendency to spontaneous improvement or improvement by the use of certain drugs followed by relapse sooner or later.

5. Examination of the Blood.
   a. Reduction in the red blood corpuscles below 2,000,000 per cubic millimetre at some time during the course of the disease, without a corresponding reduction in the haemoglobin, so that the colour index is
almost always unity or above.

1. Reduction of the leucocytes.
2. Presence of megalocytes and megaloblasts.
3. Tendency to chromatophlic degeneration in the red blood corpuscles.

Even if all the above features are present it is always as well to exclude causes of secondary anaemia, chiefly:

- Malignant diseases especially of the stomach.
- Advanced syphilis.
- Chronic parenchymatous nephritis.
- Malignant endocarditis.
- Purpura and Haemophilia.
- Thalassia.
- Intestinal parasites, especially Ankylostomum.

The features practically common to secondary anaemias and distinguishing them from Pernicious Anaemia are:

1. Well recognized cause.
2. Speedy progress of symptoms.
3. Emaciation as a rule.
4. Condition of the blood.
   a. Relatively low percentage of haemoglobin.
6. Size of red blood corpuscles diminished or normal and centres pale.
7. Nucleated red corpuscles almost exclusively of normoblastic type. Very rarely, if ever, are megaloblasts found.
8. Leucocytes usually increased especially the polymorphonuclear variety.
Prognosis

All observers are agreed that the ultimate prognosis is very bad. Very few cases have been reported cured and to have lived for years after stopping treatment. It is a question whether treatment especially by arsenic can even produce a virtual cure i.e. a maintenance of good health so long as the treatment is kept up. Some cases have been reported as having kept in good health so long as treatment persevered with, but by far the majority of cases even with treatment show periods of improvement followed by relapse ending eventually in death as a direct result of the disease.

Oliver (Practice of Medicine 1895 p. 731) gives details of 17 cases observed by him. Of these he says 4 are now under observation 2 of these having recovered with arsenic. 4 other cases which were post-partum recovered. 2 cases were lost sight of. The remaining 17 are dead.
Pye Smith (Guy's Hospital Reports Vol. 21, p. 379) gives analysis of 9 selected cases. In 65 cases reported by Biemer and Hagenrin at Zurich 4 cases recovered. In 27 collected by Richart, 2 recovered. In 94, when there was a predisposing cause and which were recorded as secondary to this cause, only 6 recovered.

Tabot (Amer. Journ. Med. Science 1900 Vol. 120) gives analysis of 79 cases out of 110, which were followed to a finish. The majority have lasted less than 2 years. 12 lasted more than 3 years and only 2 more than 4 years, the longest living 5 years. 12 were alive at the time of writing. 8 of these were going rapidly downhill. Of 4 Little was known. 14 were lost sight of the majority getting worse when last heard from.

In my own cases I have not been able to determine that there is any
feature in the physical signs or examination of the blood which would indicate a more favourable prognosis in some, than in others.

The response to the treatment by arsenic as well as the tolerance to the drug might be taken as affording some ground for prognosis, for those cases which eventually recover, temporarily at least and keep well for a considerable time, either with a continuance of the treatment or without, respond as a rule quickly and decidedly to arsenic and tolerate it well, whereas those which do not tolerate arsenic and do not begin to improve soon after its administration seem to become rapidly worse no matter what treatment is adopted.
Treatment

Rest in bed with careful regulation of the diet is essential. Nitrogenous food, or any rate at the beginning of treatment seems best to be borne well. The stomach and bowels may require attention before medicinal treatment of the disease proper is begun.

A very large number of drugs have been recommended in Pernicious Anaemia but scarcely do any of them seem to do more than effect a temporary improvement.

Iron which acts so well in chlorosis hardly ever seems to have any effect in Pernicious Anaemia although some cases are reported as having benefited by it. Thus Weeks (Hancox 1885, Vol i p. 563) reports recovery from the disease with iron.

Finlay (Hancox 1885 Vol. 7 p. 374) also reports...
a recovery with iron.

Phosphorus has been tried but has proved ineffective (Bradbury and Eichhorst).

Bone Marrow introduced by Professor Fraser in 1894 (B. M. J. 1894 Vol. i) when he reported recovery of a case with bone marrow after fe and arsenic had been tried) does not seem to be so efficacious as was at first supposed. Barr (B. M. J. 1895 Vol. i p. 358) reported case in which arsenic failed and bone marrow effected a recovery. Most other observers have not met with much success in the use of bone marrow.

The Antiseptic Treatment founded on the theory that the disease is due to toxins absorbed from the alimentary tract has met with considerable success. Various antiseptics have been used. The chief are the following.

Bismuth Salicylate which has been used with some success by several observers.
Salol. Case 8 of my series benefited slightly by the use of this drug after arsenic had been given a fair trial and had failed.

Beta-Naphthol. Gibson (13. 11. 32 July 16) reported recovery with this given in 2 grain pills three daily.

Arsenic introduced by Byron Bramwell in 1844 (Edin. Med. Jour. 1874 Vol. 23 p. 408) which probably acts both by its antiseptic properties and by stimulating haemorrhage seems to have been by far the most successful of the remedies introduced. The majority of the recoveries reported have been due to this drug and it is a question whether the disease cannot be kept completely under control if the proper dose of arsenic is constantly taken. That this drug however can completely cure the condition seems unlikely and although most cases show marked temporary benefit with its use, relapses almost invariably follow when it is discontinued.
Bramwell recommends it to be given as Tincture Arsenical in small doses three daily, gradually increased. He generally begins with ⅛ Minim three daily and increases each dose by ⅛ Minim every three days. Most cases show a peculiar tolerance of the drug in this form and large doses may be reached without any signs of arsenical poisoning.

Barr reports two cases of arsenical keratitis from its use (B. M. J. 1895 vol. 1 p. 358 and B. M. J. 1898 vol. 2 p. 234).

Henry (Amer. Jour. Med. Sci. 1895 vol. 120) also reports a case in which it produced keratitis and pigmentation of the skin.

All my 9 cases were treated with arsenic given according to Bramwell's method. Case I showed improvement for a time and then relapsed, the relapse following
the stoppage of arsenic because of other complications.

Cases iv, v, vi, and ix showed distinct improvement while under treatment.

Case iii died soon after coming under observation.

Cases vii and viii showed no improvement but rather a steady decline while arsenic was being used.

It has been remarked by several observers that the possible maximum of red cells in pernicious anaemia seems to be a low one as patients express themselves as feeling quite well with perhaps 2,500,000 red blood corpuscles present.

Many cases are certainly remarkable in expressing themselves as feeling very well when the blood count is still very low. Several of my cases said that they felt well enough to go home when the red blood corpuscles numbered only 1,500,000.
Hunter recently, because of his belief that the disease is an infective one localized to the alimentary tract and that the site of infection is often through carious necrotic teeth, has strongly advocated careful attention to the mouth by extraction of badly carious teeth and washing the mouth with some antiseptic such as weak carbolic acid solution. He also recommends antiseptics internally, preferably Perchloride of Mercury. After improvement has set in by the use of these means he recommends gradually increased doses of Biogen Arsenical. He and other observers have met with marked success by the use of this treatment in several cases and the standard reached by the blood has been much higher than in any other method. Thus among others Hunter has reported a case (B.M.J. 1901 Feb. 16) in which recovery followed oral and gastric antiseptics (chiefly with carbolic acid etc.).
for the mouth and Perchloride of Mercury (internally in three doses) combined with injection of antistreptococcus serum. For the first three weeks only the above treatment was used and decided improvement occurred but this latter being slow the patient was put on Resin and Arsenic with the result that in some month the red blood corpuscles had increased from 24% to 85% and the Haemoglobin from 33% to 10.6%.

He reported another marked result in the April 9, 1901 March 30th, where with the same treatment for 4 months, arsenic having been given for about the last 2 months, the red blood corpuscles increased from 1150,000 to 4,450,000 and the Haemoglobin from 35% to 104%.

Other observers have also met with success by adopting this treatment. E. E. Last (Harcet 1900 Vol. II p. 1191) reports a case of recovery from injection of antistreptococcus serum and soda and
Blood transfusion and saline injections have been strongly recommended by some but have now practically been given up as ineffective.


Apleck (B. M. J. 1892 Vol. 5 p. 10) reported a case improved by this treatment.

Many other workers have tried blood transfusion but have found as a rule that only a slight and very temporary improvement results.

Some cases have recently been reported as greatly benefited by Hommel's Haemogen. Thus Herbert Meggitt (Fancer 1900 Vol. II p. 28) records two cases greatly improved by its use.
Notes of nine cases of Pernicious Anaemia

Cases I, II, III and IV came under my observation in the Royal Infirmary, Dundee and cases V, VI, VII, VIII and IX in the Royal Infirmary, Edinburgh.
Cases

Case 1

Name  Mary Ann Dunn
Age    44
Occupation  Jute spinner
Address  174 Evergate, Dundee
Married
Admitted Nov. 27, 1899
Discharged Jan. 16, 1900

Complaint: Weakness; symptoms of Anaemia
Duration: 3 years

History of Present Illness: 3 years ago just after the menopause patient began to be troubled with a feeling of weakness and fatigue after exercise which also produced shortness of breath and perspiration. Legs began to swell at end of day. Had diarrhea for first year of illness. Since then bowels have been constipated 6 or 7 times. Severe pain in abdomen. Bowel movements have been irregular. Symptoms of anaemia have gradually become more marked. Has been troubled occasionally with vomiting and flatulence. Abdomen has been considerably swollen during last fortnight. Has had
numbness in legs for last few months. No history of jaundice.

Present History: Unimportant.

Family History: The brother died of "hip joint" disease when young. Mother died after a long illness in which there was loss of power in legs.

Otherwise unimportant.

Social History: Has always had good home. No alcoholic history.

Present condition: Skin of body and face very pale and has yellowish tint. Mucous membranes very anaemic. Subcutaneous fat well preserved all over. Subconjunctival deposit of fat on both sides of each eye. Has heavy Corneal coats. Slight oedema of tissues of face of legs.

Haematological System

Red blood corpuscles = 1,200,000.

White "" = 3,000.

Hæmoglobin = 34%.

Muscular System

Pulse 80, regular. Volume moderate: tension low.
Heart: Atelectasis not visible nor palpable.

No bulging nor pulsation anymore.

Percussion: Upper border at upper border of 3rd rib.
- Right: 1 1/2 to right of mid-ster nal line.
- Left: 4 1/2 to left of mid-line in 5th space.

Ascites: Skin area 1st round replaced by a faint blowing diastolic murmur propagated towards axilla. 2nd round accentuated.

Aortic Area: 1st round, the 2nd slightly accentuated.

Pulmonary: as in aortic

Respiratory System: Healthy.

Alimentary System: Appetite fairly good.

Flatulence: occasional vomiting; stools constipated.

Tongue: large, moist, clean, and glazed.

Abdomen: prominent from fat and flatus.

No tumours felt.

Tuber: upper border at 4 1/2 to mammary line.

Tuber: lower border at costal margin...

Spleen: shows no sign of enlargement.

Stomach: not dilated.
Nervous System: numbness of leg and slight difficulty in walking.
Objectively normal except that there are some haemorrhages in fundus of both eyes.

Genito Urinary

Urine: dark amber in colour; acid; S. G. 1016.
Deposit of uric acid.
No albumin.
No sugar.

Fibrous blood show: Abnormal red cells, hyperchromatic, absence of concave depression, no micropus, but macroagglutination; pericolytes, normoblasts and myeloblasts were present. They also showed polyplastic degeneration of certain of the red corpuscles. Patient was constantly diurnal and stomach to:

Towels, thought into orders with Magnesium Phosphorous and Bismuth Carbonate and Tannate at night.
She was then put on high arsenical; him tis and gradually increased.

January 7th: taking his arsenical b 1/2. Doe not
Feel is well today. Has pain in legs from middle of calves downward. Breathing for last two nights. Has had some diarrhoea since Dec. 24. Knee jerks not elicited. Some oedema of face and legs. Albumin omitted.

January 16 Discharged. Patient is determinate. Highly since last note and blood test failure. Has never had any inflammatory condition of the mouth while under observation. During period under observation he has had occasional slight rise of temperature lasting for 4 or 5 days at a time.

Details of Examination of the Blood

<table>
<thead>
<tr>
<th>Date</th>
<th>White Blood Corp.</th>
<th>Red Blood Corp.</th>
<th>Hb.</th>
<th>Colour Index</th>
<th>Lipid, Ammonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov. 27, 99</td>
<td>3,000</td>
<td>1,200,000</td>
<td>37%</td>
<td>1.4</td>
<td>H ++ F. + id</td>
</tr>
<tr>
<td>Dec. 15, 99</td>
<td>4,000</td>
<td>1,300,000</td>
<td>38%</td>
<td>1.3</td>
<td>H ++ F. + id</td>
</tr>
<tr>
<td>Dec. 16, 99</td>
<td>4,000</td>
<td>1,500,000</td>
<td>40%</td>
<td>1.1</td>
<td>H ++ F. + id</td>
</tr>
<tr>
<td>Jan. 4, 99</td>
<td>5,200</td>
<td>2,000,000</td>
<td>50%</td>
<td>1.1</td>
<td>H ++ F. + id</td>
</tr>
<tr>
<td>Jan. 16, 99</td>
<td>4,000</td>
<td>1,400,000</td>
<td>40%</td>
<td>1.2</td>
<td>Lipid increased since Jan. 4</td>
</tr>
</tbody>
</table>

Normoblasts and megaloblasts were found at practically every examination.
Case II

Name Margaret Cooper.

Age 47.

Occupation Housewife.

Address 225 Overgate, Dundee.

Married.

Admitted January 20, 1900.

Discharged April 30, 1900.

Complaint Weakness, symptoms of anaemia.

Duration About 4 years.

History of Present Illness

About 4 years ago patient began to be troubled with slight symptoms of anaemia on exertion. Since that time symptoms of anaemia have gradually increased and now she feels extremely weak and the least exertion causes breathlessness and palpitation. She has noticed that she has been getting very pale. She has never had throughout her illness any vomiting or diarrhoea until a few weeks ago. Recently she has had slight diarrhoea associated occasionally with blood in the stools, sometimes as much as half a tea-cupful and red in colour. Has never been jaundiced.
Previous History. Was always quite healthy up to onset of present illness. Menstruated regularly up to a year ago and has seen nothing since.

Family History. Unimportant.

Social History. Unimportant.

Present Condition.

Patient looks fairly well nourished. The subcutaneous fat is very well preserved. She is very anaemic and skin has lemon yellow colour. Has well marked subconjunctival deposit of fat on both sides of each eye.

Haemopithec System

Red blood corpuscles = 1,000,000
White ... = 3,000
Haemoglobin = 20%.

Fibre showed defective haemopoietic formation, absence to a large extent of concave appearance, megalocytes, polychromatophils, primoblasts and megaloblasts. They also showed polychromatophili degeneration.
Circulatory System: Pulse 112, regular in time, volume small, volume and low tension.

Heart: A. R. 4½" to left of mid-ternal line in 5° space.

Pericardial: Right border 2½" to right of mid-ternal line; left border 4½" to left.

Ascites: Soft systolic thrill following 1st sound ale over precordia.

Ventricular Trile at lower part of neck.

Respiratory System: Shows slight bronchitis.


Tongue: Fairly healthy coating. Does not show any pathological appearance.

Abdomen: No tension palpable. Some tenderness on palpation over stomach just below ensiform cartilage.

Liver: Upper border at 4th space in mammary line. Lower border 2" below costal margin in mammary line.
Spleen not enlarged.
Stomach not dilated.
Nothing abnormal made out in rectum.

Nervous System

Eye: Plane shaped haemorrhage at cornea and outer part of left optic disc.
No other abnormalities.

Urine: Pale amber in colour.
Acid.
S. G. 1020.
No deposit.
No albumin.
No sugar.

Patient was put on Fij. Absinificial and muriatic acid was gradually increased until forty tablets were being taken three daily. At this stage Feb. 25th she began to show signs of abscess forming and absinthetic was discontinued with the result that she cut ground somewhat.

Patient never had any fever while under observation.
She never had any inflammatory condition of the
Urine was never dark in colour and never showed deposit of uric acid. Occasionally it showed a trace of albumin.

**Details of Examination of the Blood**

<table>
<thead>
<tr>
<th>Date</th>
<th>White Blood Corf</th>
<th>Red Blood Corf</th>
<th>Hb.</th>
<th>Colour Index</th>
<th>Tg. Antimoni</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan. 20</td>
<td>3000</td>
<td>1,000,000</td>
<td>20%</td>
<td>.9</td>
<td>In ½ t.i.d.</td>
</tr>
<tr>
<td>Feb. 25</td>
<td>5000</td>
<td>2,500,000</td>
<td>50%</td>
<td>.9</td>
<td>In ½ t.i.d.</td>
</tr>
<tr>
<td>April 23</td>
<td>4000</td>
<td>1,600,000</td>
<td>40%</td>
<td>1.2</td>
<td>Arsenic omitted since Feb. 28</td>
</tr>
</tbody>
</table>

Films were made at each time of counting, and microcytes, macrocytes, polymorphs, normoblasts, and megaloblasts were always found.
Case III

Name: James Cooper.
Age: 30.
Occupation: Labourer.
Address: Dundee.
Single.
Admitted: Jan 26, 1900.
Died: Jan 27, 1900.

History of Present Condition: Patient was admitted in a very drowsy condition and could only answer simple questions. From a neighbour it was ascertained that for some months he had been very weak and unable to work. Three days before admission he had taken to bed and had gradually fallen into the condition in which he was when admitted.

Present Condition: Patient is extremely pale and mucous membranes very anaemic. Skin has a yellowish tint. Subcutaneous fat well preserved and he looks fairly well nourished. There is no depot of fat beneath conjunctiva. He is restless and slightly delirious at times.
Fawed frequently. No oedema anywhere. Vomited a little after admission.

**Haemopoietic System**

<table>
<thead>
<tr>
<th>Date</th>
<th>White Blood Cells</th>
<th>Red Blood Cells</th>
<th>Hb.</th>
<th>Colour Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan. 26 1900</td>
<td>7,000</td>
<td>900,000</td>
<td>20%</td>
<td>1</td>
</tr>
</tbody>
</table>

**Circulatory System**

Pulse 112 regular in time and force.

Volume ample: tension low.

Heart: Apex Beat in 5th left space 6½ to 7th mid line.

Percussion shows heart to be slightly enlarged the left border being 4½ to 6th mid line in 5th space.

Ascendation: Systolic thrill following 1st sound all over the precordia.

1st sound over sternum sharp and clicking.

Respiratory System: Healthy.

**Alimentary System**: Slight vomiting; no diarrhea.
Tongue pale and clean. Does not show abnormal smoothness.

Abdomen rather prominent. No pain on palpation. No tumour.

Liver not enlarged.

Spleen enlarged and easily palpable.

Anus not dilated.

Nervous System shows nothing abnormal except impaired intelligence.

To haemorrhages in fundi of eyes.

Urinary System:

There is incontinence of urine.

Urine: Pale amber in colour

Specific gravity: 1025

No albumin

No sugar

No deposit

Fresh specimen of blood shows absence of nucleated red blood cells, polychromatophilia, macrocytes.

Stained films show normoblasts and megablasts.
After admission patient gradually sank and

died about twenty hours after admission.

Post-mortem report --- see section on Morbid

Anatomy.
Case IV

Name: Mrs. Agnes Balmeri
Age: 35
Occupation: Housewife
Address: Grange St. Soutdy, N. Dundee
Married
Admitted: Feb. 3, 1902
Discharged: March 14, 1902

Complaint: Weakness, breathlessness, and palpitation on exertion.
Duration: About 3 years.

History of Present Illness:
3 years ago patient had a child three weeks before full time. Child was still-born. She lost blood heavily at the time but recovered and was going about a month afterwards. Three weeks after she got up she took "while swelling" on her leg which laid her up for some months. From this time she dates her anemia as she now began to be troubled with shortness of breath and palpitation on exertion. Symptoms of anemia have gradually increased and she has become very weak for the last four months.
She has practically been confined to bed. She has had attacks of diarrhoea now and then throughout her illness. No vomiting throughout whole illness. Has also had occasionally pain in back and swelling of face, hands and legs. Had baby 6 weeks ago and since that has been very much weaker. The child was born three weeks before full term and died when 5 weeks old. No history of jaundice.

Previous History 16 years ago had "drooping" with haematemesis. Recovered completely from this and remained fairly well until onset of present illness.

Family History Unimportant.

Social History Has always had comfortable home.

Present Condition Patient is extremely anaemic and skin has lemon yellow tinge. Subcutaneous fat well preserved and there is well marked subconjunctival deposit of fat on both sides, jowls.
Slight oedema of lower part of both legs. 

Left leg thicker all over than right leg - result of white leg 3 years ago.

**Haemopoietic System**

Red blood corpuscles = 1,100,000.
White " " = 6,000.
Haemoglobin = 25%.

Fresh specimen of blood shows deficient haemocytoblast formation, absence of concave depression, also poikilocytes, microcytes, macrocytes.

Stained films show normoblasts and megaloblasts, and polychromatophilic degeneration.

**Circulatory System**

- Pulse 100 per minute: Regular in time and force.
- Volume moderate: Systolic low.
- Heart Apex beat in 5th left intercostal space 4" from the mid line. It is feeble and limited.
- Percussion: Upper border at 3rd rib.
  - Right border 1" to right of midternal line
  - Left border 4 1/4 to left of mid line in 5th space.
Auscultation: 1st sound followed by a soft thrum all over precordia.
2nd sound reduplicated at base and over sternum.

Respiratory System shows nothing abnormal.

Alimentary System: No abdominal symptoms.
Bowels regular at present.
Tongue pale and shows slight white fur or dorsum not abnormally smooth.

Abdomen somewhat prominent.
No pain on palpation, no tumour felt.

Percussion note resonant all over.

Liver upper border at 5th rib in mammary line.
Lower border 1" below costal margin in mammary line.

Spleen: Girth increased. It is easily palpable well beyond the margin of the ribs.

Urine. Amber in colour.

Acid.
S. G. 1022.

Faint trace of albumin.
No sugar.

Slight deposit which shows some degenerated leucocytes, desquamated epithelium and a few hyaline casts.
No uric acid.

Put on Tincture Arsenie 1/2 in three daily.
To be increased by 1/4 per dose every three days.

Feb. 6 Urine shows no albumin, no casts.

Feb. 14 Has had attack of pyrexia for last four days, temperature never rising above 100° F.

Feb. 22 Temperature has been normal for a week. Symptoms of anaemia especially giddiness much abated.

March 2 Tinct. Arsenie omitted owing to tendency to diarrhoea.
March 12. No diarrhoea since March 6.


During residence in Hospital patient has had no jaundice and no inflammatory mouth condition.

Details of examination of the blood

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb. 4</td>
<td>6,000</td>
<td>1,150,000</td>
<td>25%</td>
<td>1</td>
<td>Pr. tric.</td>
</tr>
<tr>
<td>Feb. 14</td>
<td>7,000</td>
<td>1,500,000</td>
<td>30%</td>
<td>9</td>
<td>Pr. tric.</td>
</tr>
<tr>
<td>Feb. 22</td>
<td>4,000</td>
<td>1,800,000</td>
<td>35%</td>
<td>9</td>
<td>Pr. tric.</td>
</tr>
<tr>
<td>March 2</td>
<td>6,500</td>
<td>2,000,000</td>
<td>45%</td>
<td>1</td>
<td>Pr. tric.</td>
</tr>
<tr>
<td>March 7</td>
<td>6,000</td>
<td>1,900,000</td>
<td>45%</td>
<td>1</td>
<td>Pr. tric.</td>
</tr>
</tbody>
</table>

Frequent films were made and almost always monocytes and histiocytes were found as well as microcytes, macrocytes, and poikilocytes.
Case V

Name: Christine Muirhead.
Age: 37.
Occupation: Housewife.
Address: 47 School St., Cowdenbeath.
Married.
Admitted: May 24, 1900.
Discharged: July 17, 1900.

Complaint: Great weakness: symptoms of anaemia; diarrhoea; darkening of the skin.

Duration: 6 months.

History of Present Illness: About 6 months ago, soon after an attack of influenza, she began to be troubled with symptoms of anaemia. Up to this time she had always had a ruddy complexion, but now she began to get pale. Diarrhoea came on soon after and has continued off and on since. She has also had since illness began, frequent attacks of vomiting. Symptoms of anaemia have steadily increased. About a month after illness began, skin of face and some parts of body...
showed pigmentation and since that darkening has gradually become more marked. She has had no attacks of jaundice and no attacks of inflammation about the mouth. Has menstruated twice in last 6 months. Before this menstruated regularly.

Previous Health Has had tendency to diarrhoea all her life but otherwise has always enjoyed good health. Has had bad teeth since 22 years age.

Family History One brother died of "consumption." One brother died of cancer of the throat. One sister died from a discharging sore of the back.

Patient has had two children. Both are alive and well.

Social History Unimportant.

Present Condition Patient is thin, delicate looking and markedly anaemic. There is no deposit of
At beneath the conjunctiva

There is a dark pigmentation around eyes or forehead and temple. No pigmentation in the mouth.

Pigmentation also of neck and front of chest, especially over the sternum.


Temperature 100°.

Haemoglobin

Red blood corpuscles = 4,00,000.

White blood corpuscles = 2,500.

Haemoglobin = 15.0%.

Fresh specimen of blood shows imperfect red cell formation. Diminished number of red cells showing concave depression. Also microcytes, macrocytes, and poikilocytes.

Stained films show normoblasts and megaloblast, and polychromatophilic degeneration.
Circulatory System
Pulse 100. Regular in time & force.
Volume moderate : tension Cnv.

Heart: Apex beat in 5" left interface 4" from mid sternal line.
Percussion shows slight right enlargement of the heart both to the right and left side.
Auscultation: Soft systolic murmur following 1st sound heard all over the precordia.
2nd sound reduplicated in the pulmonary area.

Respiratory System: Healthy.

Alimentary System: Appetite poor.
Vomiting and diarrhhea as in history.

Tooth: large, moist and very pale. Not abnormally smooth.
Tooth are very carious all over.

Abdomen: not distended.
No pain on palpation : no tumour felt.
Liver. Upper border at 5 cm. in mammary line. 
Lower border 1" below costa1 margin in 
the mammary line and reaches to 
within 2" of umbilicus in middle line.

Spleen. Easily palpable beyond the costa1 
margin.

Stomach. Normal.

Nervous System. Shows no abnormality. 
No RETINEL Haemorrhages.

Urine. Dark in colour. 
Acid. 
S. G. 1022
No albumin.
No sugar.
Deposit of mucous, vaginal epithelium and uric acid.

June 13th. Patient soon after admission was 
put on lhr. Arsenical: thrice daily and 
now taking Mix t.i.d. Says she 
feels much better. Stomach and 
bowels now cause no trouble. 
2nd day after gum frozen with Iodine Chloride 
the central and lateral incisors of the lower
Jaw were extracted. Not much bleeding followed. Gum a good deal torn.

June 14. Thinn shows ecchymosis evidently as a result of extraction of teeth yesterday. Whether it is due to blood penetrating through from the gum or to subcutaneous bleeding from pressure on the chin it is difficult to say.

July 14. Discharged. Patient now taking 1g. of arsenic in 10th drop of water daily without any bad symptoms. Feels very much better. Has not had any inflammatory condition of the mouth while under observation. During residence in hospital patient has had two attacks of pyrexia temperature never rising above 100°. Each lasted about 5 days.
Details of Examination of the Blood in Case V

<table>
<thead>
<tr>
<th>Date</th>
<th>White Blood Count</th>
<th>Red Blood Count</th>
<th>Hb.</th>
<th>Color Index</th>
<th>Leg. Arsenate</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 25, 1910</td>
<td>2,500</td>
<td>900,000</td>
<td>18%</td>
<td>.75</td>
<td>h vi r. i. d.</td>
</tr>
<tr>
<td>June 12, 1910</td>
<td>2,500</td>
<td>1,400,000</td>
<td>28%</td>
<td>.9</td>
<td>h ix r. i. d.</td>
</tr>
<tr>
<td>June 20,</td>
<td>2,900</td>
<td>1,700,000</td>
<td>40%</td>
<td>1</td>
<td>h xiv r. i. d.</td>
</tr>
<tr>
<td>July 3</td>
<td>3,000</td>
<td>1,800,000</td>
<td>45%</td>
<td>1.1</td>
<td>h xvi r. i. d.</td>
</tr>
<tr>
<td>July 14</td>
<td>3,000</td>
<td>1,900,000</td>
<td>50%</td>
<td>1.1</td>
<td>h xvi r. i. d.</td>
</tr>
</tbody>
</table>

Frequent examinations of films showed hemoblasts and megaloblasts always present.
Case VI

Name: Christina Robertson
Age: 62
Occupation: Housewife
Address: Melville Road, Ladybank, Fifeshire
Married
Admitted: June 4, 1900
Discharged: July 11, 1900

Complaint: Weakness; attacks of vomiting and diarrhoea; palpitation and breathlessness on exertion; giddiness.
Duration: About 8 months.

History of Present Illness:
About 8 months ago patient began to feel weak and unfit for her household work. No cause for this except extra work in removing. She began to get pale whereas before she had had a good deal of colour. Symptoms of anaemia became gradually evident and now she had great shortness of breath and palpitation on exertion.
Two months after onset of illness she seems to have had an attack of jaundice.
was yellow, face was rather pale and
urine was very dark in colour.
Jaundice lasted about four
months. There was no pain about the
liver during this attack. She has been
so weak during the last 6 months that
she has practically confined to bed.
She has had attacks of diarrhoea and
vomiting for about 6 months.
Has been treated with arsenic for several
months and lately two feet have been
swollen. No soreness or inflammatory condition of
month before this.

Previous History 16 years ago had "inflammation
of the liver." Had similar attacks
for a year or two afterwards.
Rheumatism in muscles 7 years ago
and rheumatic pains in joints for
last year or two.
No history of Haemorrhage.

Family History Unimportant.
Social History Unimportant.
Present Condition: Patient is very pale and mucous surfaces are very anaemic. Face has a yellowish tinge. Subcutaneous fat well preserved and there is a subconjunctival deposit of fat at the outer aspect of each eye.

Haemopoietic System

Red blood corpuscles = 900,000
White blood corpuscles = 2,800
Haemoglobin = 26%

Fresh specimen of blood shows diminished RBC formation, diminished number of red corpuscles showing concave appearance. It also shows microcytes, macrocytes and poikilocytes.

Stained films show normoblasts and megaloblasts. They also show polychromatophilic degeneration.

Circulatory System

Pulse: 110 regular in time and force. Volume small, tension medium.

Heart: Apex beat is 5" left of and 3 3/4" from midline.
Percussion does not show any appreciable enlargement of the heart.

Auscultation: Both sounds heard over precordia. There is a faint vesicular murmur in the mitral area.
Venous hum in neck.

Respiratory System: Healthy.

Alimentary System:
Apathy from dyspeptic symptoms at present. Vomiting described in history was without cause. Attacks of vomiting generally lasted about two days at a time. Diarrhoea generally followed the vomiting and at intervals of a week or two. There was abdominal pain connected with the diarrhoea. Stools watery and light in colour.

Tongue clean and less pale than one would expect.

Teeth: Small and widely set. Worn away at edges. gums somewhat receding to marked caries. Good for her age.
The small stump.

Abdomen not distended. No tumour, no tenderness.

Luien not enlarged.
Spleen not enlarged.

Lunach not enlarged.

Contents contain no hydrochloric acid.

Nervous System: show no abnormality.

Fundus pata. No retinal haemorrhage.

Urine: Dark amber in colour.

Acid.

S. G. 1012.

Trace of albumin.

No sugar.

No C. u.

Slight deposit of granular debris and leucocytes.

No tube casts.

Deposit of uric acid.
June 10  Patient put on Fig. Arsenical in i. t. i. d. and dose to be increased ev. 3 days.

June 26  Patient feeling and looking much better. Muscous surface and face. Has only vomited twice since admission. No diarrhoea since admission.

July 11  Discharged. Patient much improved. Now taking in Fig. Arsenical t. i. d.

Had no attack of jaundice nor inflammatory condition of mouth while under observation. Had one attack of pyrexia lasting 3 days. Temperature rose to 101°.

**Detailed examination of the Blood**

<table>
<thead>
<tr>
<th>Date</th>
<th>White blood corpuscles</th>
<th>Red blood corpuscles</th>
<th>Ht.</th>
<th>Colour Index</th>
<th>Fig. Arsenical</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 5</td>
<td>2,800</td>
<td>900,000</td>
<td>26%</td>
<td>1.3</td>
<td>h i ve t. i. d</td>
</tr>
<tr>
<td>June 12</td>
<td>3,800</td>
<td>1,130,000</td>
<td>28%</td>
<td>1.1</td>
<td>h i ve t. i. d</td>
</tr>
<tr>
<td>. 19</td>
<td>3,000</td>
<td>1,140,000</td>
<td>30%</td>
<td>1.1</td>
<td>h i ve t. i. d</td>
</tr>
<tr>
<td>. 26</td>
<td>3,000</td>
<td>1,140,000</td>
<td>33%</td>
<td>1.3</td>
<td>h IX t. i. d</td>
</tr>
<tr>
<td>July 4</td>
<td>3,125</td>
<td>1,350,000</td>
<td>40%</td>
<td>1.3</td>
<td>h XI t. i. d</td>
</tr>
<tr>
<td>. 11</td>
<td>3,000</td>
<td>1,500,000</td>
<td>45%</td>
<td>1.3</td>
<td>h XII t. i. d</td>
</tr>
</tbody>
</table>

At each count films were made and hameoblasts and megaloblasts were found at nearly every examination.
Case VII

Name: Andrew Brown
Age: 38
Profession: Gardener
Address: 29 S. Junction St. Leith

Married
Admitted: July 17, 1900
Died: August 14, 1900

Complaint: Great general weakness; well marked symptoms of anaemia
Duration: About 4 years

History of Present Illness
About four years ago patient began to feel unfit for work, being easily fatigued and having shortness of breath and palpitation on exertion. He also began to get palpitation. He was treated for bloodlessness and got considerably better but did not quite regain his original good health. Since that time he has had several similar attacks each attack being worse than the previous one. The present attack from which he is now...
Suffering began about 10 months ago and in spite of treatment he has gradually been getting worse. He has had no trouble with stomach or bowels throughout the whole 4 years. Feet have not been bad until lately and patient blames the medicine he was taking for this. He has had no inflammatory condition of the mouth and no jaundice. Illness began without any cause so far as he knew. No history of haemorrhage.

Previous History. Has never had any serious illnesses.

Family History. Unimportant.

Social History. Unimportant.

Present Condition. Patient is very anaemic and skin shows a lemon yellow tint. Subcutaneous fat well preserved. Slight conjunctival deposit of fat on both aspects of each eye.
Seems very weak and languid.
Temperature 99°

**Haemopoietic System**

Red blood corpuscles = 1,450,000
White blood corpuscles = 4,500
Haemoglobin = 30%

Fresh specimen of blood shows deficient rouleaux formation, diminished number of red corpuscles showing concave appearance, microcytes, macrocytes and poikilocytes.

Stained film shows normoblast & megaloblast. They also show polychromatophilic degeneration.

**Circulatory System**
Pulse 100 regular in time & force.
Volume small; tension rather low.

Heart apex beat in 5th left space 4½ from mid sternal line.

**Percussion**
Upper border at 3rd rib.
Right border at 1½ breath midline.
Left border 4½ to 5½ left mid line in 5th space.
Auscultation. There is a soft lethic murmure following a faint sound all over the precordia. Venous hum in neck.

Respiratory System -- Heathy.

Alimentary System

No dyspeptic symptoms.

Boeds tend to be constipated.

Tongue: large, moist, pale, and has a distinctly glazed appearance.

Teeth: are good for his age. There are however one or two very carious teeth in both upper and lower jaws.

Abdomen: not distended.

No tumour palpable in tenderness anywhere.

Liver: not enlarged.

Spleen: not palpable.

Stomach: not dilated.
Nervous System shows no abnormality.
No Retinal Haemorrhages.

Urine

Dark amber in colour.
Acid.
S. G. 1014.
Distinct deposit of albumin.
No sugar.
No bile.
No tube casts.
Slight deposit of urine acid.

Just after admission patient was put on tie. Assaulted in usual way and this was gradually increased until he had two attacks. He never however showed any improvement but gradually became weaker and weaker and died on August 14. While in hospital he had occasional vomiting and diarrhoea. Also had 3 attacks of pyrexia, temperature rising to 100.6°F. on one occasion but never higher. Attacks lasted on the average about 6 days. He had no attacks of
Jaundice while under observation and no inflammatory condition of the mouth.

**Detailed examination of the Blood**

<table>
<thead>
<tr>
<th>Date</th>
<th>Red blood corpuscles</th>
<th>White blood corpuscles</th>
<th>Hb.</th>
<th>Colour Index</th>
<th>Ty.</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 19, 1910</td>
<td>1,450,000</td>
<td>4,500</td>
<td>30%</td>
<td>1.03</td>
<td>h x T. i.d.</td>
</tr>
<tr>
<td>July 27</td>
<td>1,400,000</td>
<td>4,000</td>
<td>30%</td>
<td>1.07</td>
<td>h x T. i.d.</td>
</tr>
<tr>
<td>Aug. 4</td>
<td>1,200,000</td>
<td>3,500</td>
<td>28%</td>
<td>1.1</td>
<td>h x T. i.d.</td>
</tr>
<tr>
<td>Aug. 13</td>
<td>1,100,000</td>
<td>3,500</td>
<td>28%</td>
<td>1.2</td>
<td>h x T. i.d.</td>
</tr>
</tbody>
</table>

Frequent examination of films showed normoblasts and regaloblasts to be present during the whole time.
Case VIII

Name: Alexander Gee.
Age: 31.
Occupation: Waggon Repairer.
Address: 14 Main St. Hill of Beatt, Tyne.
Single.
Admitted: July 19, 1900.
Discharged: ?

Complaint: Weakness; marked symptoms of anaemia.
Duration: About 1 year 10 months.

History of Present Illness: In September 1898 patient had a severe attack of diarrhoea. A month or two after this he began to grow pale and had symptoms of anaemia on exertion. Diarrhoea continued pretty bad off and on until February 1899. In January 1899 skin became yellow and continued so all that year. In June 1898 he again had severe attack of diarrhoea which lasted 14 weeks. He was steadily getting weaker...
and more anaemia. Since onset of illness he had occasionally had vomiting. The attacks generally lasting two or three days. In January 4, 1900 he was admitted to the Royal Infirmary, Edinburgh. He was treated with arsenic and improved considerably. He continued fairly well until April of the year when symptoms of anaemia again became marked and since then he has gradually become more anaemic and much weaker. He has from time to time had attacks of epistaxis some of these being very severe. He has not had any inflammatory condition of the mouth.

Previous History Before onset of the present illness he had had occasionally "gloomy attacks" with vomiting.

Family History Unimportant

Social History Unimportant
Present Condition

Patient is extremely anaemic. He seems very weak and is hardly able to move about in bed. Skin of face has lemon-yellow colour. Subcutaneous fat well preserved and there is a subconjunctival deposit of fat on both sides of each eye.

Hæmopoietic System

Red blood corpuscles = 1,300,000.
White " = 2,500.
Hæmoglobin = 33%.

Fresh specimen of blood shows defective Metheæna formation, diminished number of red cells showing concave depression. It also shows microcytes, macrocytes and poikilocytes.

Stained films show normoblasts and megaloblasts. Films also showed in a marked degree polychromatophilic degeneration.
Circulatory System

Pulse, 95, regular in time and force.

Volume moderate; tension low.

Heart

 Apex beat in 5" left space 4" from mid sternum line.

Percussion

Upper border at 2nd space.
Right border 1" to right midclavicular line.
Left border 4½" to left of midline in 5th space.

Acoustization

Both sounds heard all over precordia. Haemian murmur systolic in time following 2nd sound at all areas.

Respiratory System

Healthy.

Alimentary System

Appetite poor.

Vomiting and diarrhoea as in history.

Tongue

Large, pale and very smooth.

It shows great deal of fibrillary twitching.
Teeth

Lower jaw Right side 1st Bicuspid and 2nd molar absent
3rd molar carious; others good.

Left side 1st Bicuspid, 1st and 2nd molars absent.

3rd molar carious.

Upper jaw Right side lateral incisors and 1st bicuspid absent. 2nd and 3rd molars carious.

Left side 1st bicuspid and canine absent.

Lateral incisors and 2nd molar carious.

Abdomen Shows no abnormality.

Liver dullness not increased.

Spleen enlarged and palpable.

Stomach not dilated.

Nervous System Shows no abnormality.

There are small haemorrhages in each fundus.

Urine Dark amber in colour.

Acid.

S. G. 10 18.
Trace of albumin.
No sugar.
No casts.
Deposit of uric acid.

After admission patient was put on

Liq. arsenicosum 3 m. t. c. i.d.

Aug 9: Has severe vomiting and diarrhoea.

Put on nutrient enema, etc. Temperature up to between 100° to 102° F.

Aug 10: Last night patient became wildly delirious and had to be removed from the ward.

Aug 13: Readmitted to ward. Nervous system shows distinct affection — see reference to case under section on Nervous System.

Sept 29: Patient not to my observation. Patient showed no improvement under P. Arsenical; at any time. For the last few weeks he has been on
Isabel and is now showing some improvement.
Since late in August 18, patient has
several times had attacks of vomiting and
diarrhea. He has also had one or two
attacks of pyrexia, temperature on one
occasion rising to 102.5° F. He has
occasionally had slight attacks of
epistaxis and pain in bones all over
the body. Skin at one time showed
slight jaundice.
At present these nervous symptoms are
much improved.

Eventually some three months after
this date patient recovered sufficiently
to leave the hospital feeling
fairly well. He was treated
hetely on antiseptic mouth washes
Detailed Examination of the Blood
Case VIII

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>July 20th</td>
<td>2,500</td>
<td>1,300,000</td>
<td>33%</td>
<td>1.2</td>
<td>Ev. t.i.d.</td>
</tr>
<tr>
<td>&quot; 27</td>
<td>3,000</td>
<td>1,200,000</td>
<td>30%</td>
<td>1.2</td>
<td>Ev. t.i.d.</td>
</tr>
<tr>
<td>Aug. 6</td>
<td>4,000</td>
<td>1,160,000</td>
<td>30%</td>
<td>1.3</td>
<td>Ev. t.i.d.</td>
</tr>
<tr>
<td>Aug. 15</td>
<td>5,250</td>
<td>950,000</td>
<td>24%</td>
<td>1.2</td>
<td>T. erythroga</td>
</tr>
<tr>
<td>&quot; 23</td>
<td>6,000</td>
<td>800,000</td>
<td>20%</td>
<td>1.2</td>
<td>Solec</td>
</tr>
<tr>
<td>Sept. 4</td>
<td>5,000</td>
<td>900,000</td>
<td>25%</td>
<td>1.3</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot; 22</td>
<td>4,000</td>
<td>1,000,000</td>
<td>30%</td>
<td>1.5</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot; 29</td>
<td>4,000</td>
<td>1,100,000</td>
<td>30%</td>
<td>1.3</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

Frequent films were stained and except on one or two occasions normoblasts and megaloblasts were always found.


Case 18

Name: Elizabeth Burnett.
Age: 66.
Occupation: Housewife.
Address: 63 A. Cumberland St. Edinburgh.
Married.
Admitted: August 15th, 1900.
Discharged: September 26th, 1900.

Complaint: General weakness; vomiting; shortness of breath and palpitation on exertion.
Duration: About 2 years.

History of Present Illness: About 2 years ago, patient began to suffer from symptoms of anaemia and general weakness. Soon after this, she also began to have attacks of vomiting and diarrhoea. Symptoms of anaemia gradually increased and patient became very pale. About 8 months ago, skin began to get darker and colour has gradually deepened. Recently, she has lost a good deal of
Flesh and has become extremely weak, and breathless on the least exertion. Has had no arsenic from medical attendant. Has had an attack of jaundice but any inflammatory mouth condition.

Previous History. Has suffered from bronchitis for the last few years. Had influenza 5 years ago and again 3 years ago and thinks that hard work and attacks of influenza may have brought on present illness.

No history of Laemorrhage. Menopause at 50 – no discharge since.

All teeth extracted for headache when she was 21 years of age.

Family History Unimportant.

Social History Unimportant.
Present Condition  Patient is very anaemic.
Body is poorly nourished. No deposit
of fat beneath conjunctiva.
Dark rings around the eyes.
Neck, upper part of chest and back,
tower part of abdomen, groins, and
upper part of thighs are deeply
pigmented. There is no, or at
least very slight pigmentation of
the hands, forearms, feet or legs.
No pigmentation in the mouth.

About the middle of the chest in
front and rather more to the right
side of the sternum is a large
irregularly outlined white scar
about the size of the palm, with
a ring of dark pigment around.
This is the result of a keloid
applied to chest about 6 months ago.
The skin of the scar is very fine, scaly
and easily pinched up.
Haemopoietic System
Red blood corpuscles = 1,200,000
White blood corpuscles = 6,000
Haemoglobin = 30%

Fist blood specimen shows defective haemopoietic formation and diminished number of red cells showing a concave depression. It also shows macrocytes and poikilocytes.

Stained films show normoblasts and megaloblasts and also polychromatophilic degeneration.

Circulatory System
Pulse 110, regular in time and force.
Volume moderate, tension medium.

Heart. Apex beat in 5th left interspace
4½" to left of mid sternal line

Percussion. Upper border at 3rd r.h.b.
Right border 1" to right of mid-line.
Left border 5" to left of mid-line.
Line in 5th space.
Abdominal Bowel sounds normal.

Venous murmur in neck.

Respiratory System

Healthy.

Alimentary System

Appetite very poor.

Attacks of vomiting and diarrhoea as in history.

Tongue very pale and shows slight white fur on dorsum. It is not abnormally smooth.

Teeth are all absent in both upper and lower jaws.

Abdomen shows slight distension; there is some resistance in right
Hyphochondric region and in epigastrium probably from enlarged liver.

Liver: Upper border at 1st space in mammary line.
Lower border about 1/2 below costal margin in mammary line.

Splice: not palpable.

Stomach: not dilated.

Nervous System: shows no abnormality.
No urinary haemorrhages.

Urine: Dark amber in colour.
Acid.
S. G. 1018.
Trace of albumin.
No sugar.
No bile.
No casts.
Deposit of uric acid.
Just after admission patient was put on T.P. Arsenicals and has been on this since the dose being gradually increased.

September 25. Discharged. Looking and feeling very much better. She has had no vomiting and no diarrhoea since soon after admission. Has had one attack of pyrexia lasting for 5 days, the highest temperature being 99.8°F. Has not had any jaundice or inflammatory mouth condition while under observation.

Urine has remained dark in colour practically all along and there has been a deposit of uric acid frequently. There has been a trace of albumin occasionally but never any casts.

Detailed examination of the Blood

<table>
<thead>
<tr>
<th>Date</th>
<th>White Blood Cells</th>
<th>Red Blood Cells</th>
<th>Hb.</th>
<th>Colour Index</th>
<th>Lip Amines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aug. 16</td>
<td>6,000</td>
<td>1,200,000</td>
<td>30%</td>
<td>1.1</td>
<td>h.1/4 t.i.d</td>
</tr>
<tr>
<td>Aug. 23</td>
<td>6,500</td>
<td>1,400,000</td>
<td>35%</td>
<td>1.1</td>
<td>h.1/4 t.i.d</td>
</tr>
<tr>
<td>&quot; 30</td>
<td>6,000</td>
<td>1,500,000</td>
<td>40%</td>
<td>1.2</td>
<td>h.1/4 t.i.d</td>
</tr>
<tr>
<td>Sept. 14</td>
<td>5,000</td>
<td>1,600,000</td>
<td>48%</td>
<td>1.3</td>
<td>h.1/8 t.i.d</td>
</tr>
<tr>
<td>&quot; 22</td>
<td>6,000</td>
<td>1,600,000</td>
<td>53%</td>
<td>1.4</td>
<td>h.1/8 t.i.d</td>
</tr>
</tbody>
</table>

Formolasts and mephalolasts were found all through.
Number of Nucleated Red Corpuscles
met with in counting 500 white corpuscles (from film)

Cases V, VI, VII, VIII, IX (on admission)

<table>
<thead>
<tr>
<th>Case</th>
<th>Megaloblasto</th>
<th>Normoblasto</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>VI</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>VII</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>VIII</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>IX</td>
<td>14</td>
<td>8</td>
</tr>
</tbody>
</table>
Summary of some of the more important symptoms and signs present in each case.

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Gastric Intestinal</td>
<td>P</td>
</tr>
<tr>
<td>Cario-assis throat</td>
<td>P</td>
</tr>
<tr>
<td>Jaundice</td>
<td>A</td>
</tr>
<tr>
<td>Characteristic Blood</td>
<td>P</td>
</tr>
<tr>
<td>Haemolytic {</td>
<td>A</td>
</tr>
<tr>
<td>External</td>
<td>P</td>
</tr>
<tr>
<td>Renal</td>
<td>A</td>
</tr>
<tr>
<td>Enlarged Liver</td>
<td>A</td>
</tr>
<tr>
<td>Enlarged Spleen</td>
<td>A</td>
</tr>
<tr>
<td>Urine {</td>
<td>P</td>
</tr>
<tr>
<td>Dark colour</td>
<td>P</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>P</td>
</tr>
<tr>
<td>Pyrexia Period</td>
<td>P</td>
</tr>
<tr>
<td>Nervous Symptoms</td>
<td>A</td>
</tr>
</tbody>
</table>

A = Absent  
P = Present