Pernicious Anaemia
A Review

With an analysis of 84 collected cases, and the final result of many apparent cures.

By
Horace Strahanthorp Colman.
M.B. C. M. 1896.

April 19, 1900.
So Addison, a distinguished graduate of the University of Edinburgh, belongs the credit of first describing this disease, under the name of *Idiopathic Anaemia*. Before his time, however, several cases had been described by different observers, which were undoubtedly of the same nature, though described under various titles. Of these, the earliest was described by Dr. S. Combe in the *Transactions of the Edinburgh Med. Chir. Society* 1823. A list of 9 has been collected by R. Smith.

After Addison described his cases, the interest of the profession generally in the disease seems to have died away, except in his old hospital (Gaye) amongst those who came into contact with his colleagues' pupils. Amongst those who during that period made reference to the disease are Wilkes, who speaks of "that class of cases which has specially gained the attention of Dr. Addison, with which she has designated *Idiopathic Anaemia*", and Shakespear, another pupil of Addison, who published a case or many more referred to by R. Smith in the paper mentioned above.

In 1879, Bierem described the disease as something new hitherto unobserved, a claim that was very generally accepted, though finally successfully disputed...
by Wilks and Smith. In the present time no one would seriously dispute Addison's priority, though all admit the originality of Bream's work.

Quincke in a lecture on the disease described for the first time the accumulation of iron in the liver observed in some of his cases. The important discovery of the alterations in the bone marrow was first published by Bohemian. The next point of historical interest is the advocacy of treatment by aspirin by Bramwell, who published some cases of successful treatment.

After this came Sand's work on the pathology, his suggestion of the use of intestinal antiseptics, a mode of treatment carried out with some success by Gibson, strongly in sequence the treatment with bone marrow by Prof. Hare.

Various theories as to the cause of the disease have been advanced from time to time. It was Addison's desire to find the cause that led him to the discovery of the disease that bears his name today.

Pepper called it the "medullary form of pseudo-leukemia" believing that bone marrow change is the primary lesion. Hunter has advanced the theory that a poison is generated in the alimentary canal which in the portal system destroys the capillaries.

Stockman considers that the capillary haemorrhages
so frequently found are the cause of the difference between purpurocous anaemia and profound states of anaemia.

Mott has suggested after seeing the work of Bell on the liver that perhaps the disease is due to a functional rearrangement of the livers.

In the present instance, I propose to detail two cases that have been under my care, to review the symptoms, treatment, and anatomy of this disease, and to discuss the probable causation of the disease, comparing at the same time the 14 cases collected in Table G.

The two following cases were patients in the General Infirmary at Northampton, and under entire charge of them.

Case 1.

H. G., male 47, admitted Dec. 5th, 1898.

He had been ill about 12 months. He stated that he took too much belladonna for a cough, and the result of which he collapsed. He had had some slight bleeding from the bowels, which he attributed to piles, but none were discovered. Twenty years before he had been troubled severely by piles, but had had no other
bleeding. He had never been abroad or suffered from malaria, described himself as having been a very healthy man. He was a schoolmaster, but for 6 months before admission had been an inmate of the County Jail.

On admission, he was very weak, unable to walk, thirst, constipated. His appearance suggested myocardia somewhat on his hands were large and padlike. The speech slow; monotonous, there was a pinkish flush on his cheeks; he stated his brain had got thinner lately. The skin however was soft, rather pale, slightly jaundiced, yellowish tinge. There was a large amount of subcutaneous fat. The conjunctivae were mucous, membrane of the mouth were very acaceous.

Tendrils were pale but there were no internal hemorrhage.

The heart was a little enlarged, the apex being in the fifth space, just inside the nipple line. The pulse was regular, soft, 700 per minute. Soft systolic murmurs were present at the mitral atrioventriculated areas. The liver spleen did not appear to be enlarged.

The urine had a specific gravity of 1010, nothing abnormal was noticed in the colour or otherwise.

The blood, the corpuscles did not form rosete at all well, there were a few large rose petal irregular shaped corpuscles some with concentration
Glaemoglobin. No leucocytes or nucleated leucocytes were seen.

The red corpuscles numbered 1,140,000 the white 9,000 per c.m. Glaemoglobin 28 per cent.

She was at first given Typhoid tablets (1 each night) but often a week was put on smaller doses of other cirrhosis. This was not well borne — diarrhoea took the place of constipation she complained of a burning sensation in the rectum, for which no cause could be discovered.

The appetite was extremely capricious, thirst intense. She complained of dryness in the throat continually. The number of red corpuscles fell somewhat. She became gradually weaker; instead of at night delicious.

On Jan 9, 1879 he had a sudden attack of dyspepsia lasting for 20 minutes a then died.

Throughout the period of observation there was no fever.

Post mortem. Heart pale, flabby, dilated, valves healthy - muscles not fatty.

She lungs were slightly adherent otherwise normal.

The liver was a little enlarged the lower part was stained black to a depth of 3 or 4 inches. The spleen was normal in appearance.
Both organs were examined by the Clinical Research Association who were unable to detect any excess of iron in either.

Kidneys were healthy.

Intestines were very thin but showed no signs of ulceration, malignant disease or parasites.

Nothing was found in the stomach to account for the burning sensation.

Bone marrow in the femur was of a fawn-like colour, but seemed to be entirely absent.

I am inclined to regard this as a case in which the destructive process was so advanced, at the time of death, that the bone marrow was unable to respond sufficiently to the calls upon it, i.e., it was exhausted.

The absence of fatty degeneration was very unusual and the absence of iron deposit in the liver, but that might be accounted for by cessation of the process of destruction.

The condition of the blood, bone marrow, and the absence of any bleeding sufficient to account for his condition were, I think, adequate of Pernicious Anaemia.
Case II

W.H, male 36 admitted Aug 18th 1898

Warranted to the board as a case of jaundice.

History. In April last he began to have pain after

bespoke with occasional vomiting diarrhea.

despite appetite, occasional diarrhea had been a

source of trouble to him all his life. In June,

he noticed a change to yellow in his skin, but some

weeks before that had noticed yellow mucus in his eyes,

(evidently there was a first some jaundice)

More recently he had been troubled with weakness

of breath and slight palpitations a few weeks before

admission, his right side became very thin and he had some

headache. He said he had been healthy till the

onset of the present illness. This work for 9 months

before admission had been somewhat unhealthy,

working in a place where a large number of people died.

His house was damp and the feeding arrangements poor.

His mother, brother had both suffered from

"jaundice", they were then alive now.

On Admission. He was very weak, breathless and

giddy on reaching the top of the stairs.

His skin was a pale yellow colour all over,

his conjunctivae were poorly, not at all the

characteristic tint of jaundice.
The patient's family were nourished, there was a fair amount of fat and much muscular wasting. His weight was 13 lbs. however was nearly 2 stones less than his weight in health.

The skin was soft & smooth. There was no edema round his ankles or elsewhere.

The pulse was regular, full & not jerky. The heart was not enlarged, but the aperent was not visible or palpable. The heart sounds were rather faint. No soft systolic murmurs were present in the tricuspid area.

The tongue was moist with a slight white film, he had no diaphoretic symptoms then, but the bowels were rather loose.

The liver was 2-fingers breadth below the costal margins in the manometer line but was not tender.

The spleen was not enlarged.

The urine was acid. The pyr. was 1020 no albumen was present throughout his illness as abnormality in colour otherwise was noted at the biweekly exam. In the left eye there were the remains of a partial haemorrhage.

The nerve jerks were moderately active.

The temperature for the first 6 days rose a little at night but afterwards was normal except for 3 days at the end of his stay in hospital.
The blood. On Aug 19th, the corpuscles did not form
red blood corpuscles, many irregular shaped
corpuscles were seen, some oval, some larger than
normal, some kite shaped. Many showed a
concentration of haemoglobin at the general average
in size was larger than normal. No leukocytes present except.
The enumeration of the corpuscles and estimation of
haemoglobin are set out in Table A.
The white corpuscles were more numerous than
usually is the case, but this is partly at least
accounted for by the fact that the counts
were usually made soon after his midday meal.
Great meat progress. He was at once given per
by arimicin three times a day.
Tobe increased 1 min each day in 6, 9, 12, 15 etc.
in 24 hrs.
The above began to improve, his appetite became
sensitive stools ceased.
On Sept 5th his eyes were quite sore read
from the arsenic, the haemie diarrhea had disappeared
on Sept 5th his eyes were so sore that I stopped all
arsenic. He was at that time taking 60 min daily.
This evening temperature began to rise on the 8th reached
10.4 in the evening. He much felt very hot, there was
no rigor or headache, no intestinal symptoms.
I gave him quinine sulphate and mix tis by
administration. In two days the temperature was
normal. There was no "influence" in anything similar
in the record at the time. I refer again to this as
the probable explanation when speaking of the
use of arsenic.
He left the hospital on Oct. 22, apparently well
as a natural colour, his weight was 84.6 lbs.
The details of the administration of arsenic
are seen in Table A.
I kept him under observation myself until I left
in January 1899.
In July 1899 he reported himself as pretty well
but a little yellow again. He had taken no
arsenic since January.
I had difficulty in tracing him after that, but
at least found that he died on January 14th, 1900.
Mr. Marriott of Cottenham kindly sent me the following
notes of his last illness.
"Briefly, he continued to get more feeble and times
was rather violent, mentally excited. He suffered much
from prostrated diarrhoea, which was very difficult to
check which seemed to be largely instrumental in
bringing on the fatal result of his illness. He had
once or twice small attacks of epiptamps."
The blood was only faintly coloured. There were no pedal haemorrhages at any time. Anaemia
straining anaemia.

He was treated with arsenic, beginning with a few minims (Six Codiæ Ascorbici) amounting
up gradually to 12-15 minims thrice daily.

Great improvement for a time ensued, but
he relapsed. The diarrhoea eventually
accelerated the abandonment of the treatment.

During the last few weeks he obtained the
least relief from opium and meat juice.

The conjunctivae were deeply stained
that more than one visitor thought he had
"jaundice" (March 22nd, 1908).
<table>
<thead>
<tr>
<th>Date</th>
<th>Red Count.</th>
<th>Hg.</th>
<th>W.B.C.</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aug 19</td>
<td>1,650,000</td>
<td>33</td>
<td>26</td>
<td>0.74 white 18,000 very large shapes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>formation.</td>
</tr>
<tr>
<td>&quot; 26</td>
<td>1,740,000</td>
<td>35</td>
<td>50</td>
<td>1.43 white 10,000 great diminution in</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>irregular shapes.</td>
</tr>
<tr>
<td>Sep 2</td>
<td>2,720,000</td>
<td>51</td>
<td>60</td>
<td>1.11 white 10,000 very large shapes.</td>
</tr>
<tr>
<td>&quot; 12</td>
<td>3,030,000</td>
<td>60</td>
<td>52</td>
<td>0.86 capraels disappeared normal.</td>
</tr>
<tr>
<td>&quot; 19</td>
<td>3,050,000</td>
<td>61</td>
<td>70</td>
<td>1.14</td>
</tr>
<tr>
<td>&quot; 26</td>
<td>3,960,000</td>
<td>79</td>
<td>76</td>
<td>0.96</td>
</tr>
<tr>
<td>Oct 3</td>
<td>4,700,000</td>
<td>94</td>
<td>70</td>
<td>0.74 white 20,000</td>
</tr>
<tr>
<td>&quot; 11</td>
<td>5,000,000</td>
<td>100</td>
<td>82</td>
<td>0.82 apparently normal blood.</td>
</tr>
<tr>
<td></td>
<td>nearly</td>
<td></td>
<td></td>
<td>as 82 is about max from iron.</td>
</tr>
</tbody>
</table>

Aug 19 Arachnias began, min 2 kid.
" 26 Reached min 94 daily
Sep 2 Reached min 110 daily, increase in blood rate.
" 7 Reached min 52 daily
" 9 Stopped altogether
" 15 Reared as on Aug 19
" 19 Reached min 27 Grow new given as well
" 26 Reached min 49 daily
" 30 Reached min 100 daily.
Oct 1st Calculated at min 140 daily.
" 5 Stopped
" 9 Started again at min 84 not Joke increased
" 12 Left Hospital, to continue iron min 144 arsenic
This case shows in a marked degree the benefit to be obtained in some cases from arsenic. In 1 month the corpuscles nearly doubled in number and the haemoglobin percentage increased from 20 to 40.

The only ill effect from the large dose of arsenic (upto 30) was the soreness of the eyes and haemorrhage. The sudden cessation apparently caused a great rise in temperature.

The first sign of improvement under arsenic was the great diminution of irregular shaped corpuscles. At the same time the haemoglobin percentage nearly doubled itself. I am not quite clear as to how this latter feature was brought about, but possibly the new, more healthy corpuscles were capable of carrying more haemoglobin. This was provided by the destruction of the dehydrated forms of form that stored up all over the body (as shown by the yellow colour of the skin) from the previous excessive destruction.

In the next week there was an increase of nearly one million corpuscles (20%) the haemoglobin increasing only 10%. It appeared as if the production of corpuscles had got a head of the production of haemoglobin, this was
manifested more strikingly in the next count, when
the eosinophils had increased by 310,000 (6.2%)
the haemoglobin had fallen 10%.
A week later with only a slight increase, 20000
(0.4%) in the eosinophils the haemoglobin increased
18%.
At this point iron was given in addition to arsenic
which was followed by a rise of 910,000 (18%) in
eosinophils + 6.4% in haemoglobin.
The next week there was a rise of eosinophils
associated with a fall in haemoglobin. The
next week, but a slight rise in eosinophils with a rise of
12% in haemoglobin.
It would thus appear that the production
of haemoglobin takes longer than the production of
eosinophils — the latter after a spurt, as it were
seem to wait for the former, another weeks
after a certain number of eosinophils are launched.
Few are sent out until the first are properly
equipped with haemoglobin... see page 180
By this time the eosinophils must have
some of their haemoglobin after leaving
the bone marrow, though probably it is supplied
by the liver... as suggested by Delphine
see page 108.
Pernicious anaemia is a rare disease. I have been able to obtain statistics of the disease from several hospitals, statistics which also have some bearing on the prognosis, for which purpose the figures in Table B of collected cases are useless as naturally a very large proportion figures are reported.

In Table B are given the figures from hospitals where a large teaching school exists to which naturally very few cases gravitate. Taking the total admissions in 10 for which the figures for ten years (not quite ten years together) are given, there is a total of 250,659 in patients of whom rather less than half were admitted to the medical side. Of these only 249 were suffering from pernicious anaemia.

At the General Infirmary, Northampton an ordinary county hospital the admissions for pernicious anaemia were 12 in 10 years out of a total of 18,500 patients. There are other points in Table B which will be referred to later.
Table B.

Statistics of the occurrence of Premature Anemia in 8 hospitals.

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Male</th>
<th>Proportion</th>
<th>Female</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Infirmary, London</td>
<td>44</td>
<td>0.19</td>
<td>10</td>
<td>0.04</td>
</tr>
<tr>
<td>Royal Infirmary, Glasgow</td>
<td>12</td>
<td>0.03</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>City Hospital, London</td>
<td>17</td>
<td>0.05</td>
<td>4</td>
<td>0.01</td>
</tr>
<tr>
<td>St. Bartholomew's, London</td>
<td>20</td>
<td>0.05</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>King's College, London</td>
<td>3</td>
<td>0.01</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Guy's Hospital, London</td>
<td>8</td>
<td>0.02</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
<td>0.21</td>
<td>11</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Note: Data includes male and female admissions to the hospitals listed.
Sex. In Table B only 3 hospitals have
  divided the sexes, the figures being
  males 113, females 61.
  Bramwell gives the figures of his own cases as
  males 29 females 16.
  Below gives 17 males, 10 females from his own
  cases.
  Eydmith collected 18 males, 59 females (upto 1883)
  Broadland collected 36 males, 51 females (upto 1887)
  For the 89 cases these collected the figures are
  males 60 females 29.
  In tabular form the figures are.

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broadland</td>
<td>50</td>
<td>54</td>
<td>110</td>
</tr>
<tr>
<td>Eydmith</td>
<td>48</td>
<td>59</td>
<td>107</td>
</tr>
<tr>
<td>Bramwell</td>
<td>29</td>
<td>16</td>
<td>45</td>
</tr>
<tr>
<td>Below</td>
<td>17</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>Table B</td>
<td>113</td>
<td>61</td>
<td>174</td>
</tr>
<tr>
<td>Table G</td>
<td>60</td>
<td>27</td>
<td>87</td>
</tr>
</tbody>
</table>

It is not possible to gain any information by adding the
figures up for probably many cases affect each
hospital. There is certainly a tendency in the more
recent lists i.e. the last four, for males to appear
more frequently. This I think is due to the elimination
of what are really cases of secondary amenorrhea —
especially cases due to some trouble perhaps in


In Germany the teaching of Biermers led to a 
broader interpretation of the term pneuicnemia. Consequently many cases of what we should call 
secondary anaemia are included. So Hermann 
Muller describes 44 cases 9 males 35 females. 
It is fair to conclude therefore that accepting 
Addison's definition of the disease, it is met 
with to a greater extent among men than women.

Age: Table G shows the prevalence by age. 
The youngest was 9 years (No. 19) and the oldest was 
67 years (No. 80). Bajerak 39 
men have 2 cases and 125 the other 35 women. 
Sphyllar in each he says Biermers' type common was found in 
the blood.

In Table G, the prevalence in each decade is 
calculated as follows: 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 
28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 
46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100.

Smith gives a table of his own, confined to 
215 patients, 102 men and 113 women. In his own the greatest number occur 
between 31 and 59 years.

Cromwell found out of 145 cases 97 occurred between 
35-55.

The disease appears therefore to be one principally 
of middle life, though it occurs entirely so 
as it occurs more frequently in men than in 

women.
...seldom seems to have any bearing on the disease. Lord Cranwell quotes an extraordinary instance where a man, his brother, his mother, two uncles and two aunts, suffered from the disease via another aunt the diagnosis was doubtful.

All authorities are agreed in describing the disease as one chiefly of the lower classes, though it is not by any means confined to them. It undoubtedly seems to occur more frequently in those who have led a more active life than usual.

In the absence of complete knowledge of the pathology of the disease, it is not possible to gainsay a very complete idea of the predisposing causes.

Cases have directly followed after yellow fever or mental shock, influenza, or mental illness in the majority of cases the patient seems deficient to find anything to which to attribute his disease.

Many cases have been attributed to hemorrhage during or after parturition, but there are undoubtedly many instances where of secondary anemia, most of these cases seem to be of this nature.

Few cases seem to arise in pregnancy, but they are too rare for that to be considered more than an...
accidental circumstances the anaemia appears to be of a different nature. See Oliver, page 90.

Onset of the disease is generally gradual, as might be expected from the inability of patients to find a cause for it. Sometimes, however, the onset is rapid; in Table G it was so in 10 instances. In one case No. 52 the onset was extremely rapid, possibly only 3 weeks, but the man had not been feeling quite up to the mark for 3 months before. Though following his occupation as a gamekeeper in hilly country. In the cases that began with fright or mental strain, the onset was rapid, in case 21 not more than 2 weeks.

On reviewing the Clinical Features, leaving out the state of the blood at the moment, it is important to note that some are common to all, some are chiefly seen in parasitical anaemia, some in anaemia, that others appear only in that disease, but not constantly even there. So far, no single sign or symptom has been found, which occurs constantly in parasitical anaemia, as in that disease alone. The symptoms will all be considered in detail later. But grouped as described, they throw some light on the nature of the disease.

Common to all forms of anaemia, amongst the
natural colors, disturbances of the digestive process
-namely dyspepsia affecting, palpitations, breathlessness,
-tendency to straining, cardiac enlargement, consequent dilatation, general languor, a tendency
toward edema and the same time retention of the body
fat.

more frequently met with in pernicious anemia, though
occasionally seen in other forms re, further digestive
disturbances, as diarrhoea, haemorrhage, retinal
pedoelebral palsy, as well as (its occurrence in any
other form is uncomplicated being doubtful)
may yellow colours superadded to the loss of the
natural color.

Lastly changes only seen in pernicious anemia are
early jaundice or certain alterations in fewos
constituents of the urine.
The change in the blood are too complicated to be
thus roughly summarized, but it may be here
stated that the first group of symptoms may be
attributed to the loss of corpuscles containing
bile, some the second to a more profound stage of the
same (viz hemorrhagic digestive disturbances) the
yellow color.-

the result of increased blood destruction in
the liver or elsewhere.
In atypical cases Spherocereosis occurs, the patient’s appearance is very striking. The skin is of a wax-like tint varying from white to pale primrose yellow. The yellow tint appears to think in cases that are running a more rapid course. This same colour has been observed to increase in intensity concurrently with a general increase in the body symptoms by Hunt, Hunter, and many others. In each case, with the increase of colour, there was a fall in the number of blood corpuscles. In some cases, jaundice also appeared in the urine. This colouring of the skin disappears fairly rapidly in cases that are prone under treatment. Observed this in my second case, also in case 52, who was a patient in the Royal INFIRMARY when I was house physician.

By this colouring of the skin, Bramwell says in many cases, the yellow tint of the skin is not due to jaundice. In some cases, it is probably due to the presence of a pigment derived from the destruction of red blood corpuscles. This assumption generally is a point of some importance from an etiological point of view.

I am inclined to think that in every case of this disease, the yellow colour is due, in a few cases to jaundice in the rest to a product of blood destruction. In speaking of this yellow colour, says he has seen it in chlorotics, who have had an internal
document has various toxic anemias, in rare cases of chronic pathological diseases. In each of these cases, the last cited shows that it arises from degradation of blood, destruction circulating, being deposited in the skin. In the last, the same explanation is probably true, the products being absorbed by the stomach in some cases.

In this yellow color may be added scurvy, though less frequently. The state of the complications will usually enable an observer to distinguish between sepsis with pyemia, and a deposit of fat in previous anemia sometimes may lead to error.

Looking at a patient suffering from previous anemia one is struck by his pale, pallid, appearance, apart from the symptoms. This maintenance of fat was noticed by Addison, who says: "I view the less blemished part of the abdomen of a person with perhaps several months duration, the blemishes of the general frame, the obesity often present, as a striking contrast to the failure and exhaustion observable in every other respect." This has been confirmed by every subsequent observer.

The same maintenance of body fat is seen in cases of uncomplicated chronic anemia, probably due to insufficient oxidizing power in the blood, but it is interesting to note that the place of fat in the bone marrow..."
is often replaced by blood forming tissue in this disease.
In all the cases I have seen the expression of
the patient is purposely listless.

The Symptoms referable to the Circulatory System
are secondary to the degeneration of
the blood carrying tissue can be attributed directly to the
causes processes of the disease.
The pulse is usually quickened, in my first case it
was 100 beats, as a rule it is soft and full in the early
stages but as the disease progresses it becomes small
and of a rapid nature. Kbrnack states that tension
is high in the early stages and says it is a physiographic trace of
how this. Even slight exertion increases the pulse
rate considerably. Palpitations of palping are common.

Because I saw, who after the slight exertion entailed,
was being wheeled to a side room to have his eyes examined
collapsed of pain before he could be kept back to
bed.

The heart is frequently found dilated in the supralar
is often susceptible to death. Haemorrhage are
fainting. Bramwell says that the venous hem
is almost always the source in the back and
was not prominent in sudden myrtus, but each led
asphyxial build in the terminal area rose in the
initial also.
Necropsy occurred occasionally, but not so frequently as in chronic cases. It appears round the ankles usually. It did not occur in the two cases.

Dyspnea is a very constant symptom. It may be absent at the patient be expect, but appears on the slightest exertion in more marked cases. It is generally indicative of the pressure of the blood. \[\text{Footnote:} \] 35

Weil is usually ushered in by a state of extreme dyspnea, as in my first case.

Copland says dyspnea occurs in the Cheyne-Stokes type which he says is singular, as that type was first described in connection with a fatty heart. Other observers however state that Cheyne-Stokes respiration does not occur in the disease. I saw very marked Cheyne-Stokes breathing in a case who had had a very large hemorrhage, as the ultimate result.

Digestive System. Many of the symptoms are referable to this system, e.g., vomiting is a very common feature in this disease.
In all forms of anaemia dyspepsia and vomiting are frequently present, arising undoubtedly from the inability of an anaemic stomach to digest the food, but in pernicious anaemia the vomiting often occurs without relation to food. In chlorosis vomiting is unusually rare, and frequently in pernicious anaemia. In 80 cases of chlorosis that were bad enough to be admitted to hospital Bradwardine noted vomiting in 10, while in 45 cases of pernicious anaemia vomiting occurred in 31.

Hale White carefully examined the record of 31 cases in Guy's hospital of whom 27 gave a history of vomiting before admission, and 16 continued while in hospital.

In Pyke's cases 28 had vomiting out of 102.

In Dale's cases of 87 cases vomiting was present in 56, absent in 15 and mentioned in 16.

In many cases the vomiting has occurred before the anaemia has been noted, this has led to the suggestion that dyspepsia may be one of the causes of the disease. Associated with the vomiting or occurring alone, there is often diarrhoea, a point of great importance in serving to distinguish the disease from chlorosis.

Bradwardine's 46 cases had diarrhoea while in the 80 cases of chlorosis only 3 had diarrhoea. If any were markedly constipated, Hale White found diarrhoea in 10 out of 31 cases.
In Table G there are 10 cases in which the onset was rapid and jaundice is noted in 8 cases in 3 of these the onset was rapid.

Noteworthy attention has been paid to the jaundice as for but this is an important feature when it does occur in view of the theory that the blood destruction occurs in the liver. In case 52 the stools were of a bright yellow.
fever showing that there was little, if any, attention to the bile flow.

The liver is sometimes enlarged and tender. In one case, it was so
in case 52. In another case, it was enlarged, one
showed marked jaundice. The other probably had
and it. The liver rapidly diminished in size as the
patient improved.

The spleen is rarely observed to be enlarged,
during life, so rarely that its occurrence
is probably accidental.

The tongue in a few cases has been described as red;
and in other cases, pox. In this instance, in these
cases, there has been pronounced.

A case published by Robert Russell, attention was
drawn to an intolerable burning sensation in the prenum
for which no cause could be discovered. Nothing disappeared
on the patient recovered. In one case, an exactly similar
state of affairs was noticed because could be found after
death. Possibly this was caused by a simple haemorrhage,
in the end which in the one case was absorbed.

It will be then seen that the symptoms referable to
the objective system are very different from
much more
than those in Cholera.

Their mode of origin will be discussed later on,
when the cause of the disease is considered.
The urine. Very little attention was paid by the early writers to the urine. Addison merely states that there had been an antecedent renal disease, while Burns, James, MacKenzie, Holmblad, only observe that albumen is rarely present even in any quantity. Pye-Smith, however, in 1883 makes the following statement: "The urine in some typical cases of radio-patellar anemia is of a deep, clear colour, one of the characters which point to a destruction rather than deficient formation of haemoglobin. Albumen has generally been found deficient —... probably from loss of appetite or diminished nitrogenous ingesta. But in some cases its relation to the food taken seems to show relative increase from wasting of tissues. Light albuminuric albuminuria has been occasionally noted."

Hunters was the first to lay great stress on the importance of examining the urine.

The quantity is not usually much affected unless by diarrhea. This upon the colour that Hunters lays such stress.

In a case under his care the urine was of low specific gravity and high colour at the commencement he considers very important. The patient was liable to exacerbations of the disease. With each the urine became darker.
at the skin, more yellow spots containing pigment appeared in the urine, whereas haemoglobin remained at about 10mg-100mg. Suter thinks that this dark urine should be found in every true example of pericardial necrosis. This is not the case; however, B. A. B." describes a carefully observed case in which the urine was pale throughout the period of observation, and the observers have noted the same thing. In any two cases the colour of the urine was even noticed to be abnormal, but the examinations were only made twice a week.

In table 4 out of 84 cases the urine is noted at highbrowed in 27 cases and in 38 cases, almost 20%.

These and other observations of necrosis of the heart, high values among more frequently observed cases but also not constant among them.

This occurrence however, that if its occurrence, be only intermittent, it may easily be missed when the urine is only occasionally examined. Further many of the recorded cases are cases that improved or were cared for in these cases, may suppose that the destructive process was checked. So the high values was not then present in the urine. The high values does disappose in cases that necrosis. Pye-Smith noticed similar cases, and it was observed in case 52.
The specific gravity is usually moderately low.
Urine acid is occasionally deposited; sometimes
in large quantities as in case 52, where the
deposit was very great.

In only 9 cases in Table B was urine acid noted.
Mott has suggested that possibly the urine acid is
a product of dissociated red corpuscles.

The occasional presence of albumen seems to have
no special significance.

Hendey records a case in which there was
painful micturition for which rauscose could not
be found.locally on the urine, it disappeared as the patient
improved. It was analogous to the partial retention
mentioned before.

Hemoglobin has never been discovered either
chemically or microscopically in the urine in poisonous
accidents, but pathological hemoglobin has been
sometimes detected by Hunter and others, and the latter, Mott
Stockman have found it in excess.

Some general points about the urine are discussed
under the pathology of the disease, but it will be
seen already that the most prominent change
in the urine—the colour change—points to
an increase of blood destruction.
The Blood. Addison makes no mention of the blood in his original description except to say that examination had been made twice, if there was any excess of leukocytes. Wilks made an examination to determine this point, and ascertained there was no excess.

One of the earliest published examinations of the blood was by Bramwell, who also gave a coloured illustration, which however he announced was mistaken for a leukocyte. This error was soon rectified by Janeway, who published an account of a very careful series of observations on the blood in a case.

Since then numerous observations have been made on the blood, but comparatively little has been learnt from it as to the cause of the disease, though much can be learnt from it as to the prognosis.

A drop of blood obtained by puncture in the ordinary way (there is often considerable difficulty in obtaining it) is usually paler than normal, though the colour is not so marked as might be expected. The fluidity of the blood is often increased, so the drop tends to fall off the finger or ear with much greater rapidity than normal blood. Bramwell found that the blood when shed stained the fingers in a similar fashion to the acid and in colour; difficultly, therefore, this has been observed by others — was definitely of my second case.
Examining the blood under the microscope, the most striking feature in a typical case is the presence of encapsules present in the field. Next, it will be noticed that the red blood cells tend to agglutinate of pseudocytes; that there is a great lack of uniformity in the shape of the encapsules. The absence of pseudocytes formation is probably partly due to alterations in the serum, partly, perhaps chiefly, to alterations in the pseudocytes, many of which are immature, as will be seen later.

The forms presented by the encapsules in American, Amebic, and other very various others again are probably due to the same cause as the absence of pseudocytes formation. The encapsules can take various colors and appear larger diametrical than normal. It does not pay that all are larger, but that the average size, even including the microfics is greater than normal. Eckhard says the same, giving 8-9 by the average size. Sanger 46 is alone insisting that the average size is diminished. There is a predominance of the oval type of encapsules, Rabot gives two good figures. Often encapsules have the shape of hollow balls, hollowers, horsehocks, etc. Sitten regards the horsehoe form as pathognomonic of the disease. Some cases show very much less deformity than others, in one of Rabot's cases there was
no deformity worth mentioning, but he does not think that this has any relation to prognosis. In very many cases, the haemoglobin is accumulated in the centre giving rise to a nucleated appearance, the true explanation of which was given by Morison in '85. The white corpuscles are as a rule considerably reduced in number. Leabot found the average for cubic millimetre to be 2500 in the case. In some cases just before the fatal termination a very great rate of rise in the haemoglobin has been seen, according to Leabot the increase was in the polymorphonuclear cells. There are other cases described which seem to be a combination of leukaemia and pernicious anaemia, such a one is published by Lea-Jones. In blood platelets of those are said to be diminished.

It will then be seen that the microscopic changes of any importance are confined almost entirely to the red corpuscles, the diminution in the white being sometimes of importance in diagnosis. The examination of the red corpuscles of great importance. In another disease is the diminution in number to great extent. The use of the haemocytometer in many doubtful cases at once establish the diagnosis. The prognosis of the case under the effect of treatment is largely based from its use.
It is not easy to state what is the average number of red corpuscles present in the millilitre of the blood in the disease, as progressive or a case gone under observation at varying periods.

Table B gives large number of blood counts, the average of which is 1,056,000 per c.m. as the observations of L. Cabot, Bramwell, Schoen, and others quoted. The average of their observations is 1,246,000 per c.m. in the first counting, in 110 cases.

The number of the corpuscles bears some relation to the state of the patient, but this is not an absolute. The body is capable of accommodation in the absence of allowance of red corpuscles. Cabot mentions a case where red corpuscles numbered only 500,000 per c.m., at which point the patient remained stationary for some weeks; at this time the patient was able to go about his duties daily as a fairly comfortable. I knew a patient in the Royal Infirmary who had red corpuscles varied in spite of large doses of arsenic between 1,131,000 and 1,170,000 for 8 weeks during which period he was fairly comfortable,advanced, and as far as I could see.

The corpuscles remaining at about the same level would point to the cause of the disease being temporarily suspended but that the blood forming organs are unable to make up the lost ground, unless that a balance has been attained between destruction and formation.
Babot remarks that cases seldom remain stationary at 200,000 to 250,000, without picking below 1,000,000. The second case died with the corpuscles at about 1,200,000 to 1,300,000 for cm.

The lowest recorded figure is 114,000 by Dr. Reau's case and also by Dr. Reau's in his case. Macleod states that the corpuscles always fall to a low point, when the corpuscles fall to 664,000, that is the lowest figure in Table 8.

Munter observed that in one patient there was a great fall in corpuscles, with obvious signs of destruction at each examination of the disease. It has been noticed to a greater or lesser extent by others.

Such briefly are the most generally met changes in the corpuscles of a typical case of Parvovirus Anemia.

There are other changes met with fairly frequently in the blood, changes of the most part in the red corpuscles. Salkeld, in his book, observed a very curious change in the blood, which was absolutely characteristic of the disease. He observed some peculiar bodies, a quarter the size of a red corpuscle; in even smaller forms much deeper and rather than the bicconcave shape.

In several of Parvovirus Anemia he has seen them.
that failed to find them in any other form of anaemia. Further research however has shown his conclusions to be erroneous. Very few two cases were described by Brainger Stewart in which a careful search had failed to reveal the presence of these bodies, since then the fact has been practically established that though present in some cases they are not present in all. In addition, below I found these bodies in his own blood of people quite free from disease. In two cases of hemolytic anaemia he found them in one of these he found them in the bone marrow. I don't think there is any evidence of their being formed in the bone marrow, probably they were carried there.

These bodies are now spoken of an Ehrlich's granules but unfortunately a few observers call them microsomes an exclusive use of the word which is confusing. In Table B. only cases Ehrlich's granules were present in 40 about 20 were mentioned in 61 Bramwell only has seen them in two or three cases, Cabot makes reference to them 68 may he has seen them in nearly every case he has observed.

Their occurrence is undoubtedly frequent. Viewed in the light of recent research by Huntz...
Walshe's theory, as I have already mentioned, will be made later, I
think there is little difficulty in coming to the conclusion
that they are the products of blood destruction; that
when they are found their presence is of great signiﬁcance
I have only seen them once (case 52) in that case they
were found only at the beginning of treatment, was
the patient improved, under arsenic they disappeared
from the circulation. If they were formed at an
impression, one would expect to see them increase or
improvement followed, and the fact forming the view
that they are products of blood destruction is that, in 2
of the 6 cases in which they were found, the onset of
the disease was very rapid. I think it very
possible that these parasites might be more frequently
found if the blood were examined every hour for
infections in cases that are progressive.

Another change sometimes present but by no means
constant is the appearance of nucleated red corpuscles
in the circulation.

In Table C, their presence is noted in 16 cases
and their absence in 16 examination periods in 165.

They probably appear with greater frequency than that, but
unless the blood is suitably prepared stained, they are
not at all readily found. Cabot says, "They are not always
difficult to find, indeed in many cases they
were nearly as numerous as the white cells, but
as a rule we don't get off with less than 2 hours work.
Therefore 2 hours is the minimum time required to
find these enucleated by a trained observer of the
blood. It is not surprising that they are seldom
recorded.

Before coming to any conclusions as to the significance
of enucleated red corpuscles appearing in the blood
it is necessary to have some idea of that much
debated subject, the normal formation of red blood
corpuscles.

In the embryo they are developed in the mesoblast in
the "vascular area." First a network of protoplasmic
enucleated cells is formed; the nuclei multiply and
accumulate around themselves some cells protoplasm to
acquire a reddish color (hemoglobin). The network
becomes hollowed out into a system of branching
canals in which these colourless corpuscles float; the
remaining protoplasm is differentiated round the
remaining nuclei as form the blood corpuscles.

There is no direct evidence of the colourless corpuscles
becoming changed to coloured.

Soon before fetal life is ended the enucleated cells
have almost, if not entirely disappeared. How this
process occurs is not known, probably they are converted...
into non-nucleated discs arising from the nucleated red corpuscles of the marrow of the adult, which are probably the direct descendants of the nucleated red cells of the embryo.

Schöffer and Rokitansky also describe an intra-embryonic origin of red corpuscles.

In extra-uterine life there is a nearly universal belief that the bone marrow is the main seat of production of red corpuscles.

56. J. Gibson maintained that the red corpuscles arose directly from the white action no longer supported by evidence. He also demonstrated that under exceptional circumstances the lymphatic glands generated red blood corpuscles. E. Behring also records a case of sclerosis of bone in which the marrow was obliterated in which the lymphatic glands contained numerous nucleated cells ordinary red corpuscles.

The same change has been recorded in Purpura Anæmia by Weigert and others. Neumann and the same change in the lymphatic glands in a case of anæmia from haemorrhage, but such cases are undoubtedly rare and exceptional.

The spleen has been supposed by some to be a seat of blood formation obtrusive to a seat of destruction. The evidence is strongly against the
spleen having blood-forming functions under ordinary circumstances, though Bizzygyno has found nucleated red corpuscles there after prolonged haemorrhage. Nucleated red corpuscles have been found in both spleen-lymphatic glands in the case of a woman dying of intense haemorrhage by Neuman e who supposed that they were caught there. It is quite conceivable that nucleated corpuscles circulating in the blood might in the calm of the spleen

nucleated red corpuscles to complete their development.

Presumably anaemia of spleen is as a rule

mentioned as will be seen later, but both in

one case observed in the spleen, cells of a pale green colour which he considers were undoubtedly being transformed to red corpuscles, which he looks upon

as a form transitional condition.

Many observers have seen in the spleen, blood corpuscles

holding cells whose function is almost certainly destructive. Gibson figures the process of destruction.

In 1868 Neumann 68 just described the nucleated red corpuscles in the marrow. Bizzygyno affirms that these nucleated red corpuscles of the marrow are not developed from the leucocytes of the marrow but are
corpuscles "de generis", which multiply by karyokinesis

...
become transformed (in mammals only the appearance of the nucleus) into red blood corpuscles.
These erythroblasts closely resemble the precursors of the embryonic nucleated red corpuscles and are transformed into the ordinary blood globes by a trophic disappearance of the nucleus. The vanishing of the cell substance into a baso-are cortex. Some say that the red corpuscles are formed by budding, others by extrusion of the nucleus.
Buds can be obtained from normal blood by the action of tannic acid, but never occurs in a neutral preparation. Probably the buds that Malmesey observes were due to methods of preparation, though Mott says that in one case of pernicious anaemia he saw buds being formed from the nucleated cells of the marrow. It is likely that the case where many nucleated corpuscles are circulating in the blood as extended nuclei have been observed. One would expect that such would be likely to be found, either brought from the bone marrow or else extruded by the corpuscles in circulation. The erythroblasts in the marrow are accordingly...
Bivioptus. The entire intra-vascular in birds,
though in mammals there is not so as the peris walls
are not complete. Schäfer 55, and Hackenzie 64,
were in complete agreement with Bivioptus. Hackenzie
sufficiently repeated confirmed his experiments
on birds.

Hackenzie inclined to attribute to the nucleus
the power of attracting the hemoglobin to the cell, or
therefore that when that is accomplished, it is no
longer required. Bivioptus observed in anatomized
animals red corpuscles in the axis of the medulla of
the marrow, external to the yellow thalamus.

The actual propelling influence that makes the
red corpuscles start on their journey is not quite clear.

Probably the state of the plasma plays an
interaction between it and corpuscles. The
alterations caused by the constant destruction of
red corpuscles leads to the young mature corpuscles
loosing the adhesiveness, which they exhibit in
the early stages, so they are swept into the circulation.

But this supposition is so not clear, how greatly
increased destruction will lead first to a greater
production of normal red corpuscles, then to a
calling out of the immature cells (nucleated
red corpuscles) to abnormal formation.
produced (a reaction to the fetal type) clearly to a complete exhaustion of the producing mechanism.

Coats describes three kinds of nucleated red corpuscles appearing at times in the blood in
pernicious anaemia: (a) normoblasts (b) megaloblasts
(c) microblasts. The last are rare and consist of
anuclei with a few threads of protoplasm
hanging on, but its clinical significance is
supposed to be the same as that of the megaloblasts.

(a) The normoblast is simply an immature red corpuscle
that resembles the mature form in size and colour—
differing in the possession of a nucleus.

(b) The megaloblast does not occur anywhere in the
healthy adult not even in the bone marrow,
but is seen in the early foetal marrow in the marrow
and circulating blood in grave forms of anaemia.

Ehrlich maintains that they are always present
in pernicious anaemia and considers that their presence is a
sign of a sebrenia to the fetal type of blood formation,
which he says has been confirmed by Pappenheim.
The typical megaloblast is 15–20 μ in diameter
with a very large nucleus and cells frequently
show signs of degeneration in its protoplasm.

Ehrlich regards this as a bad prognostic sign
in which Coats again says that atypical states
may certainly be expected if they are discovered, with the single exception of anaemia due to intestinal parasites. Engel. However, while failing to find them in several cases of pernicious anaemia, found them in cases of simple chlorosis. There is no doubt, however, that their presence is absent, for Babot in all his cases found the megaloblasts to exceed the normoblasts, their inequality grew greater as the anaemia worsened. Tustin he says "In several hundred cases of severe secondary anaemia I have never yet seen the numbers of megaloblasts exceed the number of normoblasts" he thinks the search for nucleated hypophase is of the greatest importance as throwing some light on the process.

Nucleated hypophase are met with in all forms of anaemia. May be found them in the bloody cases of anaemia patients, the cases are gastro-intestinal haemorrhage 12 cm.

They are certainly not always present in pernicious anaemia, as stated above, Engel failed to find them in several cases. In case 52, W. found they failed to find them. That case was a rapid one seen early, therefore it is probable that
the strain on the marrow was not such that immediate enucleated corpuscles were forced into the circulation.

Summ up:- nucleated corpuscles are a sign of great strain on the blood forming tissue. In cases of only moderate degree normoblastophy alone or in the majority, the appearance of myeloblasts is a sign of still greater strain & a premonition to the fatal type was regarded as a worse sign as regards prognosis their significance is extremely bad.

Nucleated corpuscles are not always present in puerperal anaemia; maybe present in any anaemia provided the strain on the blood forming tissue be sufficiently great, probably along continued loss of destruction of blood effects the blood forming tissue more powerfully & permanently than a single rapid and sudden loss of destruction. In support of this point compare the rate of recovery from anaemia the result of haemorrhoids & that resulting from one large haemorrhage.

Cabot says "It has been thought by some observers that the absence of great numbers of nucleated corpuscles indicated lack of any effort at regeneration on the part of the blood making functions whereas especially malignant types of the disease..."
There have been cases in which no nucleated corpuscles were present, but their reactions have seemed to come from a tube associated with a non-fatal type of the disease.

Various observers have at different times believed that they have discovered organisms in the blood of patients with anaemia, but further research has always disproved their statements. Amongst others, Koelliker has described a flagellated organism, and Sütten has dismissed them as absolutely unapparent. The fragments of broken up red corpuscles are easily mistaken for bacteria if carelessly examined.

The alterations in the haemoglobin are profound and of equal importance with the changes in the corpuscles. The percentage of haemoglobin is greatly reduced in pernicious anaemia. In my two cases it stood at 28% and 26% respectively when first examined. Babot found the average of 50 cases to be 26% of Bramwell’s 11 cases 28%. The latter points out that Lewis’ instrument reads too low, 85-90% instead of 100% to ensure complete accuracy.
Signs require a correction giving 33 m as the average.
Catot finds that von Bleichrodt's instrument is
giving figures that are unreliable for low values so probably both
will be replaced by others more accurate in nature.
In Table 8 the average in 37 cases is 25.3 m
with highest being 100 m; the lowest 10 m.

The important point about the haemoglobin
in connection with pernicious anaemia is,
however, not the actual diminution of haemoglobin,
but the fact that the loss of corpuscles exceeds
very frequently the loss of haemoglobin. In other
words the haemoglobin value of the individual
corpuscles is raised in the disease.
A glance at Table 8 will show this at once, if
the percentage of haemoglobin be compared with the
percentage of corpuscles; the colour value of the
corpuscles being expressed by the figure by dividing
the percentage of haemoglobin by the percentage of
corpuscles, as will be seen from the Table.
It is usually a whole number.
The average in Table 8 is 1.35.
Bromwell gives 1.3; Leech [1.04].
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<td>1.16</td>
</tr>
<tr>
<td>61</td>
<td>13</td>
<td>560,000</td>
<td>11</td>
<td>1.15</td>
</tr>
<tr>
<td>62</td>
<td>14</td>
<td>732,000</td>
<td>15</td>
<td>0.96</td>
</tr>
<tr>
<td>63</td>
<td>15</td>
<td>450,000</td>
<td>9</td>
<td>1.6</td>
</tr>
<tr>
<td>64</td>
<td>18</td>
<td>1,200,000</td>
<td>24</td>
<td>0.75</td>
</tr>
<tr>
<td>65</td>
<td>20</td>
<td>1,050,000</td>
<td>31</td>
<td>0.95</td>
</tr>
<tr>
<td>66</td>
<td>17</td>
<td>1,300,000</td>
<td>26</td>
<td>0.65</td>
</tr>
<tr>
<td>67</td>
<td>900,000</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>30</td>
<td>800,000</td>
<td>16</td>
<td>1.8</td>
</tr>
<tr>
<td>69</td>
<td>39</td>
<td>790,000</td>
<td>16</td>
<td>1.0</td>
</tr>
<tr>
<td>70</td>
<td>20</td>
<td>800,000</td>
<td>16</td>
<td>1.2</td>
</tr>
<tr>
<td>71</td>
<td>30</td>
<td>1,560,000</td>
<td>31</td>
<td>0.61</td>
</tr>
<tr>
<td>72</td>
<td>850,000</td>
<td>17</td>
<td></td>
<td>1.2</td>
</tr>
</tbody>
</table>
### Table C continued

<table>
<thead>
<tr>
<th>Number</th>
<th>Red corpuscles</th>
<th>Yellow corpuscles</th>
<th>Colour Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>1,800,000</td>
<td>36</td>
<td>1.05</td>
<td>These cases are 151</td>
</tr>
<tr>
<td>54</td>
<td>1,860,000</td>
<td>37</td>
<td>1.4</td>
<td>From the two last papers.</td>
</tr>
<tr>
<td>12</td>
<td>780,000</td>
<td>16</td>
<td>1.2</td>
<td>These cases are not enough.</td>
</tr>
<tr>
<td>40</td>
<td>1,230,000</td>
<td>24</td>
<td>1.6</td>
<td>Data not included.</td>
</tr>
<tr>
<td>34</td>
<td>1,390,000</td>
<td>27</td>
<td>1.2</td>
<td>As in Table C.</td>
</tr>
<tr>
<td>28</td>
<td>1,600,000</td>
<td>32</td>
<td>0.89</td>
<td></td>
</tr>
</tbody>
</table>

In 37 cases Haemoglobin averaged = 25.3 \%.
In 53 cases corpuscles averaged 1,056,000 or 21 \%.
In 36 cases colour value averaged 1.35.

Ebelin in 50 cases found Haemoglobin 26 \%.
68 " red corpuscles averaged 1,200,000
colour value 1.04

Branwell in 13 cases found Haemoglobin 33 \%.
15 " red corpuscles 1,250,000
colour value 1.3

Schaeumann in 38 cases found corpuscles 1,290,000

The numbers refer to Table C where other details are present.
This high corpuscular value is the most characteristic feature of the blood in pernicious anaemia.

Given a very great diminution of red corpuscles and the same time a great fall in haemoglobin
both at the same time a high colour value for each corpuscle, then the diagnosis of pernicious anaemia will generally be correct.

Labot mentions seeing two patients in adjoining beds having an extremely yellow colour without emaciation;
one had 10,000,000 or 20.4 p red cells the other
4,100,000 or 8.2 p. The haemoglobin in each being
about 50 p. The first was pernicious anaemia the
second nephritis.

In chlorosis the colour value is low. Labot says
the average is about 0.50 p.

It is probable that the colour value of the individual
corpuscle is not quite so high as the figures would
appear to indicate. Haemoglobin, possibly altered in
some way, sometimes dissolved in the pernicious anaemia disease, or with present method of estimation
it is not possible to determine if in every case the
haemoglobin is all held by the corpuscles.

Nanford in describing the blood of one case (No. 13)
said that in some red corpuscles the haemoglobin was
in a mass (the concentration referred already) or adhered
to be in process of extension, producing a budding appearance. It is difficult to be certain that this budding appearance was not artificially produced.

There is undoubtedly some profound change in the haemoglobin. The fact has been noticed of the power of retaining the fumes formed by the blood in some cases: a recent investigation points to the likelihood of haemoglobin (altered in some way probably) circulating in the blood. The yellow colour of the skin is another indication.

Copenhaver, in examining the blood in some cases of pernicious anaemia, made an interesting discovery. In healthy human blood, haemoglobin is very difficult to obtain in crystalline form, if it be possible; but in cases of pernicious anaemia Copenhaver found that if the blood were rapidly dried, it broke up in a peculiar fashion. "The red corpuscles readily broke down, sometimes disappearing entirely, while sometimes a coarse, granular appearance was left. These specimens after time showed in place of the corpuscles an aggregation of rhomboic crystals of haemoglobin, the spontaneous occurrence of which in normal anaemic blood has not been noticed apparently before."

In the cases in which the corpuscles persisted
crystals developed, but amorphous masses of brown pigment appeared instead; in the first class Copeman thinks haemoglobin is formed externally that haemoglobin is extruded and the globulin remains in the stool.

These and two other points of considerable interest, one that the blood was to obtain haemoglobin from the corpuscles of the guinea pig, into act in them with bile salts, a point interesting from the question of the fact that the liver leaves in the disease, and another that when arsenic had been given to the patient these changes could not be obtained, I desired to know if this change had been observed in any other condition as Copeman kindly gave me the following information (Feb. 15, 1900). I found subsequent to the date of my paper that haemoglobin is apt to separate out from the corpuscles in the allied disease of leukaemia also in some cases of leucopenia 9 of jaemia so that alone this point is not diagnostic. Referring to the latter latest conclusion that the suppressive organism plays some part in pernicious anaemia he adds "It is so if it is not surprising that the occurrence to which I first called attention showed similar cases be common to these various conditions."
Haemoglobin has been recorded as occurring in the prime infectious anaemia, a point of diagnostic importance, a point to be considered in studying the causation of the disease.

Comparatively little work has been done on the specific gravity of the blood in infectious anaemia. The difficulties are considerable; the apparatus is cumbersome and the time required is great, anyway until experience has been brought with its rapidity.

The specific gravity is diminished as would be expected with polaige loss of red corpuscles, but it is impossible yet to say that all the variation is due to the loss of corpuscles alone. Alterations in the serum.

The specific gravity of average normal blood is stated by Boston by 1056, Seid Jones gives 1058 females & 1055.56 for females the latter states that there is a direct correspondence between the specific gravity of the blood and the number of contained corpuscles. He would probably be more correct, he had said there was a direct relationship between the specific gravity and the amount of haemoglobin present.

Conrad in his opinion that estimating the specific gravity the haemoglobin can be estimated more easily than by Fleischels haemocrite equit no accurately.
but he makes an exception in dropsical cases and says that the haemoglobin is about 2° higher in pernicious anaemia than the specific gravity would lead one to expect. Bobst prefers the method of Hug, as modified by Hammer, where a mixture of blood with sufficient sugar is mixed in proportions such that a drop of the blood falls into it, in which point the specific gravity is taken. Tables are published with it, giving the haemoglobin percentage corresponding to different specific gravities.

Few observations have been published on the specific gravity of the blood in pernicious anaemia. Some are published by Prof. Sachs' Case 16. The specific gravity was carefully taken at the same time as the capillary haemoglobin were estimated.

The following were the observations:

<table>
<thead>
<tr>
<th>Red Corpuscles</th>
<th>Haemoglobin per cent.</th>
<th>Specific Gravity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,160,000 - 1,260,000</td>
<td>28 - 30</td>
<td>10.38</td>
</tr>
<tr>
<td>900,000</td>
<td>18</td>
<td>10.36</td>
</tr>
<tr>
<td>1,800,000</td>
<td>35</td>
<td>10.42</td>
</tr>
<tr>
<td>2,450,000</td>
<td>55</td>
<td>10.49</td>
</tr>
<tr>
<td>4,100,000</td>
<td>75</td>
<td>10.59</td>
</tr>
<tr>
<td>3,400,000</td>
<td>70 - 75</td>
<td>10.59</td>
</tr>
</tbody>
</table>

Sachs states rise in specific gravity of haemoglobin, though they did not advance equally.
The increase in specific gravity of the serum of corporcles is not equal, but the method of treatment may have been based on this.

Gould and Hopkins published one observation.
Red cells 1,200,000 or 24% Haemoglobin 18% Spec. 1042.7

John Jones made 9 observations on cases of previous
anaemia as follows:

<table>
<thead>
<tr>
<th>Red Corporcles</th>
<th>Specific Gravity</th>
<th>Result.</th>
</tr>
</thead>
<tbody>
<tr>
<td>970,000</td>
<td>1034</td>
<td>1033.5</td>
</tr>
<tr>
<td>860,000</td>
<td>1030</td>
<td></td>
</tr>
<tr>
<td>696,000</td>
<td>1032</td>
<td>1030</td>
</tr>
<tr>
<td>1,700,000</td>
<td>1036</td>
<td></td>
</tr>
<tr>
<td>1,150,000</td>
<td>1030</td>
<td>1034</td>
</tr>
</tbody>
</table>

In the case that recovered (anaemia) there was a gradual improvement coinciding with a steady rise in specific gravity.

Pernicious anaemia chlorotic stood alone enjoyed a lower specific gravity. In each case there is great loss of haemoglobin, in the one from great diminution of red corporcles even though the value of each be raised or in the other from lowered value of the corporcles.

As will be seen the specific gravity of the blood in pernicious anaemia is considerably lowered at this.
free bears a relation, though not an exact one to the bone red corpuscles haemoglobin.

The blood changes may be briefly summed up as follows:-

Great diminution of red corpuscles with irregularity in shape and size; diminished tendency to rouleaux formation, due diminution in number being greater than in any other diseased condition.

Coincident with this is the total amount of haemoglobin but as a very general rule increased haemoglobin value of each corpuscle - lowered stability of haemoglobin - lowered specific gravity. - Renunciation as a rule of the number of white corpuscles - blood platelets - Abnormal shapes of red corpuscles viz. Eckhov's stellated corpuscles, normo megaloblasts.

In close relationship to these state of the blood are the haemorrhages peculiar to this disease. Consideration of these is of great importance since Stuckner 1772 asserts that 'nonvious anemia' is but a distinct disease and that those cases of anemia which we placed as nonvious derive their special features from the capillary haemorrhages in them seen.
In connection with the external haemorrhages much confusion has arisen. Bremer, Litt, and others are inclined to include under the heading purpurae haemorrhagiae nearly every case of profound anaemia, even if the case is obviously haemorrhage large or small. This is quite inconsistent with Addison's definition of idiopathic anaemia, which is generally accepted in this country through his name. The disease has fallen out of use.

Comparatively few cases of true purpurae haemorrhagiae are troubled with external haemorrhages at the beginning of the disease. This comparatively rare tendency to bleed in the patient remembering any previous bleeding to account for his condition. On the other hand, bleeding from the gullet is very common as a fact that an occasional case of purpurae haemorrhagiae has suffered in this way does not prove connection merely.

When the disease is far advanced haemorrhages of acute and both external and capillary (subcutaneous, submucous, jaundice) are prone to occur. In my second case epistaxis occurred at the end but only once.

Stephen Bruce Rennie has shown that when the red blood corpuscles fell below 50%, there is trend to...
to the occurrence of haemorrhages. Bramwell adds that the longer the capillaries remain below the greater is the liability. Authorities are agreed that the haemorrhage is due to vascular degeneration (Quinck, Conradi &c.) the general view is that there is fatty change in the vessel walls, in other words that the vessels more in the general tendency to fatty degeneration seen in the disease.

Hemorrhages by reason of their frequency are the most important. Quinck found them in 37 out of 110 cases. Bramwell in 15 cases found them in 28, in 12, they were absent, examination made in 5.

In Table 6 they were present in 42, absent in 19 a examination made of renal examination in 26.

Like several other points in the disease, when first discovered, they were believed to be absolutely diagnostic. Bjermer noted their presence in pernicious anaemia and believed that they occurred always in that disease alone, but further observations especially those of Stephen Mackenzie have shown that they may occur whenever the corporcles fall greatly whatever may the cause, but still they are of great importance in aiding the formation of a diagnosis.

In 31 cases in Table 6 these mentioned observations
submucous haemorrhage, in one instance it did not occur till after transfusion.

Most authorities are agreed that external haemorrhage is not uncommon towards the end of the course of the disease, but Bramwell says that as far as his cases are concerned they are rare. In 145 cases epistaxis occurred in 5, haematemesis in 2, and bleeding from bowel in 2.

In table G, external haemorrhages are noted in 24 cases as follows:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>14</td>
</tr>
<tr>
<td>Epistaxis minor</td>
<td>2</td>
</tr>
<tr>
<td>Epistaxis large</td>
<td>2</td>
</tr>
<tr>
<td>Bowels</td>
<td>5</td>
</tr>
<tr>
<td>Stomach</td>
<td>1</td>
</tr>
</tbody>
</table>

Epistaxis is the most common form of haemorrhage, against the view of the haemorrhage being due to vascular degeneration, as epistaxis is the commonest form of haemorrhage in apparent health.

This is to the small capillary haemorrhages that Wickersham attributes the characteristic feature of pernicious anaemia, namely that the iron found in the liver is not available for use. It is possible that these capillary haemorrhages are present in only 13 of these cases. If capillary haemorrhages were present, it would be necessary to examine the evidence closely.
Fever is a very characteristic symptom of pernicious anaemia. It is not always present, but very few cases have been carefully watched for a length of time, without some rise of temperature being observed. The fever can only be described as irregular. It is not as a rule high—100°-101° being about the most usual. In my second case the temperature rose somewhat for the first few days of treatment, but in the first case the temperature did not rise above normal, (this was a case seen not long before death).

In 89 cases in Saive & Joffe's series was present in 56 cases absent in 33 and undetermined in 2.

In other cases than atypical come Pye-Smith has noticed that a few days before death there is a subnormal temperature. This was so in my first case.

On the other hand, Bramwell states that in some cases there is a rapid rise of temperature before death, possibly in such cases a cerebral hemorrhage or other hemorrhage in the course.

Fever has been observed to increase at times with exacerbations of the disease; Lebrie makes a strong point of this in his papers on the disease. A rise of temperature is said to occur in chlorosis where seen in patients suffering anaemia from hemorrhage possibly the slight fever seen in pernicious anaemia
to be attributed to the same cause, probably—

in irritability of the heat regulation mechanism
resulting from a deficient supply of blood.

The paroxysms of fever however are almost certainly

due to increased blood destruction and consequently

the darkened urine, yellow colour and skin jaundice

observed at the same time together with a

fall in the number of red corporcles.

Frequently when the patient begins to improve under

treatment the fever both paroxysmal slightly falls.

A large amount of attention has
 recently been directed to some nervous symptoms

that are occasionally developed in pernicious anemia

nematologically referable to the spinal cord.

The ordinary nervous symptoms that are common to

anemia of any form may be present to any degree.

These are headache, paresthesia, tinnitus aurium,

sleeplessness when the anemia is extreme, a general

tired feeling insensitivity for any exercise mental

or physical at the end there may be delirium.

In my first case there was no delirium

in fact the patient was more in an anemia so severe

and the attendant of his habits became exceedingly

crude. In the second case delirium also occurred at the

last.
Complaint. Edema in one or two cases that developed a transient hemiparesis which also occurred in one of Damescenez cases, but such an occurrence never seen.

Sicklemie in 1899 first called attention to the changes in the cord in pernicious anemia. Taylor in 1899 read before the London Medical Chirurgical Society a remarkable description of the end changes in hemianemia. A careful study of the literature is very interesting. Toorson followed his first account of these changes closely. It occurred in front of the hardening pernicious anemia, especkly severe. Profound anemia following diarrhea, dysuria, with the position of the lesions in the cord. Most of it all of the cases have been fatal, though some have had partial improvement. Some brains of these led to the thought that there is sometimes the correspondence to canine chorea in which disease there are always hemorrhages into the cord.

The cord has been found by Minnich to show signs of sclerosis in degeneration in patients suffering from pernicious anemia who have shown no signs of spinal trouble.

In many cases there has been very severe spinal trouble except perhaps the neural sensation beforementioned.
In examining the body of a patient dying from pernicious anemia, the most striking feature is the general bloodlessness of the tissues, the smaller amount of blood that is contained in the vessels. Contrary to the usual state in diseases of long duration, the body fat is well preserved. This preservation of fat is a very common feature of the disease, Addison speaks of the subject of the disease as "with a strongly marked tendency to the formation of fat."

The same feature is seen in chlorosis, and all probability is due to the disease to the peculiar combustion from imperfect oxidation. It appears in this connection that in the healthy body according to Voit all albuminous substances, when undergoing retrogressive meralaphoses, yield a fixed water, that which undergoes combustion to pass off in the form of carbouic acid from the lungs. This being the case, the albuminous body chiefly concerned is probably that contained in the polyvalent corpuscles, which are extensively destroyed in the disease.

The sympathetic glands are seldom enlarged. Below rated the enlargement in some cases, but they are seldom unusual in regard of polyvalence. It seems when there...
was great excess of white pulp scattered to the ordinary features of pericardium, the lymphatic glands were greatly enlarged.

Reynolds says the lymphatic glands solitary or conglomerated lymph follicles are much enlarged. Slight swelling of the mammae has been occasionally noted which he says is due perhaps to precedent disease.

In no case in Table G are the lymphatic glands described as enlarged.

The spleen is exceedingly anaemic. The sinuses usually empty. Breamble later lays great stress on this point.

The heart is almost always feltly degenerated.

This feature strongly impressed Addison;

William in 1667 described some cases of the disease anæmio-pathic fatty degeneration.

In the 1660 recording pericardium in Table G the liver was fatty in 33, doubtful in 6, not fatty in 3 and mentioned in 4. In one of the 3 where the heart was not fatty the disease was very rapid.

3. Sayler in 1678 examined the remains of 23 cases seen at Guy's Hospital in the previous 40 years and found that the heart was fatty in 19, in 2 it was not, one of these during a rapid case.

Campbell out of 76 cases found the heart fatty in 64.
healthy en to eost mentioned in 6.

By Smith in 102 collected cases found it fully in 78 absent though looked for into most mentioned in 191.

There thus be seen that fatty degeneration of the heart is one of the most common lesions found in the body of a patient dying of pernicious anaemia.

The same condition has been observed after extensive bleeding from the uterus. It also occurs in chlorosis. Partly by means of repeated resection produced the same condition in animals.

There is no doubt that the condition is secondary to this anaemia.

The stomach intestines are not often the seat of a lesion. In my first case the intestines were remarkably thin, but otherwise no lesion was present.

Intestinal ulceration has been met with in few cases but so rarely that it must be considered as an accidental complication.

A rare exchange has been discovered in the stomach but Stearnick published in his lectures on "Aphthous of the Stomach" 4 cases which had the symptoms signs of pernicious anaemia with associated
atrophy of the stomach she was inclined to attribute the anaemia to the gastric condition - Bailey's case published on similar case with full microscopic drawings of the stomach. This case however was undoubtedly a case of pernicious anaemia occurring in a man of pronounced alcoholic habits of long standing, which may quite possibly have led to the atrophy of the stomach, to which in the last quarter of his life pernicious anaemia was referable.

The association of atrophy of the stomach with pernicious anaemia is so rare that the occurrence must be considered to be accidental. However, in his recent paper however, claims these as valid cases as confirming of his theory of spleen being the fundamental cause of the disease.

The spleen is not uncommonly the seat of any change. It is sometimes enlarged, sometimes shrivelled, but more usually normal. Probably the variation in this disease is no greater than would be found in any other series of postmortem examinations. However, it is inclined to consider that the size of the spleen varies with the state of blood destruction immediately before death.

This quite possible that the presence or absence of...
pale at the time of death with affect the size of the spleen.
In some cases an excess of iron has been demonstrated in the spleen, but there is great difficulty in estimating this as the blood is not at all easy to remove entirely.
In table G the spleen is mentioned as enlarged in 9 cases normal in 14 vast mentioned in 23.
The kidney sometimes show in the fatty degeneration
In table G they are recorded as fatty in 9 cases not so in 7 doubtful in 1 vast mentioned in 29.
A greater change has been observed which is of considerably more importance.
In 11 cases in table G pigment has been observed in the kidney, it was not found in 4 no mention is made in 31 cases.
This pigment was first noted by Pepper 90 but the significance was first realized by Mitchell 91 won many cases recorded since then the pigment has been seen in this not always present a careful search failed to reveal it in my first cases others have been equally unsuccessful.
The significance of this pigment is discussed later.
The Liver. The recent researches on the disease
point to the liver playing an
important part in the disease. Its condition must
be fully discussed.

The organ is sometimes enlarged, often fatty.
The enlargement is seldom great.

In tables the liver is fatty in 19 cases, not so in
9 doubtful in 2. Not so mentioned in 16.
The fatty change was noted by Welles, in the early
observers it seems to be a direct reason of the anaemic
state in no way to differ from the fatty degeneration
observed in other organs.

The bile has been observed to be thick and yellow by
Mott 92. Hunter records a similar observation.

Many of the livers in this
disease if treated with extra ammonium sulphide
in potassium ferro cyanide a hydrochloric acid (weak)
give a black or blue reaction and frequently, denoting
the presence of iron (iron in its combination to
form haemoglobin does not give this reaction).

In Table 9, the reaction was obtained in 22
cases in it was doubtful, "haemoglobins into
the fatty patches are described" in 1 it was looked
for not found (this was an apparently cured case
dying of pneumonia) in 22 cases somatic fever
The author insists that the pigmentation is always taken as evidence of parasitic anemia. This is, however, as cases of undiagnosed parasitic anemia have been recorded in which no iron deposit was found in the liver. Such cases have been recorded by Randorin in his first case no such deposit was found.

The same remains however that in the majority of cases where the reaction has been looked for it has been found. Nevertheless states that in all his recent cases such a deposit has been found.

This deposit of pigment granules within the liver cells was first described by Pepper, but Duhrkoop first drew attention to it as a point of importance. At first there was considerable hesitation in accepting it as having any significance owing to the possibility that it was thought of as being due to the injection of iron. A belief not held by anyone now.

Steiner describes the pigment in the liver cells as follows: "It lies within the liver cells and not uniformly distributed amongst all the cells of the lobules. It is most abundant in the cells at the periphery of the lobules, while little or none is found in the cells of the inner kind of the lobule. These latter are far the most packed with fat and quite free from pigment. The pigment"
is in the form of granules fairly uniform in size. It appears to occupy the axis of the round liver cells, but on careful examination with high powers in some cases seen to occupy a more definite relation to the bile capillaries. It lies close to the edge of the cell, as in the process, the cells are being excreted into the bile capillaries. In some cases, the amount of pigment found is less in the liver than ever exceeded—it may even approach that seen in pernicious anaemia. This distribution at once distinguishes the pigment from that found in chronic severe congestion, where the pigment is situated round the central vein of the liver does not react to ordinary reagents, and also distinguishes it from the pigment often seen in cirrhosis in which the pigment is irregularly scattered in masses amongst the connective tissue of the organ.

A considerable number of chemical analyses have been made of the amount of iron in the liver in the disease, and each as will be seen in Table D there is a very considerable excess over the normal amount. Considerable care must be taken to remove all blood from the organ. Shuter rejects Quintin's analyses.
thinking that they must be inaccurate as they read so high, Bowland Hopkins" has no reason to regard them as having included them in the table.
The average in normal livers is given as follows by different authorities.

Hunter 98 0.078 9/10 dried liver as Se 0.3
Vag 100 0.080 - 0.1 9/10 9/10 9/10
Stockman 98 0.070 - 0.09 9/10 9/10 9/10
Stockman in an article on the analysis of liver in the liver spleen gives a table of 19 cases of disease in which anaemia is a prominent symptom including two cases of pernicious anaemia excluded in table. Unfortunately he makes no statement as to the distribution of the iron, which lessens the value of the paper considerably and was written to contradict Hunter's statement.
In 5 cases where in bleeding had occurred - "pernicious anaemia, intestinal obstruction, myxedema, acute tuberculosis - chronic nephritis the average was 0.074 9/10. In 6 cases, 113.8 amyloidosis, nephritis and intestinal bleeding when blood had been extracted the average was 0.026 (highest 0.05 lowest 0.018). A case of benign hypertension gave 0.33 9/10, a case of Addison's disease 0.120 9/10. 2 cases of tropical anaemia 0.166 - 0.262 9/10, haemorrhage into pancreas etc. gave 0.160 9/10, cases of chronic malaria 0.257 9/10.
<table>
<thead>
<tr>
<th>Author</th>
<th>Liver</th>
<th>Spleen</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stadel</td>
<td>0.611</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Graenhearn</td>
<td>0.360</td>
<td></td>
<td>Diagnosis removed doubtful</td>
</tr>
<tr>
<td>Grünke</td>
<td>1.890</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>0.539</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>0.364</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>2.100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>0.600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galaski</td>
<td>0.623</td>
<td></td>
<td>These q are quoted v2</td>
</tr>
<tr>
<td>Rosemaul</td>
<td>0.518</td>
<td>0.227</td>
<td>Hunter 95</td>
</tr>
<tr>
<td>Kelympack</td>
<td>0.702</td>
<td>0.1425</td>
<td>Base bq</td>
</tr>
<tr>
<td>Hunter 97</td>
<td>0.207</td>
<td>0.097</td>
<td></td>
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<tr>
<td>Hunter 159</td>
<td>0.517</td>
<td>0.023</td>
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</tr>
<tr>
<td>Stockman 98</td>
<td>0.230</td>
<td>0.086</td>
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<tr>
<td>&quot;</td>
<td>0.140</td>
<td>0.170</td>
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<tr>
<td>Ratinaud</td>
<td>0.720</td>
<td></td>
<td>Case 32</td>
</tr>
<tr>
<td>Hopkins 124</td>
<td>1.638</td>
<td>0.301</td>
<td>Case 74</td>
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<tr>
<td>&quot;</td>
<td>0.204</td>
<td>0.325</td>
<td>Case 76</td>
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<td>&quot;</td>
<td>0.300</td>
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<td>Case 77</td>
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<td>&quot;</td>
<td>0.190</td>
<td></td>
<td>Case 78</td>
</tr>
<tr>
<td>Stevenson</td>
<td>0.370</td>
<td>0.184</td>
<td></td>
</tr>
<tr>
<td>Mott 92</td>
<td>0.114</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mott 17</td>
<td>0.290</td>
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</table>
The average of the above 22 analyses is 0.581% of iron in the dried liver.

The normal is variously stated as from 0.070 to 0.1.

Taking the average in a healthy liver at the highest figure stated, we see that in pernicious anemia the amount of iron is nearly six times as great as in the normal liver.

The average of the 10 exceptional cases quoted by Starkman is only 0.210% or considerably less than half that seen in pernicious anemia.

Much more remains to be said in the proper place about the iron in the liver, but these analyses show that in this disease there is a much greater deposition of iron in the liver than in any other condition. The distribution of the pigment is also unique.
Sympathetic glands. Weigert\textsuperscript{102} describes a case in which the lymphatic vessels were dilated. The mesenteric glands were swollen and their sinuses filled with lymph containing red corpuscles. Weigert was inclined to believe that this was a supplementary formation of red corpuscles, thus supporting Gibbon's view of blood formation. Reed\textsuperscript{103} describes a case in which there was some swelling and redness of the lymphatic glands. The same author describes another case which seems the peculiar anaemia but in which the white corpuscles were 10 x 10 x 10. There was a marked glandular enlargement. Beier\textsuperscript{186} says that in 3 of his cases the lymph glands were of a rich deep red colour resembling spleen tissue.

Bunting\textsuperscript{105} says that Neumann found the same changes that Weigert describes, in cases of melanoblastoma in which also the bone marrow was hyperplastic.

In no case in Table 4 are the sympathetic glands said to be hyperplastic.

P. Smith\textsuperscript{83} says the sympathetic glands, solitary augmented lymph follicles are more enlarged. "Light swelling of the mesenteric lymph" has been occasionally noticed which he says is due perhaps to precedent diarrhea.
The Bone Marrow. In 1876, Bohmheim published an account of the state of the bone marrow in a patient dying of pernicious anaemia. Previously to that, Pepper had observed that there was great alteration in the bone marrow in some of his cases of pernicious anaemia. The later Sander and Stiller published a case, where the changes corresponded to those described by Bohmheim. At first these changes were thought to characterize a distinct disease from pernicious anaemia, apart which, Peelsmith emphasizes. Bunting makes the following statement that the bone marrow has been found perfectly normal in the majority of cases.

Duinre stated in 1877 that the bone marrow was normal. Neumann showed that the changes occurred in other conditions as atrophy in 6 months, 6 weeks, and 6 days by repeated bleeding.

Considerable discussion was roused as to whether the bone marrow changes were primary or secondary. It was due to the anaemia in many cases, and whether the changes were secondary compensators.

Bohmheim, Pepper, Müller, Rhind, Fleisch all considered that the starting point of the disease
was in the bone marrow, but Neurmann believed that the change was compensatory.

Rhinelander believes that the nucleated red blood corpuscles fail to become transformed to ordinary red corpuscles - Tuller thinks the change is analogous to some tumour growth.

In view of the fact that the same, or nearly the same, changes have been observed in other conditions, it would seem far more likely that the changes are compensatory and not primary. This is the more generally accepted belief.

Huiz 113 however is very emphatic in stating that the changes observed by himself and Rhinelander are not to be observed in any other condition, at least he says none have been recorded.

In many cases recorded however it is made of the bones examined, but this in the shaft of the long bones that the changes are most strikingly shown.

In 7 of 20 cases the bone marrow is said to be hyperplastic. In 20 bone marrows it is made of it, in 1 it is said to be small and that was a case published in 1876 (case 1) - the note is nearly "yellow marrow normal."
This is the only case recorded in recent years where the bone marrow was found unaltered. In a well marked case the marrow from the shaft of a long bone the femur for example has a purplish red colour—something like an overripe strawberry—of presents a very marked contrast to the yellow marrow normally present. This appearance was very marked in my first case unfortunately the piece of the femur kept for microscopical examination was spoiled.

The microscopic appearances are fully described in a paper by Muir, whose description however generally agrees with that of Cohausen & Rhind Flesch.

Muir examined the bone marrow of five cases of purpuric anemia and found the changes most marked in the case of longest duration, a case that had been observed for 15 years. In one case, however, it reappeared again several times and finally died of the disease. The case of the shortest duration least severity was terminated by an intercurrent sickness in which case the bone marrow changes were least developed.

In the most advanced case the whole of the shaft of the long bones except the very extremities was devoid of fat
the long tubules absorbed. The marrow at
the epiphyseal ends was apparently normal.
In other cases, however, the same changes with a
ranging degree of completeness.
Microscopically, there was seen to be an enormous
increase of nucleated red corpuscles.
Some were of great size, 20 μ or more, and two
or three nuclei otherwise showed degenerative
changes which might have been ordinary adult
marrow.
There was no change in the colorless cells.
Cells containing pigment, disintegrating red blood
corpuscles were present in considerable numbers
except in one case, where pigment occurred free, and
without the iron reaction (in all the cases there was
excess of pigment in the liver).
Muir does not attach much importance to the presence
of pigment carrying cells as they are found in many
other conditions, but he notes that they were most abundant
in the case in which the progress of the anaemia was
most rapid just before death.
In the venous sinuses of the pancreas, many transformed
marrow red blood corpuscles were packed close
together, but many of the sinus contained only a few
scattered corpuscles, showing that something further.
was needed to render these cells fit to circulate. The whole process resembles young marrow when a life blood formation is going on, except that the coloured elements largely preclude the nucleated red haemolitic features.

Muir is convinced that the changes in the bone marrow are secondary to the disease, that when the increased demand has lasted for some time, there is a return towards an embryonic condition.

The feature that seems to be peculiar to Pericentric Anaemia is the presence of “giant blast” i.e. colored nucleated cells of large size, with often more than one nucleus other nuclei showing degenerative changes. Muir does not think these giant blasts take any part in forming red blood corpuscles, i.e., thinks their degenerated appearance is in part of their inability to do so.

This corresponds to what has been shown by Howell and others to occur in the embryonic state. N.B. When non-nucleated red cells first appear in the circulation they do not correspond in size to the earlier large haemoloblasts, but to smaller ones that have more recently appeared.

This point out later on there is some reason to suppose that the bone marrow changes are influenced by the administration of arsenic.
Capillary haemorrhages. Stockman insists that these are the cause of pneumonia. In cases of pneumonia, he says, they are not found after death, nor when they have existed before absorption.

Sherwin 117 refers to this point by his experience in the course of Stockman's, and does not find that capillary haemorrhages are so common as to suggest that in his two most recent autopsies, there were a number of scattered haemorrhages in the subdural space. In the retina, he says, elsewhere, in the other three cases none were to be found in the whole body.

Pye-Smith 118 says: "In haemorrhage, since constant or almost as constant a post mortem occurrence as fatty degeneration, this sometimes extensively distributed --- but is rarely large ---. Next to the retina, the most frequent site of haemorrhage seems to be the para-nudus, the surface of the cerebrum, the inner surface of the dura mater ---, then the nerves, meninges, endocardium, the mucous membrane of the stomach and lungs. The Kruyff system of Heintz. Beamwell says, "Small, petechial extravasations are in the great majority of cases present in the retina and in many cases in the pericardium, pleura, beneath the endocardium, on the meninges, sometimes in the skin, and frequently on the surface of the brain."

In Table 4, capillary haemorrhages are only noted.
as being present in 13 cases, as absent in 2 and mentioned in 21.

Only two of these instances are transverse or sub-massascular hemorrhages noted during life.

Some of the cases in Table 9 are said to have had hemorrhages in the last cases I found, but I did not examine the head.

Though there is some divergence of opinion as to the commoner sites of these hemorrhages, there can be little doubt that they frequently occur, though not constantly.

The Spinal Cord. In changes that have been observed in some cases are almost if not entirely confined to the white matter. The sclerosis, frontal is the brain, is most marked in the cervical region, least in the lumbar. In most cases, principally confined to the posterior columns, though in some cases the lateral columns have been affected also, as in me of Taylor's cases.

In some cases capillary hemorrhages seemed to be the starting point of the patches of sclerosis, as others this was not apparent. At a discussion on Taylor's paper at the London Medical-Chirurgical Society, the consensus of opinion seemed to be that something added to the hemorrhage was necessary to induce such marked changes. If this be the case, it would
point to the destruction or blood in the disease being due to some poison circulating in the blood, or else that some product of destruction had a deleterious action on the spinal cord.

Symptoms such as these described by neighbour and others are rare in the disease, comparatively few spinal cords have been examined to see if any lesions similar to those described exist, but probably the occurrence is as rare as the symptoms.

Pernicious Anaemia is I think undoubtedly a special distinct disease, not merely a stage of anaemia but a disease. The result of various causes, but with probability there is one pathological feature underlying the condition known as pernicious, essential or idiopathic anaemia.

There is certainly some divergence of opinion on this point and confusion has arisen which makes the study of the disease more difficult. Some observers hold the opinion that pernicious anaemia is but a stage that may be reached by any anaemic patient whatever may be the original cause of his malady.

Holding this opinion it is quite consistent for them to include any advanced case of anaemia under the title
pernicious anaemia on the other hand to include a large number of conditions as predisposing or causal of pernicious anaemia. The majority of writers in this country however are of the opinion that pernicious anaemia is a distinct disease.

Many of the points that show pernicious anaemia to be a special disease have already been referred to, others will be discussed when the actual process of the disease is examined.

Checking points that have been noted may be again recalled.

First the apparent recalculation of the disease referred to Addison nearly every observer since.

Lips cases have had a previous haemorrhage but they an as small part of the whole, though during the course of the disease some have a tendency to haemorrhage more or less marked.

Considering the number of people who at some period of their lives suffer from epistaxis, haemorrhoids, naevus haemorrhagia, it is only natural to expect that some cases of pernicious anaemia should have in their lives suffered in this way, but the combination is so uncommon as to make it very unlikely that this more than accidental.
Then as other forms of anaemia, be it chlorosis, or the anaemia following malignant disease or frequent haemorrhage, shows a state of blood similar to that seen in a typical case of pernicious anaemia.

In pernicious anaemia the number of red cells is lower than many other conditions (see Table 4).

Babot 121 reports that malignant disease may reduce the corpuscles to 1,000,000 but that is rare in these cases. leucopenia is the rule and the colour index is always below 1 though not below in every case.

In chlorosis he says that out of 109 cases the average number of corpuscles was 1,112,000 equating Thaysen who found an average of 1,076,554.

Bromwell 122 found in 80 cases of severe chlorosis an average of 3,437,300 as a colour index of 0.49. Babot and Thaysen give the colour index as 0.41 to 0.42.

Another point of difference is the age group.

Young females are chiefly attacked entirely, affected chlorosis while pernicious anaemia affects middle-aged people as a rule, males rather than females (see Table 4).

Secondary anaemia Babot says that if the corpuscles fall below 2,000,000 leucopenia is always present. The colour index is always below 1.

Further in leucopenia chlorosis in secondary anaemia
does the blood show a great variation in size of corpuscles or nucleated corpuscles especially nucleoblasts among much more frequent occurrence in pernicious anaemia, their presence in other forms being exceptional.

The chief point in the morphologic anatomy that serve to distinguish pernicious anaemia from other diseases are the absence of any proliferation to account for the disease, the presence nearly always of iron in excess in the liver sometimes in the kidney subfoliculal distribution as observed microscopically. The very marked changes in the bone marrow.

Lastly there is the very important difference in the treatment successfully adopted for the various conditions.

There are certain other conditions which resemble in many particulars pernicious anaemia but which are really distinctly to be differentiated therefore.

Anæmia due to parasites in the intestines resembles in many particulars pernicious anaemia, so also does a rare condition called Sphæric Anæmia obliterata. J. B. has described as a 'Anæmia of Brona Characters occurring during Pregnancy,' which might be mistaken for pernicious anaemia, if carefully observed.
The anaemia due to intestinal parasites is usually the result of the aklysobomia duodenale, or the Bothrioccephalus latum, both highly prevalent in this country.

As the parasites harbouring these pathogens, the patient becomes extremely anaemic even before the anaemia. The discovery of these bodies, however, places these cases in a distinct class for a cause has been found sufficient to account for the anaemia.

Furthermore, point of distinction is about when the parasites have been removed the patient usually recovers. There is some divergence of opinion as to how the parasite acts. Bovin Rate insists that in aklysobomiasis the intense anaemia is due to less loss of blood from the intestine caused by any toxic blood destruction in the liver or elsewhere. While the average percentage of iron in the liver is less than in other diseases. Stockman agrees with him on this point. Again, in 5 cases from cases of aklysobomiasis that the iron was considerably less than normal. 0.21–0.50%, as against a normal of 0.07–0.09, but severely, he found in two cases of tapeworm, anaemia a percentage of 0.16%–0.36%. And against the iron present in the liver. Daniels, after a study of many cases of aklysobomiasis and tapeworms, found that the evidence pointed to a toxic effect.
of the parasite and the loss of blood—being the cause of the profound anaemia, a belief which is not supported by the analysis of the livers.

The greater perniciousity of the anaemia due to parasites compared with the pernicious anaemia of anaemia is another point in favour of a distinction between these two conditions.

Scheiner—72 cases—anaemia due to Proteuside and no cured 50, mortality of only 16%.

The evidence seems on the whole to be in favour of regarding the profound anaemia produced by these parasites, as being due solely to the constant abstraction of blood, but whether this is an anaemia resulting from direct loss of blood, or one just totally distinct from true pernicious anaemia.

Scheiner generally held this view but apparently he now thinks that the presence of these parasites in the intestine favours the production of the infective process that he believes to be at the bottom of the disease.

Splenic Anaemia is an extremely rare condition characterized by enlargement of the spleen, profound anaemia but no leucopenia. The haemoglobin is usually considerably reduced, while changes in the
Anaemia described by Blaize as occurring in pregnancy of some interest.

She saw three cases in which marked anaemia developed during the latter months of pregnancy, labour was safely accomplished with no unusual loss of blood, but the patients all sank after it. Grafe had collected 25 similar cases nearly all died, probably many of Dr. Keats and Biemans's early cases in which pregnancy was given as the starting point were of this nature.

Blaize is convinced that in these cases the anaemia was due to defective formation of the symptoms described point that way.

These cases would seem therefore to be more allied to chlorosis, yet identical with it.

Chlorosis is supposed to arise from failure of the blood forming organs to cope with the extra strain involved in the establishment of full sexual activity, and it is reasonable to suppose that in these cases the blood forming function had broken down under the strain involved in keeping up the placental circulation.

It would be interesting to know what proportion of these cases suffered from chlorosis in earlier years.
Pernicious Anaemia being considered to be a separate disease, how is it caused?
The insufficiency of red blood corpuscles must be the result of deficient red blood cell formation or excessive destruction or combinations of the two.
When the bone marrow changes in the disease were first discovered the knowledge of the blood forming function was not so well established and was thought by Pepper to be that in this change in the marrow to be the cause of the disease.
Pyelomatic stated that the bone marrow was normal in the majority of cases thought that those cases where it was found to be altered were to be distinguished from "idiopathic anaemia". It is quite possible that in many just all of the cases in which the bone marrow was said to be normal only the normally red marrow (red bone) was examined, in some cases this was stated to have been done, therefore the change from yellow to red was not observed.
Nearly all just all the cases recorded in more recent years have shown that the bone marrow is hyper trophyed and evidence tends to prove that
It is purely emperative, a point upon which Russell most emphatically.

The fact that the same hypertrophy has followed in cancerous prolonged anaemia, when repeated bleedings experimentally performed on dogs is practically conclusive.

We may therefore conclude that the deficiency of red corpuscles is not due primarily to deficient formation, that is, as evidence to show that there is defective formation i.e., that the disease starts from corpuscles of lowered vitality being launched into the circulation, whatever may occur when the disease is established the demand becomes too great for the bone marrow.

That this state of affairs does exist, let us assume, for the corpuscles become irregular in shape, enucleated corpuscles appear also, indicating that the marrow reacts equal to the strain put upon it.

If there be an insufficient deficieut formation at the beginning, because the diminution in the number of red corpuscles, then there must be excessive destruction for loss of corpuscles by external bleeding has been excluded.
The points that must be considered are:

1. Is there a destruction of red corpuscles uniformly?
2. If so, where does it occur?
3. Is it an active destruction or merely the disposal of effete corpuscles?
4. Is there any evidence that this destruction is increased in pernicious anemia?
5. Lastly, given an affirmative answer to the above questions, what is the actual factor that causes the increased destruction in pernicious anemia?

The first 3 questions fall to be discussed together.

Strickman denies that there is any active destruction in the liver, but gives no facts to support his denial, nor evidence to refute the contrary statements of others.

Professor White in answer to an inquiry, says: "With regard to the destruction of blood corpuscles it is generally admitted by pathologists that it must chiefly occur in the liver, though there is not much direct evidence on the point."

Sir Michael Foster, in an article recently published, says: "Though we have no means of directly determining the average duration of life of a red..."
corpuscles, it must be short, since the whole quantity of bilirubin secreted in the bile is supplied by the haemoglobin of red corpuscles. The production of this must entail a large daily destruction, although the origin of the main urinary excretion pigments is at present obscure, we might probably conclude that an additional destruction of red corpuscles takes place in order to provide an additional quantity of haemoglobin for these.

"Somehow this daily destruction along also daily birth must also be going on."

Russell considers that blood destruction occurs in three sites, of importance, namely, named viz. liver, spleen, bone marrow.

As regards the latter two, in each large corpuscle, holding cells have been described in which the corpuscles are destroyed in man;

it would seem that this is a means of destroying dead or effete corpuscles which entirely from the process believed to occur in the liver.

Neville Paton in two papers on the "Relationship of area formation to bile secretion" and on the "Nature of the relationship between area formation to bile secretion," details some most elaborate extensive investigations this conclusions are.
most valuable.

The first showed that drugs that increase bile secretion also increase the production of bile, performing his experiments on animals that had been brought to a state of nitrogenous balance. Next he set himself to study the nature of this relationship.

She quotes the experiments of Baranoff, Stadelmann and Saranjiw, who showed that the injection of haemoglobin, distilled water or toluidinedrene increase bile flow especially the pigments of distilled water. Toluidinedrene is known to break up the haemoglobin in the blood, therefore it is to be supposed that they thereby increase the bile flow.

He further quotes Parren, David e Vredenhagedes as all agreeing that blood corpuscles are destroyed in the liver. The lastmentioned found during digestion a great diminution in blood corpuscles in the hepatic as compared with the portal vein, in fasting animals this decrease was very much lessened.

Noel Poton adopted an identical formula for haemoglobin advocated by Charles and then conducted a series of experiments by injecting various blood destroying
substances into the circulation of animals in a state of nitrogenous balance. She then found that allowing fats to increased production that necessarily follows destruction the amount of protein corresponded very closely with the amount of haemoglobin lost. In an old animal where reproduction would be less active, the correspondence was most close. This noteworthy that one of the animals became jaundiced immediately after the injection. She then examined the effect of salicylate of soda on the blood outside the body (Salicylate of soda being chosen on account of its great power stimulating the bile secretion). She pricked the finger through a neutral solution of the substance, then examined the effect on once under the microscope. These observations are worth recording in full as they seem to shed some light on the process of destruction. The changes occurred in the following order:

1. Tracheal crepitations appear round the pharynx of the neck.
2. These crepitations become sharper longer with the enchelis shrink in size assume aspherical shapes.
3. The pharynx next become more numerous, entire
covering the surface of the enpurasles at the same
time they become shorter.

2. The epips finally disappear leaving a small
highly refractile deeply pigmented sphere.

3. I would here point out how exactly similar this
body is to Liebent's enpurasles.

6. The haemocyte now slowly increases in size
becoming paler on close examination it is
seen to be granular, the granules appearing to be
an active state of granulation within the haemocyte.

6. The granules become more more apparent
agrow larger and seem to collect the pigment
around them, so that we have a colourless cell with
a thin layer of pigment under the membrane
throughout the mass of pigment in the cell.

These faint granules seem to be exactly similar
to those found in live liver cells in perennyporous areas.

7. The pigment is gradually dissolved out-
re-colouring the blood serum - spheres within the
cell colourless masses of the extracellular
stroma (Schäfer denies the existence of this stroma).

8. These masses become less and less distinct finally
and almost homogamous colourless transparent, a faint
shadow is left which resembles detection very
delicate focussing. (These two changes correspond
very closely with what Telephine states occurs as a normal process in the liver).

These experiments are not necessarily an exact reproduction of a natural process but as he had shown that salicylate of soda had a marked effect in increasing bile secretion had shown that the increase of bile secretion was due to increased blood destruction, it is quite reasonable to suppose that salicylate of soda would act on the blood in a similar manner to that which it does in the liver.

And Paton's conclusions are as follows:

1. That the destruction of blood corpuscles must be considered as a powerful stimulant to bile secretion, the liver having as one of its functions the elimination from the system of excess haemoglobin.

2. That urea production is also increased by the destruction of the blood corpuscles.

3. That bile secretion and formation have a distinct relationship to one another, that this relationship is due to the dependence of both on destruction haemoglobin.

4. That the cholagogue action of salicylate, either pae of soda, colchicum, of chloride of mercury, as well as their influence in increasing the production of urea is due in a great measure at least to their direct haemolytic action.
Koch \textsuperscript{92} insinuating on the subject says: "The pigments of the meconium which is really bile in a concentrated form, is the outcome of a breaking down of the red corpuscles during the latter period of fetal life. Moreover it is well known that during the last tenth two of embryonic life the nucleated corpuscles have disappeared, their pigment it maybe assumed, having gone from bile pigment. Yet during that period when the bile cannot possibly have any function, it is still formed by the liver, indicating that it is only a product removed from its haemolytic function."

Hunter \textsuperscript{129} in his lectures on the destruction of blood discusses the subject very fully. He observed that there was little doubt that bile pigments were a product of blood destruction, that though attempts had been made to show there was a quantitative relationship between the loss of haemoglobin and the amount of bile, they had not been absolutely conclusive.

He further points out that haematoxilin, is often found in old extravasations of blood, is chemically identical with bile pigment, that the pigments that cause the colour of bruises are indistinguishable from bile pigment.
She pointed out that this pigment, the results of extravasation is sometimes found in the liver in certain chronic cases; but that, that this is confined to the lining of the capillaries in the fat tissue. Described however in the central zone of the lobule, in one case of chronic cases, a yellow pigment which gave copper reaction against which supports Delépine's view.

In birds, where he found iron containing pigment frequently in the capillaries in animals where corporacles are large, he rarely found it in mammals other than to a much lesser extent.

In birds, in mammals but none in the former. Careful examination showed granules of pigment of a uniform size inside the liver cells, but not to a great extent in health.

The note of great points of distinction from the irregular masses found in the capillaries, that found within the cells being uniform and the granules small; wherever the size of the corporacles, which are that found in the capillaries is not more abundant in old than young animals.

It was also rather diminished by absence from food exercise, in which he agrees with Delépine who found it much increased by digestion.
Hunter did not find in diseased or healthy much accumulation of pigment in the spleen; there was sometimes an accumulation but generally in old animals it was also seen after transfusion. There was great variation in different healthy spleens.

Very much the same state of affairs was found in the bone marrow, a small quantity of pigment usually being found as a rule more in older animals than younger.

Hunter, however, distinguished two modes of blood destruction, active and passive.

In the former, consisting in effete corpuscles being taken up bodily by leucocytes, the spleen cells, then the pigment becoming deposited in granules of varying size in the capillaries of the spleen or liver (chomeneus).

The active form he considers occurs in the haemoglobin being liberated. He considers that this occurs in the plasma, that the haemoglobin is liberated in the most part carried to the liver where disposed of in the bile, some escaping disposal in that manner becoming deposited in the granules of blood pigment.

This will be seen later is not quite the case as Wellcome's view, but the two are not irreconcilable but rather complementary one of the other.
Druez showed that bile formation is exclusively the function of the liver cells, and that the accumulation of pigment in the capillaries has no effect on that formation.

His experiments with the injection of toluidine showed him that an increased formation of bile pigment is more frequently associated with an increased deposit of blood pigment within the liver cells than it is with increased deposit within the capillaries.

Further, that such an increased formation is frequently attended solely by an increase of blood pigment in the serum situation, not a particle of pigment of a single pigment cell being discernible within the capillaries.

And lastly that a large increase in the pigment cells within the capillaries can take place without any increased formation of bile pigments.

Druez does not believe that the actual destruction in the active form takes place in the liver. By injections of toluidine into the circulation of rabbits (these animals were chosen because the drug had not a very toxic effect on them) he believed he was able to reproduce the features of active destruction in his description of the effect on the blood resembling very much what Chevalier describes as occurring from the direct action of phenylephrine upon the"
by "small coloured phænæs", granules appearing in
the thymus & "shadow corporacles".
The effect of small doses was limited to the spleen
in all cases that effect was much greater in
the spleen than in the liver.
He then injected the drug into animals whose spleen
had been excised, with the result that small doses
had no effect, large doses very little. There was not
the increase of bile pigment observed in cases where
the spleen was present.
He concluded therefore that the haemolysis chiefly
occurs in the spleen, the haemoglobin being carried
to the liver at the disposal of which the presence of
bile pigment in the liver is not necessarily a sign of
destruction having taken place there.
Next in importance to the spleen he notes the gastro-
intestinal capillaries because when the spleen was
excised he found more evidence of blood destruction
there on injection of large doses of staphylociæmic
than anywhere else.
The spleen the liver is the true place, considering its
function in haemolysis is largely if not exclusively
to excrete the products of haemolysis.
He thinks that probably some of the haemoglobin is
set free during digestion (on which time he states the
process of haemolysis is most active) that one need expect blood formation, the rest being excreted as bile pigments.

He adds a note that his observations on the spleen being largely to give it more licence.

The great difficulty in the way of accepting Hunter's work on blood destruction is its entirety, in that it is so very largely based on the effects of one drug on one part of animal.

This time that thymethylamine acts in quite a different manner to propylamine acid only cause a distilled water in that the blood destruction is induced takes place in the portal system entirely that it never induces haemoglobinuria as expected and by stimulating the blood destroying function and by direct action on the enzymes.

Again, however, the standard clinical experience or other experimental observation does not agree with Hunter in allotting any special role to the spleen in blood destruction.

Hunter certainly found that the spleen became rapidly engorged after the injection of thymethylamine that removal did not stop or severely limited.
the processes of destruction which also found the products of destruction most abundant in the spleen.

The question is, did he by these means reproduce in an exaggerated form the natural process? Further observation is needed to confirm this, but supposing it to be true then we must regard destruction as taking place chiefly in the spleen, the function of the liver to be merely to excrete the haemoglobin seen simply as bile pigment.

The granules of pigment to be seen in the liver cells are merely stored there, not manufactured there.

Sherrington has written in a paper on the cholinergic junction in the liver, which was the outcome of some work done in cooperation with Leonard de Quinton, makes the following statements which are founded on his experimental observations.

A. Pigment is found constantly in the liver cells, also in some of the endothelial cells of the intra-lobular blood capillaries.

Certain variations are observable in this pigment.

1st It may be in particulate form, i.e., precipitated.

2nd It may be diffused through the cell, i.e., in state of solution.

Variations are observed in amount quantity, size, coloration, distribution.

B. The pigment gives not clearly the reaction of
Ferric salts, the reaction is most intense between 2 and 12 hours after meals; it reaches a maximum immediately after ingestion of food.

C. The iron reaction is easily obtained with Sulphide of ammonium, or Barro Sulphydroxal of Potassium.

D. "I have not been able to find any trace of pigment giving the same reaction either in the blood vessels (portal, hepatic, capillaries, etc.) or in the bile ducts, large or small.

Under certain exceptional conditions (pathological) I have found occasionally a small quantity of iron-containing pigment in some of the main bile capillaries, but under normal circumstances I have found the bile capillaries free from iron-containing pigment except at their point of origin."

E. The iron-containing pigment was a pale, most abundant in the portal zone; it has even at certain times becomes comparatively abundant round the hepatic veins.

F. "The pigmented cells of the capillaries seem at times to be free within the capillaries." I have however never found them elsewhere than in the capillaries. On one occasion however I found in the same capillaries small cells of the size of red blood corpuscles giving the reaction.
c.) When through obstruction of a terminal bile passages bile accumulates in the bile capillaries, more containing pigment accumulates than in an extraordinary extent in the portion of the liver tubes corresponding to the point of junction of the secretory excreatory parts also in the endothelial cells of the capillaries surrounding the abovementioned tube. (This should be read in the light of Besseigne's description of the liver structure i.e. that "the liver tubes instead of being grouped round the terminal hepatic veins are distinctly arranged as small pyramidal masses, which correspond to the lobules of the gland.")

From these observations he wanted to the following conclusions.

1. After the destruction of red blood corpuscles in various parts of the body a soluble albumino-granular compound is found which does not give the reaction of jec vision. This is supported by the analysis of Besseigne 1872.

2. This comparatively stable compound is decomposed slowly, partly decomposed by the liver cells, then the iron can be revealed by some tests not by others.

3. This compound is at first in a soluble form, is probably mixed with the raw bile just produced.
by the cells, but as that bile passes between the liver cells, part of the iron is probably absorbed or precipitated in the cells in the shape of granules, a part remains in the elaborated bile as is proved by the observations of Htzenz of Leipzig.

6. This insoluble albuminous ferruginous compound accumulates in the cells, whilst the elaborated bile is excreted. The amount of iron thus separated gives probably a fair idea of the amount of bile produced.

7. When the active secretion of bile has stopped, the ferruginous pigment is slowly redissolved—-passes back into the vessels.

8. It is probable that this ferruginous elaborated deposit is absorbed in certain endothelial cells which may thus have a haemogenic function. Serum may also absorb that pigment, which is also carried by the plasma to various organs of the body. The plasma would thus always contain a certain quantity of iron ready for assimilation by the red corpuscles.

9. She therefore believes that the liver has "ferruginous" function by which she means—

A. preparation of iron ferruginous iron containing pigment

B. A storage of that iron in the form of a loose compound

C. The gradual formation of an iron stable
albuminoid compound analogous to haemoglobin ready for assimilation by the young red corpuscles.

In another paper Delboeuf insists on the necessity of excluding excess of potassium ferrocyanide. The equal importance of preserving an nearly definite hydrochloric acid in testing for the iron, if that method be used to detect the presence of the iron, is shown in ammonium sulphide which favors sulphur.

It is also found that when tissue has been immersed for some time in a mixture of 2 parts proof spirit and 1 part glycerine the per reaction will often appear when it has been absent or doubtful before. In the instance of the case of "pernicious anaemia" in which the kidney is said to have the per reaction, the liver being doubtful, after a few days in the mixture the kidney reaction was more pronounced, with a faint green of the liver gave an abundant reaction.

It thus seems therefore it is quite logical to assume that the iron was a little greener in the kidney than in the liver that the iron in the liver was evidently an intermediate product between those colorless albuminates which do not yield the per reaction before their organic connexions have been artificially broken up, those other compounds which are found accumulated in the liver a certain number
of hours after a meal via certain diseases (such as "pernicious anaemia").

Wolff-Pack makes a statement which supports this belief. He says "In distribution of iron pigment as detected by the carminoid test does not correspond entirely with the arrangement of the brown pigment as seen in stained sections; suggesting the possibility of the existence of iron in different combinations, one giving the microchemical reaction the other not. Moreover, it appears very likely that a portion of the iron may be present in an insoluble colourless condition. This would explain the diffuse staining as described."
examined by these observers. After the injection of various drugs, careful examinations were conducted on the livers of rabbits kept in similar circumstances without drugs.

Then it occurred that many drugs increased or diminished the "ferroenic function" of the liver among those that very markedly diminished the amount of free iron in the liver, and Tolkmitt, in the drug upon experiments which Hunter based his belief that the destruction takes place in the spleen.

The evidence above cited shows very definitely that there is a great daily destruction of red corpuscles required for the production of bile pigments in the parvoes.

The exact locality in which the actual destruction occurs is not proved with absolute certainty.

Hunter has satisfactorily demonstrated that it occurs in the portal system.

The majority of observers among whom are Trotter, David Hott, Niedrals, Peter von Schäfer all agree that extracting points to the destruction within the liver. Niedrals' comparison of the blood entering and leaving the liver together with Tolkmitt's proof that the elaboration is but the actual separation.
of the haemoglobin, takes place in the liver, make a strong case for the belief that the actual destruction does occur in the liver.

Hunter however regarded the spleen as the chief site of destruction. He bases his belief on the action of anodyne drug, Ethylmorphine, which he supposed stimulated the normal process, on the observation of an exceptional ease of pernicious anemia in which the spleen was found enlarged, engorged with blood and some products of destruction. There is not much evidence to support Hunter; on the contrary, directly traversing his belief we have Prof. Schäfer's statement that there is no evidence of any marked alteration in the blood in the spleen, as shown by comparing the artery veins.

The fourth question must now be considered...
In the case of increased blood destruction in Pericardial Arteria?

Such evidence, if it exist, would be expected to find, in the blood itself, in the excreta, or in the intestines and the liver; and the question is,

The Blood. I have already shown that the number of corpuscles is greatly reduced in some cases, while in almost any other condition the exception being extremely rare. I have also shown that there is no reason to think that there is any diminution in production, but that on the other hand, the evidence shows an increased effort to cope with the great loss, as shown by the hypertrophy of the bone marrow and the condition of normal blood formation.

If then the corpuscles are greatly reduced in number and production is still undiminished, we are driven to the conclusion that there has been a great loss of blood corpuscles. This loss may occur in two ways, by bleeding in that the corpuscles are lost to the body, or by an increase of the normal destruction of the corpuscles.

Numerous cases have been recorded where throughout the disease no bleeding of any kind
occurred in the course of the disease (except in the cases referred to).

Also in cases where bleeding has occurred, it has not been at the beginning but at the end of the course that it has occurred, as unless my second case.

Further, when haemorrhages have been recorded, they have seldom or never been sufficient to account for the presence of purpurae in the blood. We must therefore conclude if the above facts be accepted that the loss of blood is due to destruction —

I shall refer later to the theory that the capillary haemorrhages are capable of causing the disease, as it is sufficient here to state that I think it is inconceivable —

If the loss of corpuscles were due to bleeding the haemoglobin value of the corpuscles would be diminished, at least such is the case. During the early stages of restoration after haemorrhage, the corpuscular count never reaches a point above the normal.

In praecocia anaemia as those already pointed out, the haemoglobin percentage is usually even below normal colours the percentage of the corpuscles in many cases.

The haemoglobin or done value is much above the normal.
This excess of haemoglobin may possibly be the factor that explains why in pernicious anaemia the corpuscles fall lower of red blood figure than in any other condition except the febrile conditions.

This purely said, that this excess is entirely due to the corpuscles holding more haemoglobin than normal, but this I rather doubt. There is no doubt of course that the corpuscles do hold more haemoglobin than normal, but also I believe some is held in the serum in solution.

With the ordinary haemoglobinometry of parasitic infections possible to determine this, but those in some cases when examining the blood microscopically that the individual corpuscles did not seem so highly colored as one would have been led to expect from the haemoglobin estimate.

Stevens made a similar observation. Broadhead noted in one case that the blood stained the finger very tenaciously (this of course would be explained by the colour being dissolved out of the serum by the action of the air).

This excess of haemoglobin carried by the corpuscles is possibly by the serum can be explained by supposing so great a destruction of red corpuscles to have
occurred in the liver that all the haemoglobin is not excreted, but some of it (or modifications thereof indistinguishable by colour methods) remains in circulation. It is absorbed by the capillaries remaining in coagulation in the serum; this explanation is quite consistent with Telephine's observations also with Hunter's.

In the blood of many cases bodies called leukocytes have been found; they seem to be normal in cases of rapid progress. They were especially numerous in case 52, a case where destruction seemed to be intense. They have also been seen exceptionally in other diseases in health.

It will be remembered that Polon Telephine Hunter each describe similar bodies as the products of destruction. Telephine in the normal liver, the other two as products of artificial destruction, the fact outside the body, the last native.

I think their presence in the blood may perfectly well be accounted for by supposing that they are products of blood destruction that their occasional appearance at other times (ie in health or other disease) indicates some slight alteration in the destructive process in the liver, or that their appearance in large numbers in man cases of typhus as some indicates.
that there is still further a much more pronounced arrangement of that condition.

Another thing in favour of their being a product of destruction is that they disappear as the case improves.

Dependent on the blood in the prurigo, that is frequently seen in the skin, a tint which is to be carefully distinguished from jaundice.

This is another evidence of destruction or at least gangrenosity of the blood, so it can only be explained as staining due to haemoglobin or pigment, derived therefrom, the staining body exuding from the capillaries into the surrounding tissues.

This staining of the skin is another point inferential of there being some haemoglobin in many cases at least, in relation or suspension in the blood.

The evidence from the excreta is of great value.

The bile may for the present purposes be regarded merely as an excretion.

As has been shown, the pigments of the bile are formed from haemoglobin, the more so that this be increased in destruction of the blood and on consequence anaemia.

An unusual eruptive redness that bile is increased and that the pigments are increased.

In some cases of purpuric anaemia, though at a black
numbers, there has been jaundice. This has usually occurred in the early stages of the disease, especially in cases of rapid onset, e.g. case 52.

In many cases the liver has been enlarged or tender, it was so in my second case, in case 52 — in the latter of Bowland Hopkins' cases in all of which destruction was active. Rarely, however, the stools were of a normal or nearly normal colour. Only one recorded case has been found in which the stools, noted as white as leucokalanthasa (as that is recorded by Gibbon) 

Observations on the Jaunee are however very rarely made or recorded.

The enlargement of the liver is frequently noted, coupled with the appearance of jaundice - the maintenance of the colour of the stools (for it is true, almost certainly, as noted) but more decided than a being an increased production of the pigments of the diet (as a rule milk) is the tend to make the Jaunee lighter in colour.

Further stimulation of the liver causes perioisis. Palmer has shown that some chologogues act by causing blood destruction. Therefore it is probable that the appearance of this disease is due in part at least to the blood destruction.
In this way it is possible to account for the vomiting disturbances of jaundice. Vomiting is well known to occur in many conditions when the liver is involved.

If the watery constituents of the bile are found as fast as the pigments then the bile is green carried into the intestine, but should there be lack of the watery constituents then the bile becomes thick, it remains flat consequently the liver becomes enlarged and as the bile is greed into the intestine jaundice results. When the patient improves, i.e. destruction diminishes these disappear.

But this point Hunter says, "In observations of Stedlerman and Galenius have shown how frequently some degree of jaundice is associated with increased destruction of blood induced by the action of such drugs as lobelia, cochineal. These observations also show, in part, at least an explanation of the jaundice.

The increased flow of bile (polycholia) which always in the first instance results, is soon followed by increased consistency of the bile, greater viscosity consequently obstruction in the biliary ducts. A similar explanation doubles applicability in many instances in the case of jaundice..."
rrot" I found in the case of Mrs. E., that when destruction was more rapid, the bile was "thick and yellow". Hunter also found a similar observation, but apart from these two observations, the state of the bile is not well known.

Cases have been recorded by D. Smith, R. M., T. Broadbent, in which, the patient was observed to become worse at the same time the yellow colour of the skin increased or reappeared. In each case, the skin was diaphoretic. In the case of Mrs. E., the skin became very dark, and the urine became dark also, owing to the cells holding pigment. In Mrs. Smith's case, the umbilical red empyema was found to be greatly diminished after this exacerbation. The evidence from the medical and anatomical history has been stated before. It will be remembered that jaundice disease has been found to cause a great percentage of iron deposited within the cells, as in other conditions in the liver, and in iron poison poisoning. In short, there is evidence that whatever part the liver plays in normal blood destruction, it carries that part to excess in jaundice, and jaundice.

The percentage of iron in the spleen is not, as a rule, greatly increased.
In some cases it is increased. The explanation of this is not easy to find. Such cases have been recorded by both Hunter and Hopkins.

If, of course, if Hunter's theory be accepted as correct, the actual destructive process takes place in the spleen, then it is easy to understand that either death has taken place while destruction has been going on, or products of destruction have been left behind in the spleen, possibly because the liver was unable to take them up.

Such a view would, of course, be supported by Hunter's case in which the blood destruction had been extremely acute just before death. Hunter himself suggests that the spleen may have a larger share in the blood destruction in the disease than is generally supposed. On the other hand, Kellogg's published a typical case in which the spleen presented an increase of iron, as shown by bacteriological and chemical analysis.

Further there is the fact that the majority of spleens in the disease show no change.

A possible explanation of the occasional excess of iron in the spleen is that the destructive process in the liver has been so acute that a large amount of the products have been forced into the general
circulation have been retained by the spleen, perhaps stored up until the liver can dispose of them, it is interesting to note that Hunter found, in this case, only haemoglobin in excess in the spleen, the red corpuscles were few in number.

The urine. The evidence of excessive destruction is very well marked here in many cases.

In the first place, many cases of those that have been recorded lately, the greater number, are characterized by a urine of dark colour, low specific gravity.

But the dark colour is not due to concentration; it is shown by the quantity being normal, the specific gravity low.

The dark colour is not constantly present; when intermittent, may account for it being missed in many cases.

Little attention was paid to the urine until Hunter drew attention to the dark colour in papers on its influence. At present, comparatively little work has been done on the urine in infections anaemia, but what has been done, goes to show that it is the pigment abnormal generated from haemoglobin that is high colour just as in asphyxia.
Haemoglobin itself has been found in the urine of pernicious anaemia patients, nor have bile pigments except in those cases that are suffering from jaundice.

In Hunter's case the urine became much darker with the exacerbations of the disease. The same was noticed in Hopkins' fourth case (case 11). On the other hand, the dark colour has been observed to disappear in cases that responded favourably to treatment of case 52 according to Smith.

"Pernicious anaemia has been demonstrated by Hunter. Hopkins & Smith" in the urine of pernicious anaemia, but Hopkins is strongly inclined to believe that this pathological produbin is merely a mixture of ordinary produbin or decompofosphin. He also notes that though pathological produbin is usually found in febrile conditions it is seldom seen when pyrexia is not slight as in pernicious anaemia; it may be seen in pernicious anaemia with a perfectly normal temperature.

Hopkins has also seen it in cases of leucocytosia with slight pyrexia, in hepatic abscess or other conditions where the function of the liver is greatly interfered with, but he considers its presence rare.
Normal for him: he found almost constantly in the
wine of the five cases of pernicious anaemia; the
quantity was not increased that found in normal
wines, but there was a characteristic feature
present in pernicious anaemia, that the absorption
had at, that the speckle was present in perfectly
good wine, it was not so in other wines.

Staphylin says that the qualitative analysis is
vague, but he doubts mobilin much increased-
supernuous anaemia. "It is certainly not responsible
for the whole of the hyperpigmentation of the wine,
for other pigments are also increased; take a
large piece of this." Leigien use quoted by Matt
states that mobilin is always increased in all
diseases where there is increased disintegration of
red blood corpuscles.

The evidence to be found from the pigments of
the wine is not perhaps conclusive, but the fact
that they are increased at the increase is correlated
concurrently with other manifestations of destruction,
taken in conjunction with the generally accepted
feeling that primary pigments are ultimately derived
from the destruction of haemoglobin, are a further
indication, though not perhaps actual proof, that
there is increased destruction of blood in pernicious anaemia.
The evidence upon the excretion of iron in the urine is very inconclusive. Hamberger and Jacobs found that very little iron was secreted by the kidneys when introduced into the body; the one by estimating the amount obtained from the feces compared with the amount introduced into the plasma; the other by injecting intravenously iron salts and collecting the urine from the urinarius.

Suter states that the amounts secreted in health are variously from 2.59 milligrams to 16 milligrams.

As will be seen from the analyses collected in Table 6, there is not sufficient data to form any definite conclusion as to the amount of iron excreted by the kidneys in cases of anemia.

Suter's observation of iron pigments in the urine of one case which carried iron containing pigments has not as far as I can find been repeated by any one else.
### Table E

<table>
<thead>
<tr>
<th>Author</th>
<th>Condition</th>
<th>Iron in urine</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunter</td>
<td>Health</td>
<td>5.65</td>
<td></td>
</tr>
<tr>
<td>Hopkins</td>
<td></td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Hunter</td>
<td>Chlorosis</td>
<td>1.4</td>
<td>Some two cases were</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.96</td>
<td>Degeneration of retinal vessels.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.61</td>
<td>No treatment.</td>
</tr>
<tr>
<td></td>
<td>Purpurae</td>
<td>32.26</td>
<td>Three observations on same patient.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.52</td>
<td>of same patient.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.00</td>
<td>Patient relapsed.</td>
</tr>
<tr>
<td>Hopkins</td>
<td></td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velpeau</td>
<td></td>
<td>6.6</td>
<td>Quality 320 grains.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.96</td>
<td></td>
</tr>
</tbody>
</table>

The amount of iron excreted in 24 hours.

**Urea.** Dr. Paton's observations he correct, since there is nothing to show that they are not, we should expect to find in jauniceous cases an increased excretion of urea. Such increase should be more marked in the exacerbations of the disease, when such occur, unfortunately no continuous observations on the urea excretion seem to have been recorded.

There are of course many difficulties presented by the frequent diarrhoea, & other causes.

There are a few peculiar observations on the urea.
excretion in the cases in Table 4.

Table 150 gives a table of the analyses for a week on one patient. The average was 2.61 gm. of urea. The urine was little daily variation, the patient all the time was troubled with diarrhoea.

Hunter records an observation of 1.7 gm.

Sheal by six cases found that 211 gm. of urea were excreted per day.

The normal was given by Sandoris Stirling 187 as 2.5 to 3.2 gm. or a total of 30 to 40 gm. in the 24 hours.

Pye-Smith says that the excretion of urea is increased when one takes into consideration the state of the patient. Sibbe186 says that both urea and acid are increased.

Until however a continuous series of observations on the urea excretion are recorded, it is impossible to draw any definite conclusions from these scattered observations, but it seems probable that there is a considerable excretion of urea excreted compared to the amount that would be excreted by a normal subject kept in similar conditions of diet and exercise.

From the marked analogy of the kidney itself, much more satisfactory evidence...
is take obtained.

Numerous cases have been recorded in which the kidneys gave the iron reaction in pernicious anaemia cases. I can discern this reaction in other conditions.

The pigment is disposed in the convoluted tubules of the broad part of the loops of Henle.

Hopkins gives a very good microscopic drawing of this. It should be noted that in haemoglobinuria, the haemoglobin is found within the glomeruli, not in the epithelium. It also that foreign particles, such as carmine when experimentally injected into the blood are excreted by the epithelium.

This is an evidence to show that the kidney exerts any destructive action on the blood, indeed it is very unlikely.

It is a little difficult to explain the presence of the pigment granules as such in the kidney.

That the kidney should give the iron reaction in the disease is only to be expected from what has been said before, but the question arises as to whether the kidney takes up the pigment into granules from the blood or whether the epithelial cells absorb some degenerated product of haemoglobin that are circulating in the blood more or less in solution and then become altered in the cells to granules.
further explanation is possible, against the
first it may be urged that pigment proteins are
very rarely to be seen in the blood if it be examined
under the microscope, but on the other hand the
analogies of the fate of carmine supports it.

In passing it should be noted
that there are two conditions other than pernicious
anæmia in which blood destruction is known to
occur in excess. These are malaria favosa and
heemoglobinæmia.

They differ however very markedly from pernicious
anæmia. In malaria there is a definite
organism known to be the destroying agent in the
destruction to take place anywhere, although the
pigments stored up (often in the liver, this not
in the cells but in the capillaries).

Hemoglobinæmia differs from malaria in always
occurring always a history of syphilis or infection,
the products of destruction are excreted as heem-
organic by the urine, a thing that never occurs
in pernicious anæmia. Further the destruction
does not occur in the general circulation, but
indirectly produced by external stimuli
such as cold.

These conditions need not therefore, in further considered.
The evidence set out in the foregoing pages, points conclusively, I think, to there being in pernicious anaemia a greatly increased destruction of red blood corpuscles, and further that such destruction is confined entirely to the portal system and almost entirely, though this is not absolutely certain, limited to the liver.

This leads to the discussion of the last question: What is the actual cause of this increased destruction in pernicious anaemia?

The most probable theory is that tentatively advanced by Mutt.

He published a full account of a case of pernicious anaemia in the same number of the Proceedings as Delépine, and published his work on the normal storage of heminin.

He says: "It might be suggested that pernicious anaemia is an exaggeration of a normal physiological process analogous to diabetes: for under physiological conditions there is a constant tendency to maintain the normal qualitative and quantitative standard of the blood; e.g. a physiological process takes place when a small quantity of glycogen is converted into sugar, but a pathological anaemia as it overshadows the normal. When the ablation of the products of digestion occurs..."
the blood is replenished by new materials, depletion would occur if there were not a proportional destruction of the plasma corpuscles to form new epigments, which leave the body by the natural channels. May we not therefore look upon 'pernicious anemia as a disturbance of one of the normal functions of the liver?"

This theory is beautifully simple. A very little of the evidence contravenes it. Sudre's work does not yet the most part oppose it, but rather tends to amplify it.

As Mott says, the "sorogenic function" of the liver as described by Delépine may perhaps need further examination by independent observation before it can be completely adopted, but as there is shown by the evidence is overwhelmingly in favor of blood destruction taking place in the liver in health as in this disease. It is not a far-fetched conclusion, to believe that the increased destruction characteristic of pernicious anemia is but a result of the disturbance as aggragation of one function of the liver. Even if this be true however, we have still to find the reason why the function of the liver being disturbed in other words to find the real fundamental cause of the disease has still to be found.
So this and Hunter had devoted much labour to thought. In the past twelve years a great deal of his work has been referred to at various parts of this thesis, but certain points being more particularly on the determining factors the destruction need to be considered.

It was as has already been pointed out, largely upon the condition of the spleen since one case, coinciding with the results of the injection of lobular chymotrypsin into rabbits that Hunter concluded that the spleen was the seat of active destruction.

She found the spleen enlarged soft of lobby 10 10 dark purple in colour. It seemed a tube exceedingly rich in blood, the red corpuscles were few in numbers in one tube. The colour was found almost entirely due to free haemoglobin, the red corpuscles being so rare numerous than in other organs.

The spleen tissue gave little or no colour reaction with ammonium sulphide contained in excess of blood pigment. At the same time there was a great excess of pigment in the liver cells a quantity of the intense deep stained bile both in the bladder as a part of the intestine.

Hunter infers this by saying that destruction must have occurred in the spleen. The products then carried...
to the liver.

Those who have pointed out that an equally possible explanation is that the destruction has been so great that products have been freed from the liver into the general circulation which have accumulated in the spleen the absence of encapsules points this way.

Gautier himself supposed that Tolugeleamine had a specific action on the liver cells, as by this means only could an account for the action so long as he considered that the drug reproduced normal destruction.

Delepine & Gautier have shown that Tolugeleamine does exert a specific action on the liver cells but in exactly the opposite direction to that in which Gautier supposed it to act.

Arguing from his conclusion that Tolugeleamine exerts a specific action on the blood destroying tissues he further concludes that the agent (agents) which induce the excessive destruction of the blood in purpuric anemia is one whose action on the blood on the liver cells is the same as that of Tolugeleamine etc. is strengthened by the consideration that the form assumed by the throughout affects liberation from the corpuscles is,
in cases of purulent anemia, similar to that assumed by other poisoning until today be disease.
Shehe goes on to say "With regard to the precise nature of the poison—my observations do not yet supply me with any definite information".

The states that gastro intestinal symptoms are present in the disease that gastro intestinal lesions are frequently the only lesions discernable after death. (The rarity of these lesions has already been noted).

She concludes that there is produced in the gastro intestinal tract of poison of acedemic nature in small quantity, but constantly would this is the cause of the disease. This, he thinks, would explain why lesions of the gastro intestinal tract may be of eelological importance, even though they may exist on the other hand without giving rise to the disease "they rarely pass the production of the essential pathological changes underlying the disease.

Still following this line of argument, he published the account of some extensive researches upon the case of cases of purulent anemia, the parallel of which he himself considers are not conclusive but thinks they can form his observations.

She researches on the purin were terrible that in
pernicious anaemia there was an excessive amount of putrefaction in the intestinal tract. He says: "Considering how important a part played by putrefaction in the change within the intestinal tract below the duodenum, my first thought naturally was that excessive putrefactive changes might be the cause of the condition; it might lead to the formation of such poisons."

The aromatic sulphates found in the prunes are the result of combination of sulphuric acid with aromatic bodies like skatol, indol, phenol, etc., and the estimation of the amount of sulphuric acid is a reliable guide to the amount of putrefaction in the intestine.

There are two groups in which sulphuric acid is present in the prunes. By aromatic acid combined with the taste of the food derived directly from these prunes.

By an aromatic sulphate in combination with the aromatic compound the prunes is derived from the sulphur in the fruitoids of the food. I believe the ratio of these two to each other is fairly constant: A:B::10:1.

In intestinal obstruction they become almost equal, contrary to the opposite use of purgatives B almost entirely disappears.
In pernicious anemia Shuter found the ratio much diminished, even to 2 to 1.

He says he was convinced from the total amount of free sulphuric acid, that the amount of putrefaction was not in excess of the normal, but that the ratio indicated that putrefaction went on 3 times more rapidly than normal.

By placing the patient on a carbohydrate diet, the amount was greatly lessened. The patient improved, took more food, sleep was increased, no aromatic bodies, showing that more was assimilated.

Hopkins 13th examined the excretion of the sulphates, in some cases made a large number of observations.

His result confirm Shuter's as to the alteration in the ratio, but he never found so great an alteration as Shutes, 51 to 1 was the least he found.

She makes an interesting speculation as to the possible bearing of this excess of aromatic sulphones upon the disease. "be it led to wonder" he says. "the any abnormal accumulation or in the former (the sulphur compounds in the liver etc) might be associated with the fixation of the iron in the hepatic cells."

It seems quite possible that this increase of aromatic sulphones is merely the result of the destruction of red corpuscles in excess of re
as it were, a by-product of the general action. The fact that in the latter case the excretion of aromatic sulphates tended to become normal as the patient improved (i.e. as the destructive process lessened or ceased) is quite consistent with supposes this view.

Mott 1914, speaking on this point, says: "The aromatic compounds that are found so abundantly in the urine, in conjunction with anaemia, are an expression of the breaking down of the tissues, as is shown by the increase of the sulphates, but would not this also occur in any case in which there was rapid tissue waste such as starvation?"

The latter was also able to isolate from the urine two bodies apparently identical with the phenomena of acridiniline-acridine, which he says have been found in the urine in a slow condition. As these bodies are bacterial products he concludes that their presence points to some special organism being concerned in their manufacture.

"For points out how many of the characteristic clinical features both general and local, fit in with the view of a special infection. By the obscure origin, the slow but sure progress toward the fatal issue, marked generally by toxæmic phenomena such as.
fear, dreams, or unusual reactions, but chiefly by the
continued progressive destruction of blood and locally
by evidence of gastro-intestinal derangements such
as sickness, retching, vomiting, diarrhoea, etc.

The toxic encephalitic symptoms which he lays down, have not, except in the fever, been observed by anyone
else. Two papers in the Précis de Médecine
are interesting but are practically a précis
of his other papers.

In 1895, in his opening address at the
British Medical Association he adhered to
his views recorded above.

Since recently he has published some further
researches in elucidation of his theory.

She was struck by the frequency of marked dental
caries, stomatitis, and gastritis in a series of eight
cases of which he gave details.

Certainly in this series these conditions were very well
marked, but she did not think they were due to weakness
or any other marked at the commencement
when the anaemia was slight.

She does not very frequently see cases of gastritis following
diseases where there is a considerable amount of nausea
and loose stools, but she considers it worthy of more attention
in the various gastro-intestinal lesions that have at times
been found in association with purulent sanguineous
inflammation. It is considered that the symptoms of this disease in these
cases are due to the mode of onset. Characteristically, these
diseases have an acute onset. The clinical picture points to an infection of a
definite character localized to the alimentary tract. The disease is not
always progressive but sometimes it may be self-limiting.

In some cases the fact that the symptoms exhibited
some periodicity suggests the likelihood of an
infective process occurring down the alimentary
tract itself disappearing leaving no trace
behind.

In 100 cases he only found stomatitis ulceroid
in 18 but gastro-intestinal trouble he found
in 224 cases out of 273.

He grants the absence of acute lesions in
the stomach and duodenum but thinks the microscope
would reveal more.

He thinks the infection is a mixed one but beyond
suggestion as to the organism concerned.

"It must remain for further observation to determine
the nature of the organisms concerned in their relative
role."

In regard to Prof. Adam's views colleagues have
recently done some work which suggests that the bacillus of bacillary has something to do with the production of puriciuous anaemia, though not apparently directly.

Maitre's latest description of the disease is as follows:

"Puriciuous anaemia: a chronic infectious disease localized to the alimentary tract, caused by a definite infection of certain parts of the mucous and alimentary tract, chiefly of the pharynx occasionally also of the mouth and the intestine. It is characterized by:

1) Intermittent destruction of blood, increasing anaemia, with other pathological clinical changes, conseaseive to these - eg pallor, leucopenia, anemia, hemorrhages, dyspepsia, palpitation, oozing - as the result of absorption of poison into the blood.

2) By periodic disturbances of the alimentary tract, chiefly of the chyme, intestine, and these effects of the infection of the alimentary canal. Occasional "toxicemic" attacks, characterized by fevers, sweats, sweating, general nervous symptoms, with frequently effects - eg numbness, tingling, ataxia, ataxia, hypothermia - leading deeper nervous changes, such as peripheral neuritis, ulcers of the gum.

Maitre's last paper was published after the greater part of this thesis was prepared, it would
The possible to criticize it fully without going through the whole literature again, searching for points that may contain a contradiction to his thing. In the first place however he has not made it certain that the dental caries in his cases was in any way caused.

This true that the coincidence was remarkable, but on the other hand it is quite consistent to look upon them as cases in which parasitic anaemia had occurred in people who were suffering from caries teeth. Hunter makes a great point of the apparent simultaneous occurrence of the anaemia and the caries.

In answer to this it might be urged that the lowered vitality resulting from the anaemia caused an increase in the caries, besides the fact that physicians' attention to it.

Nothing is more common than those in patients, whose health has deteriorated for some reason or other, a rapid decay of the teeth.

Then the absence of lesions to represent his gastro intestinal mixed infection is a very strong point against such things existing. As to makes the periodicity explain their absence but their other observers do not agree with him as to the constant occurrence of this periodicity.
There again, sufferers have not been able to indicate or suggest the organisms he considers to be at the bottom of the mischief. He has only found parasitic organisms in the mouth and stomach for which he claims a special part in the disease. The absence of any indication of the organism or of any lesions caused by it in the alimentary canal is a strong objection to the acceptance of Hunter's definition in toto.

But this subject must "say a" another very attractive theory is the absorption from the alimentary canal of some chemical products of the growth of microorganisms... It does not seem at once certain that this theory is proved, for in many diseases in which there is irritation of the intestines lasting from months to years, in which the whole contents must come in contact with microorganisms of the bowel fluid, with everything to favor absorption of the products these microorganisms produce, chronic anemia is accompanied by severe constipation. Anemia certainly is gotten by curbing the former, the latter is much benefited by frequent evacuations of face or poisoning the septic stools are not broken down, but insufficient coloring matters are made.

In this Hunter might reply that the special organism required is rare, he might quote as supporting...
his theory a case recorded by Rees Llinas in which parasitic anaemia suddenly and rapidly subsided in a case where causes of the parasites had existed for some years which suggests that some organism had been implanted in favourable soil in the parasitized stomach.

The idea that the disease is caused by the absorption of something from the intestinal canal did not originate with Rees Llinas.

Mr Jones in 1889 published a case which seems to have been a case of parasitic anaemia associated with very marked clinical signs (white faces &c.

But further investigation the case would be described as a typical one of parasitic anaemia.

The real interest lies however in his remarks on the case. He says "To put the matter shortly, the nutrition of the red corpuscles takes place chiefly in the portal circulation, while that of the other tissues takes place in the systemic circulation." Then after stating Sumner's statement that malarial poison (organism) may remain in the portal system for a long time, he beleives the suggestion that parasitic anaemia may be due to a poison in the "portal system vessels." Now in parasitic anaemia we do not know of any definite poison but it is possible that some abnormal
produced digestion or even some digestive ferment itself may act as a poison" she thinks the facts support this view.

The paper appeared in the transactions of the edition of Brownon adds a note to the following effect: "If we suppose that some ferment in a gaseous condition is present in the portal circulation occasionally passes in greater or lesser quantities into the systemic circulation, we can understand both the destruction of red corpuscles and fever" (It is not necessary to suppose that the ferment passes into the general circulation to exert its destructive influence as we know the destruction does not occur in the general circulation)

After referring to Stadthäus's observation that apparently the pancreatic juice becomes when absorbed a zymogen in itself inactive but under proper conditions able to yield an active ferment he says: "It is happen that from some alteration in the liver or spleen such transformation should be arrested if the ferment were to circulate in the blood we might have such a condition as that supraneurism latent".

For Brownon's suggestion to hold food is must be modified. the unchanged ferment supposed to
act within the portal circulation.

Mott makes a similar suggestion, he says "We know that peptone has a very marked influence on the blood, it is possible to conceive that if this substance, when it was absorbed, was not changed, it might lead to such an altered condition of the portal blood as to give rise to increased haemolysis. In connection with this may state that the liver spleen of a dog which had been injected with peptone solution yielded the iron reaction very markedly, but this may have been accidental so means to make further experiment on the subject."

Russell while agreeing that the disease is characterized by great blood destruction, as shown by the deposit of pigment in the liver, kidney, spleen, rejected the theory that for some reason the liver cells have an increased "hunger" for blood. He was induced to do so because the liver cell nuclei did not stain with Mitchell's logwood or picrocarmine indicating that the liver cells had been materially affected by the increased working destroying the blood corpuscles" she thinks that an increase in function dependent on excitation of the function of the cell world
not produce this result, while the presence of abnormal blood would inevitably lead to exhaustion of the cell.

In the presence of the same failure to retain in the kidney, she considers, still further supports this view. She thinks there is some change in the blood generally that necessitates great destruction; i.e., the corpuscles are in some way enigmatically used or are in some way used to perform the function of corpuscles. She is convinced that bone marrow changes are secondary and are primary changes do the suggestion that some blood-purifying organ or organs are faulty.

This last suggestion opens up the whole field of the relationship of the corpuscles with the serum as the composition of the serum in the disease.

In this subject very little is known that there is not enough to draw any conclusions, but it is quite possible that research in this direction might considerably modify all our ideas on the blood in general and on diseases in particular.

There is little doubt, therefore, that the great characteristic of the pathological process in pernicious anaemia is an excessive destruction of red blood corpuscles at that this destruction occurs...
chiefly, if not entirely, in the liver.

Beyond that it is premature to make a definite statement in spite of Sturz's contention.

Whether the destruction be due to a purely functional derangement of the liver, or,
whether something be carried to the liver,
digestive product, digestive ferment, or toxin,
which stimulates the cells to activity, or
whether some blood purifying organ be at
fault, the blood reaches the liver in such
a state as to encourage destruction. Further
research alone will make clear, for at
present proof is wanting for each.

It must not be forgotten that
there are some observers who maintain that
pernicious anaemia is but an advanced form of
other anaemias. It is very interesting to note
however that Sidney Cotton's, who in his Fabianian
76
declared that no hard and fast rules
could be drawn between the forms of anaemia
defects from this standpoint in a later article
on the subject agrees that pernicious anaemia
is a separate, distinct disease.

James Andreadt sets the idea that pernicious
anemia is a separate disease, but really only manifests that denial in a different form throughout the paper. One interesting point however is the stress he lays on the gastric-intestinal symptoms. Stockman contends that purulent anemia is but a further stage of anemia generally, that the only element in which it differs from a secondary anemia is in the capillary hemorrhages.

On reading his paper one is compelled by several statements to conclude that he has quite a different conception of the disease to most other people. He states that the onset is gradual always, that the majority of cases recover, that to begin with there is nothing to differentiate it from ordinary simple anemia.

Each of these statements I think I have shown to be erroneous, and I have already discussed his statement on blood destruction on the amount of iron in the liver.

His main contention is that all cases of purulent anemia originate as ordinary simple anemia, that some cases take on degenerative changes, which result in the capillary hemorrhages, that the iron pigment resulting from these hemorrhages is stored up in the liver, that the amount of iron...
in the liver in this disease is solely due to these haemorrhages and that from these haemorrhages a constant drain is set up which constitutes the pernicious element.

She says that these haemorrhages are always present where only been overlooked or else reabsorbed when not recorded. In support of this she refers to experiments he made on rabbits. He caused subcutaneous haemorrhages then later killed the animals and found the iron in the liver exactly as in pernicious anaemia. Munro repeated these experiments and denies that iron was not found in the liver as in pernicious anaemia, saying he found the spleen choked with pigment in the liver only a small quantity that distinctly confined to the capillaries.

Histoplasmin to explain the complete divergence of these two observations by comparing them with Delépine's work supposing that the "eryrogenic function" of the liver was at a different stage in the animals killed by the two observers.

As to the capillary haemorrhages themselves, Stephen MacKeanes has shown, as I have already noted, that they are prone two cause whatever the
corpuscles fall below about 50 per cent. whatever may be
the cause of the fall. They often occur in cases of
chronic Bright's disease, but these do not become
cases of pernicious anaemia.
The figures in Table G - mentioned in 13 cases
out of 36 - do not point to their occurring so
constantly as Stockman supposed.
Shuter records one case where not even subcutaneous
haemorrhages were to be found, but the liver contained
an unusually high percentage of urin (0.517) together with
very few haemorrhages existed yet iron in abundance
was found in the liver.
Shuter also makes a very damaging criticism, he
says that if the pigment in the liver were the kernel
of old haemorrhages scattered throughout the body,
surely it should have been found lurking through the
lymphatic vessels also is not found to be the case.
In another paper Stockman still regards his
view but fails to make his argument any
more convincing.
Course and Prognosis.

Were the statement to be made that the course of the disease was always or less steady, progress to a fatal issue, that the ultimate prognosis was utterly bad, only a few rare exceptions would be found to be urged against the truth of the statement. What Addison said many years ago is almost as true now of the experience of every observer. "With perhaps a single exception I have observed in my own experience (restricted all remedial efforts and) sooner or later terminated fatally." In part in brackets stands indeed a known modification and, as will be seen when the treatment is discussed, the experience of various observers is nearly unanimous.

Bramwell 165 says: "In one of my cases [that must be] the patient remained well for 22 years after relapse; noticed of the disease (13 ½ years after the first attack); in another of my cases in which the result is known, the patient lived more than 3 years again; he just came under my observation; in one case death was due to an intermittent attack of pneumonia—not directly at all events to precocious
acemic, in 3 cases only in which the ultimate result of the treatment is known do the patients still survive; two of them are in good health.

Other says "Of 27 cases (up to 1899) 23 were under observation 20 of them having recovered under arsenic, 8 of the remaining 23, 4 of the postpartum cases recovered; 2 of those at Montreal, 2 of these had remained in good health for several years. Of the remaining 18 cases two were lost sight of, had improved very much. The remaining 16 were dead. Six of these fatal cases recovered from the first attack, one had an interval of nearly 8 years another nearly 2. One patient in hospital in 1890 recovered, completely cured in 1896 of cancer of the stomach, one of my patients made an apparently complete recovery, resumed active human life.

Hale White 36 says "With one exception there is no evidence that any of the cases which have been discharged from any Hospital during the last ten years as having improved have recovered at least for any length of time; one leg no address, six could not be found, the seventh had died, of those he communicated with, another was known today shortly after leaving the tenth was alive and well.
Four years after, Osgood White wrote to me "March 21st 1900. I have since got your letter and have tried to trace Richard P. but I regret to state that I have totally failed."

P. Smith collected 20 cases of severe Stalin White. Smith stated that one of these cases treated with arsenic in 1880 was alive and well in Jan. 1890, though he had had relapses. To this same patient I obtained further record from W. F. H. Hoare, who wrote "now 18th July 1895 their now alive and well 72 years of age. He has recently made a complete recovery from influenza."

This is I believe the longest authenticated case of cure.

Richard Babot of Boston Mass in answer to an enquiring from me wrote Feb 6 1900 by the 104 cases of persistent anaemia which I have been seeing one case as I have lived over 4 years. Some have been lost sight of impossibly but alive, but everyone that I have been able to follow up has died within that period. The cured cases represent I believe simply among the remissions in the disease during which the patient passed out of observation so that the subsequent death was not heard of."
My second case is an instance of how cases may be recorded. When last saw him, he seemed in perfect health, lately keeping in touch with him. I heard of a relapse — finally of his death about 18 months after his first attack.

The statistics of various hospitals that I have collected in Table B may not of course give a perfectly accurate idea of prognosis, for some cases may appear several times each relapse being noted as a fresh case in the general tables of the hospital, but in spite of the trouble even they are instructive. They work out as follows:—

Cases 2660
Cured 319 or 11.94
Relieved 77 or 28.4
Mentioned 31 or 1.16
Died 131 or 4.92

In Table F these collected from Table G 22 cases published as cured. I have not taken into account those published as relieved for it is safe to conclude that they died very shortly afterwards.
I have endeavoured to follow up each case by the kindness of the original observers, I have been able to collect much interesting information.

Only one case (No. 9) is known to be alive this year (1900).

Nine are known to have died of the disease. Four have been completely lost sight of. Seven I could gain no further knowledge. The reporters of two being dead.

The remaining five are known to have lived for some time after their deaths have not been heard of by the original reporters.

By these No. 10 was known 4 years after a sudden return to labour in perfect health; No. 26 was well two years after convalescence; No. 57 had a relapse six months after but 3 months after that was well enough to walk two miles at sea; No. 57 was alive 2 months after convalescence, alive, some months later, No. 54 was alive and well, not sick, 13 months after.

The more fact that I have been able to trace many cases shows what a profound impression the cure had made on the reporter's mind. It is rarely such a fortunate result occurs.
After history of case published as Broadheath.


Treated with arsenic in increasing doses, which caused some vomiting but progress was steady to cure.

After history: 1st night.

No 5. M. 64. Starnhan

After some time the case was diagnosed as pernicious anaemia and treated with arsenic cleared.

After history: Mr. Starnhan writes Feb 1st, 1900. Mr. C. is not only being well but is enjoying better health than he had during illness. Some several years he continued to take arsenic every alternate month, but he has long stopped all treatment except careful and simple dieting. He is very fit and robust, looks fresh in health leads a fairly active life.


Recovered steadily under arsenic.

After history: In case was unable to obtain any.


Transfusion afforded temporary relief. Arsenie (up to 36 mins.) cured here.

After history: Mr. Luckie writes Feb 5th 1900. Patient was shortly afterwards the subject of another relapse died before another transfusion could be effected. I cannot remember whether she took arsenic in the internals.
No 13. In 171, Miss...ford.

Red corpuscles had fallen to 161,000, haemoglobin to 10.
Treated with arsenic up to 30 min daily and prothamide hydrochlorate for 5 days, then prothamide hydrochlorate alone for a week and arsenic for 3 days. Slight improvement, but continued prothamide hydrochlorate alone for 3 months. Slight improvement continued. Treated with arsenic and prothamide hydrochlorate, with slight improvement.

After history: Miss...ford writes Jan 20th 1940. Was last heard of in 1926.

No 14. In 58, Miss...elle.
Treated with arsenic up to 30 min daily with 45 grains of iron, then discharged cured.

After history: Miss...elle writes Jan 30th 1940. I regret to say that the patient had a relapse which lasted 6 weeks and she was able to go to work again treated with arsenic as before, passed out my hands.

No 16. In 60, Prof. J.K. Fraser.
Treated with ferrous chloride, arsenic, and iron. Prothamide hydrochlorate was discontinued on the 1st of August. The patient improved and was discharged cured.

After history: Prof. J.K. Fraser writes Oct 10th 1940. He left the hospital well in May 1940 and was examined privately in August and was in a good state until July 1944, when he...
became ill after an exposure to cold a damp. He
received ice in Aug. with much deterioration in
the state of the blood, but treatment with bone marrow
the bone produced a rapid improvement to the
satisfactory state. The patient did not continue with
The bone marrow as directed after severe exposure
to cold a cold perbronchic paper and there
was evidence of recovery for a while, but a deterioration in the
blood. She died in Nov. His chest condition the vomiting
presented the administration of bone marrow to the appropriate
remedies.

No.18. Mr. 55. Dr. Gibson.
Anemia could not be administered, iron was useless
transfusion of the temporary benefit. Beta-naphthol was
then administered and we improved followed
by months but the patient was in good health.
After history: Dr. Gibson writes Nov. 24. 99 that the patient
died of a relapse sometime after.

No. 20. Mrs. 43. H. A. P. Bowen.
Patient was given arsenic up to 75 min. a day. There was
some improvement but in severe peripheral anemia followed.
Bone marrow was given at the red count rose improved to
100% eventually the anemia disappeared.
After history: Mr. Bowen writes Jan. 30, 1900 "The man for whom
I was seen to be lying well 2 years since. He left the hospital. He was anxious otherwise he would be
great difficulty in tracing him."
Case 31 J. 24. W. Mitchellson

Arsenic case. Dop for 3 weeks was ineffectual. Arsenic cured her.

After history:—Unreatenable Mitchellson died shortly.

Case 36 M. 61. W. Pye-Smith.

A typical case cured by arsenic.

After history:—W. Pye-Smith writes Feb 1810 “He died soon afterwards but I do not remember the symptoms.”

Case 37 M. 65. J. Taylor.

A very typical case. Arsenic administered at once did no good though tried for months. Then sulphate of iron was given but no steady recovery ensued.

After history:—J. Taylor writes Feb 1810 “The man was under my care for 2 or 3 subsequent occasions for relapses. He lived 14 years and died 1823 for 14 or 15 years.

The cause of his death has never been ascertained.

About 8 years repeated his first attack from his first relapse.”


A typical case cured by arsenic.

After history:—who traced the patient out.

Case 45 M. — W. Barton.

Various treatment was tried but with no success until arsenic was given which cured the patient.

After history:—W. Barton realises his mistake. The patient had a relapse months after cure was recorded.
under arsenie 40 months later the note was "Patient quite well observed with some coldness of upper abdomen with colic in the lower patient has been lost sight of."

Note by H. Evans.

Arrows did good last seemed diarrhoea was stopped.

When patient was apparently in extremis transfusion of blood was not successful under arsenic again with iron quinine treatment a cure was effected.

After history: "W. Evans aged 72 yeas 7 months. In 3 weeks after transfusion he was about six months was able to walk five miles. Unfortunately he went to London for a trip (150 miles by rail), diarrhoea occurred almost directly after return returned rapidly. Transfusion was again performed in town but he died 24 hrs after. The subsequent family history in particular. The brother developed Graves disease was ill for long time. The mother for 5 years bedridden from recent arsenic were said to have died of it"

No 47 J. 53 Dr. Smart

Eaten by arsenic iron.

 GHC history: The patient was alive 6 mos after leaving hospital.

Dr. Smart writes July 1904 with the exception of hearing indistinctly often continued in present case. Some lost patience after case."
No. 138 5, 49. W. Kent.

A typical case. Extensive lesions of the skin were found in the forearms. Bone marrow was tried with no success. Arsenic passed her through the severe fever.

Afterhistory: She died under Feb. 10th. She passed a remission and recovered about 2 years later. She recovered (I believe) and ultimately died.

No. 52. M. T. Bramwell.

A rapid case with every appearance of extreme blood destruction. Arsenic after 2 days was given, feeling unrelieved. A complete recovery followed with some herpetic.

Afterhistory: She was taken in June, 1898. In March, 1899, she was entirely well, with very slight symptoms. In May, 1899, she fell ill again, but the state of her blood was not so good. Bramwell tells me that she died in the autumn.

No. 54. M. T. Gladstone.

A typical case, red extenuation of the large arteries of the neck, small, round, scarlet, constricted. Arsenic was given. No relief. Large doses of arsenic given with massage produced very successful.

Afterhistory: Passes about as well as ever after (i.e. in 1898)

M. Gladstone died in Sept., 1900. I haven't seen the patient since Oct., 1898. He had been following his employment as a boy messenger after leaving the convalescent home.
was apparently quite well rating in all ways. I have little doubt that the massage gave him a little aid. In other cases with similar results.

No. 31 Mr. Williams.

Iron administration were made. There was a steady improvement.

After history: Mr. Williams writes Feb. 7, 1900. "She left the hospital practically well, but I am sorry today. Subsequently quite lost sight.

No. 50 Mr. Broadhead.

A case successfully cured by phosphorus.

After history: Mr. Broadhead writes Apr. 6, 1900.

"I am sorry that I cannot identify the case which you refer (No. 5, 13490) but most of those who have died of the disease have lived many years.

No. 37 Mr. Bradby.

Iron was useless but the administration of arsenic was followed by recovery.

After history: Mr. Bradby having died.

(This case was accidentally omitted in the report.)

It will be noticed that these cases don't seem to differ in any way in their clinical features from other cases that died. They were
of both sexes, all ages apparently in all stages of the disease.

The agent by which cure was brought about were various but arsenic greatly predominates
in 15 years arsenic caused the favourable
result; in 15 years arsenic, in 20 years
in both iron, phosphorus, vita unphilit.

Relapses are undoubtedly
a common feature in the disease.

Each relapse unfortunately seems less easily
recovered than the preceding one.

There is certainly a tendency to improve relapse
in many cases without the intervention of drugs
of which Smith says that some cases have recovered
without treatment; i.e., a tendency to improve has been
very marked in these cases.

Hunter, in speaking of the relapses says he is
justified in regard the interval between the relapses
as a period of self-immunization against the
noxious effects of the infective process; he
suppose to exist.

Many cases have several relapses before the
fateful issue, the interval between seems to
become shorter and shorter each time.

It is obvious that if a case be not followed up
After an apparent cure there is a great possibility of a mistaken arising if such a case be followed down as a cure. The cure, too often being the natural tendency to improve aided by appropriate remedies.

This tendency to improve + relapse is by no means present in every case. Some cases go straight to fatal termination as did my first case.

There may be periods when the disease is not proceeding apparently as rapidly as at others but the general progress is downwards. "Tendency to improve" is probably too strong a term to use as it would be more accurate today than some cases the destructive process seems for a time to be inhibited so the blood forming organs are enabled once more to bring the corporales up to a normal standard or nearer that standard. Some further points with regard to the relapses are discussed with the treatment.
Treatment.

In a disease that is so fatal as pernicious anemia is, it is obvious that treatment as at present carried out can offer but little promise of effecting a permanent cure.

On the other hand, the statement of Addison that the disease resists all remedial effort, is now not correct as means are known today by which life can be prolonged in a fair proportion of cases that patients can restore to health or in a time of a few years or at least cases the disease absolutely cured.

As has already been seen, the means by which a favourable result is brought about are various each having its advocates.

The general surroundings of the patient are worthy of attention. 

Sunlight and pure air are undoubtedly of value in all cases of anemia, whatever be the cause. in a profound state such as is seen in pernicious anemia are of the utmost importance.

Equally important, probably in every case, certainly in all in which the disease is marked of progressing, is rest—complete rest—in bed.

The great tendency of the heart to become fatty in the disease
would alone care for this, but in addition, exertion of any kind must add to the working of the blood as another increased work leads to an increased demand for production, and we have seen the destructive characteristic of the disease is already carrying a great drain upon the producing tissues.

Here T. Bramwell, 75, is seen in all his great strenuous upon the necessity of rest in bed.

In the light of the late's most recent statements it is now clear that any decaying teeth or other parts suffering should be removed if they exist.

Food. The frequency of vomiting and diarrhea at once points to the necessity of a bland, soothing diet that at the same time shall be sufficiently nourishing.

Undoubtedly a patients' small diet is the most suitable. For the majority of cases especially when the disease is far advanced, it is often difficult to feed the patient even on this diet, constant vomiting hastening the fatal issue by practically starving the patient, or rectal feeding is often prevented from being effective by the frequent occurrence of diarrhoea.

Coupled, insists on the importance of a small diet, for patients. Stephen Hackney, 75, stated that a

insipid diet increases normal blood destruction
Though as the former points out the increase of that necessary for a generous diet is not so great as to outweigh the consideration of the general nutrition of the body.

Though a generous diet is probably the most suitable it must not however be rigidly adhered to in cases where anorexia is marked. A diet associated with improvement may be continued, on the other hand, where the patient does not seem to be sufficiently nourished by a generous diet, thin strong meat essences, raw meat juice, beaten up eggs, and other prepared foods should be given.

Alcohol is often very useful.

Certain symptoms may need special attention. Though as a rule improvement of the blood condition will remove these symptoms.

The toning may be difficult to control since cases impossible, most useful will be found—morphine, champagne, rice.

Diarrhea often becomes excessive even when things have been recommended to control it but caution must be placed on care for delaying on the use of opium in some forms, with the aid of minerals or vegetable astrigents. Bromwell recommends—
The dyspnoea may be relieved by inhalations of oxygen a method which can only be palliative but affords great comfort to the patient sometimes. There seem very pronounced beneficial results from the use of oxygen in a profound case of anaemia from haemorrhage in which the anaemia seemed to tide the patient over the interval until more blood was formed. The same might very well happen in pernicious anaemia.

Any haemorrhage that occurs in the course of the disease must be promptly treated.

Treatment directed to cure the general condition may be divided as follows:

A: - Principally directed to stimulate blood formation. Precedent in this class is arsenic with or without phosphorus alone or with the use of salicylic medication.

B: - Directed to prevent the excessive fermentation existing or believed to exist in the alimentary canal, under this head some lavage of the stomach or the use of salicylic medication.

C: - Directed to act upon the blood immediately by transfusion in all its modifications.

D: - Other treatment whose mode of action is doubtful viz: massage.
Arsenic was first seriously introduced into the treatment of pernicious anaemia by Bramwell. He was led to use the drug in pernicious anaemia from observing the good benefit following its use in lathyrism, degeneration of the heart. Though this was the first use, undoubtedly, of arsenic in response to a definite clinical reasoning, it had been used before.

Wilks mentions some cases cured by arsenic some years before 1870, but he gives no details.

Poppet in a case published in 1876 mentioned that arsenic was given along with iron in cases but without success.

Bramwell, however, was the first to publish a case where the arsenic had been used with success. By the efficacy of arsenic in many cases there can be no possible doubt.

A glance at Table I will show what a large proportion of successful results are due to arsenic. An interesting case to note that these, particular known to the author, of these, was treated by arsenic, the case of Mr. Smith's still alive, was also treated by arsenic 20 years or more ago.

There are numerous cases recorded in which the patients benefited temporarily at least from...
arsenic. My second case is an excellent example of this. He appeared to be completely cured and was able to start work again, but relapsed. He died in 18 months.

So great then is the benefit effected by arsenic in many cases, temporary though it usually is, that no responsible physician would undertake the treatment of a case of hemorrhagic anemia by any other means without first trying the effect of arsenic.

This best given in the form of the liquid arsenicate but it may also be given in full form.
The dose should be small to begin with, 2 or 3 minims three times day largely diluted. The daily amount should be increased gradually to the limit of the patient's tolerance.

Increasing the dose by 1 min (ie 3 min every 24 hours) every day every other day is usually successful.

It was so in my second case, where the dose was daily increased until the patient was taking 1 dram after breakfast.

When a large quantity of this is being taken it is well to divide it up into 3 or 4 even more doses spread evenly over the 24 hours, the chances of irritability of the alimentary canal are then lessened.
The drug cannot be taken in the mouth. Hypercemic injections shown to tried a WilCoR Anderson
washed sucrose with this method.
Drayer recommends this method strongly if the
mouth be intolerant. Miller reports 35 cases
of arsenic by all routes, as treated with good result.
The arsenic has also been given by the rectum.
Large doses of arsenic are not without
their danger.
The earliest toxic sign is redness surrounding of
the eyes, this was the only disagreeable reaction
from large doses (30) in my second case.
Herpes has been described by Stanfield in
which case there was increase of pigmentation also.
Ovarian masses marked herpes in case 52.
Neuritis has also been observed. Herpes is due
occurring frequently when some neuritis appeared —
Barr, a case where the arsenic (min 40) caused
little enlargement, but the patient recovered
with bone marrow a gradually the neuritis (the
residual must drop 80 which, is well shown in
photographs) disappeared.
The accidents all occurred to patients who were
taking large doses (600 min. or more) without
as warnings that these large doses require careful
watching.
There seems to be no doubt that arsenic as the drug in any causing toxic symptoms was well borne by the stomach; it is a remarkable thing with it, watching the blood for signs of imperfection, keeping a careful watch for the earliest sign of poisoning.

In many cases improvement does not follow until large doses are prescribed, such a case is published by Gladstone. 180

Unfortunately there are many cases of this disease in which arsenic even in small doses cannot be tolerated.

There seems to be nothing to indicate when it will be the case where poisoning fails but to try the drug to watch its effects.

Naturally cases with marked vomiting diarrhoea are less likely to bear the arsenic well, but still cases are recorded where the gastric intestinal symptoms have

ceased under the influence of arsenic. On the other hand cases where this was and any gastric irritation have been quite intolerant of arsenic, such a case was my first.

Other two cases have been recorded where the administration of arsenic appeared to cause a great deposit of uric acid, one such is published by Mentz 150; in this
case the arsenic caused an improvement in the general condition.

On the other hand, in cases in which the urine is depressing urine acid gradually, the deposit disappears as improvement follows the use of arsenic.

I think it probable that the deposit of urine acid is a process of the disease not cured by the arsenic in the cases it appears to me.

In my recent case a curious thing happened. The patient had been taking large doses of arsenic, varying from 40-60 minims for some days; it was stopped suddenly because of the sores of his eyes.

His temperature then upon began to rise on the 3d of the same day to 104°. The patient's skin was thin and dry, he was sweating a little, but beyond feeling "tremendously hot," he was symptomless; I could find nothing to account for the fever.

I ordered him remaining of bismuth arsenical daily with the aid of phrenelin; by the time his temperature became normal, two days after.

I was quite at a loss to explain the occurrence at the time, but two months later, a similar state of affairs in a girl being treated with large doses of arsenic for Hodgkin's Disease, was witnessed.
This led me to conclude that in some way, the
head-regulating mechanism is upset by the sudden
administration of arsenic when it had been
taken for a considerable period in large doses.
I have been unable to find any mention of this occurrence
elsewhere, but it is an indication that the sudden
removal of arsenic is not a wise procedure.

While all agree as to the
efficacy of arsenic in the disease, there is considerable
divergence of opinion as to how it acts.

Metz considers that the action of arsenic is purely
local and supports his own theory. He says, 'I
conceive that the action in such cases may be more
simply explained as an indirect local one on the nervous
membrane of the stomach or intestine, but especially of
the latter.'

It is quite possible that the large doses of arsenic may
be sufficiently large to upset an already existing action on the
nervous membrane of the stomach, intestine, and very
likely some of the beneficial effect of arsenic
resides therefore in cases where for some reason
another nervous irritation is going on, digestion
consequently decreased.

But I think this is the only good effect of arsenic; I do not
think at all likely, for there is very direct evidence that
it also increases the formation of red blood corpuscles by stimulating the bone marrow.

Steele and Gracey 1891 together experimented on rabbits with arsenic. The drug was given subcutaneously over long periods to some animals. Others were kept under circumstances without arsenic, to act as controls in the experiment.

While effects followed the arsenic except paralysis, no change was observed in the hemoglobin or red corpuscles of the group of animals. Post-mortem however there was a striking change in the bone marrow of those treated with arsenic.

There was a great increase in the number size of the capillaries, which were distended with red blood corpuscles. There was a much greater number of red blood corpuscles among the marrow cells. The fat cells had to large extent disappeared.

The marrow cells were greatly increased, more closely packed together. The large marrow cells contained bodies which seemed to be red blood corpuscles.

In rabbits, a general stimulation increase of function in the bone marrow.

In an adult rabbit a similar change was produced but not to so great an extent.

In dogs as the result of administration of arsenic.
by the mouth the bone marrow change was slight.

They concluded that arsenic stimulated the bone marrow markedly, but did not in health increase the red corpuscles in the circulation; for they found no evidence of increased destruction, which must have occurred, if these new corpuscles had been launched into the circulation in the total amount just increased.

There seems to be a physiological limit to the number of red corpuscles circulating, whose mechanism is paralysis—so far only by change of altitude has it been overcome in any degree.

Stockmar says that in cases of the administration of arsenic in poisonous arsenic as merely a symptomatic mode of treatment, though valuable.

It seems probable however that besides the stimulant action of the arsenic on bone marrow into possible and specific action, it has a further influence on the blood corpuscles directly.

Copenhagen observed that haemoglobin no longer crystallized out in those cases that had been treated with arsenic.

This may of course be due to the stimulated bone
narrow series of test cases, in which the haemoglobin is reduced more rapidly, the arsenic acting on the bone marrow to act directly on the formed red corpuscles.

If this instability of haemoglobin be due to the exhaustion of the bone marrow resulting in its forming to function incompletely it is as to understand why Copeman found the same instability in some other conditions.

This is an indirect evidence of the arsenic having any direct influence on the liver to control the destructive process acting. This evidence leads some colour to the theory that by some means, whether as Russell suggests, by the failure of some bile-pumping organ, or not, the blood is rendered unstable so more readily destroyed.

Foxwell however makes the statement, that the arsenic lessens the ferrocenic function of the liver and hence the crystallization of haemoglobin is that it is quite likely therefore that it aids the haemopoeitic function which he attributed to the liver.

Generally speaking from the standpoint that pernicious anaemia was due to ferrocenic anaemogenesis, but what has been quoted would support the theory that it is due to increased haemolysis in the liver which the arsenic prevents the excessive destruction.
As I have pointed out already there is no reason to suppose that at the beginning of the disease the bone marrow is feeding on unhealthy corpuscles, but undoubtedly after a time the strain on it is enough that the corpuscles are immature and therefore probably more easily destroyed.

This strain consequent exhaustion of the bone marrow explains, I think, the fact that in some cases, where arsenic is not found, no improvement follows — the marrow is too exhausted to respond to stimuli. Thus I think the explanation of some early cases of being recorded in which no change was observed in the bone marrow rests on two points:

(a) there was not so much arsenic in the function or structure of the bone marrow as the only bone normally containing red marrow were examined, or naturally osteoelastic in nature would not be removable.

(b) these cases had not, as a rule, been treated with arsenic.

The well-known fact that arsenic causes no specific alteration in the pulp of the disease would seem to be due to the bone marrow failing to respond a second time to the stimulus, or at least not so well.

At the same time it would seem that the patient has the best chance of remaining well after apparent
recovery is the end of time to take arsenic for a long period, even many years as in the case published by Dr. Strickan (No 9 in Table 7).

Bennett insists very strongly on the necessity of this.

Possibly the bone marrow is less likely to fail if the stimulus be maintained steadily and not omitted for a time, then repeated, but it may be that the arsenic maintains a controlling restraining influence on haemolysis.

Phosphorus, which chemically is allied to arsenic has been successfully used in pernicious anaemia. In Table 4 two cases are recorded which were treated by Phosphorus (Nos. 1 & 3).

Sir W. Broadhead has advocated the use of phosphorus more strongly than anyone, still holds to the same view. In answer to an enquiry from me as to the fate of some cases he added: "... a third an old lady, over 80 has taken phosphorus constantly for 25 years, though she was considered to be in a helpless condition from pernicious anaemia, when S. F. died.
her. Phosphorus is the most active member of the arsenic group of elements. as it is more effectual than arsenic.

In general, opinion is divided as to whether it is favourable to phosphorus, but there is no doubt that in many cases doses increase the toxicity and enuresis, though in animals variable results have been obtained experimentally with phosphorus.

Iron is generally condemned as useless. Iron is often harmful in the disease. A case has been recorded, however, by Biely, that recovered when treated with iron alone; the after history of this case appears in Table 3. Bramwell & Quinlivan also published similar cases but these are quite exceptional. In my second case iron seemed to do good after arsenic had been given for some time. Bramwell, who formerly was unfavourable to iron, says that in his later cases he has been able to obtain good results in addition to arsenic, though it requires careful watching, may do harm, in one case, certainly increased the diarrhoea.

An interesting observation on this point was made by Aferis. A dog was repeatedly bled and seemed very anaemic. Afterwards he was given a
intra-venous injections of arsenic for a week or so immediately after that, intra-venous injections of iron. The results obtained were fairly constant; after the arsenic, the enaphalases augmented in number, after the injections of iron, the haemoglobin equivalent was raised. The author mentions several clinical cases that seem to bear this out, but conveys it.

I am convinced from the experience gained in my second case that pica maybe of great benefit.

Possibly the reason of failure with pica is twofold.

Firstly, the pica may irritate an already irritable alimentary canal and cause harm to the patient before good could possibly follow from absorption.

Secondly, there is undoubtedly in many of these cases an excess of iron in the body, that has already been shown to be the case. It may not be readily assimilable, but the study of the blood changes in my second case rather tends to show that, given an increase of enaphalases, this iron may be assimilated.

I think that the iron therapy is advisable in the early stages of treatment, but that when improvement has occurred, as shown by the increase of red corpuscles, it should certainly give it with caution, especially if desirable is the increase of haemoglobin in lagging behind the increase of enaphalases.
The mor should be given in the least irritating form. The best is freshly prepared carbonate in a gelatin capsule.

Bone marrow. The first case in which bone marrow was tried was published by Prof. Ingersoll (case 16). In this case, arsenic sulphuretum had already been tried without success or harmful but under bone marrow (red) rapid improvement appeared success followed by a late relapse again yielded to the bone marrow.

Daws records a case (No. 30) in which although improvement with arsenic alone was effected with bone marrow.

Dawe of Chicago records a case (his own wife) which was cured by bone marrow.

Sturges tried it in conjunctivitis arsenie ointment although his two cases were ultimately fatal he regards it as of use in stimulating blood formation.

These are the only two favorable reports I have found on the use of bone marrow in the disease.

It is unfavorably reported on by Bent, Drummond eto unfavorable cases are recorded in St. Thomas' Hospital Reports. Billing tried it in two cases with no good result. So, in all, Anderson had equally unfavorable results with it.

Bone marrow has been used with favorable results.
by various observers in chlorosis, spleen, leukaemia, estoma lactica, the anaemia of the prone, leucopenia, purpura, etc., etc.

There is no evidence to show exactly how the bone marrow acts, but it seems almost certain that it merely acts by stimulating in some way the existing bone marrow.

The fact that in so many different anaemic conditions it has been of benefit points to there being generally stimulating effect on blood-forming tissue, and this would explain the favourable results in some cases and not in others—the marrow being capable of responding to the stimulus in some cases and not in others.

W. L. Bums recommends that it should be given raw with mashed potatoes, but even then it is very liable to upset the stomach.

Stockman made another interesting enquiry into the bone marrow supplied to the Edinburgh Hospital Dispensary, when two successful cases were treated.

He states that it was yellow marrow consisting of fat and connective tissue with an impalpable quality of iron. He was informed by the butchers that a calf would only yield 3-4 ozs of red bone marrow.
Intestinal Antiseptics. The use of these was advocated by Hunter on purely theoretical grounds. The recommended beta-naphthol as being the most suitable.

Webberon observed with that drug very favourable results in a case in which arsenic, iron, strychnine had been tried successively without any benefit, though later, after the paroxysms had increased under beta-naphthol, some further benefit seemed to result from the addition of iron.

Webberon tells me, he has had successful results with beta-naphthol in one or two other cases, in one of which another drug was used. Hunter in his recent paper obtained some improvement in cases where septic processes were very marked. He used salicylic acid with this relieved the acute symptoms existing, recommends sodium, naphthol, calomel, mercuric chloride for the intestine. Rig symptoms present both severe constipation, he advises caustic salicylic acid.

It is worth noting that mercuric chloride the salts of salicylic acid are powerful photogogues with proper action should be carefully watched. Sanday records a case which was much benefited by washing out the stomach, another
similar in action to antiseptic treatment. All Hunter's recently recorded cases seem to have benefited by the use of antiseptics, though most had additional treatment, it must be recollected that these cases were complicated by (Hunter would say caused by) a very septic condition of the mouth, relief of which would lead to improvement in any case, and all Hunter's cases died of the main disease eventually.

No other observers beside Hunter & Gibbon have recorded any benefit from the use of intestinal antiseptics, though they have been tried in many cases.

The favourable results recorded might lend some support to Hunter's theory, but at the same time it is quite easy to understand that, given an underlying septic condition of the alimentary tract in some cases of the disease, removal of it would certainly cause some improvement in the general condition of the patient.

Transfusion. As would be expected in a disease characterized by leukocytosis, attempts have been made to remedy the deficiency by direct means.

Like nearly every other method of treatment it has been
followed by a series of startling successes and many failures.

Once considered a time that only temporary benefit could result from transfusion, through some years later, he published some cases where greater
benefit had resulted.

Drake [194] published some cases in which transfusion had been used with marked success. In five cases transfused, one died of urinary tubule nephritis. The other four recovered though one had
pleuritis. The operation was performed on some of the cases 1-2 hours after blood transfused at each sitting.

Ableek [194] also published a case that after one transfusion steadily recovered, the capillary hemorrhage rising from 500,000 to 20 per cent. He remained well for two years — died of
pneumonia.

Evan [195] published a case where transfusion was employed when the patient was in anemic, with the result that great improvement followed. It was carried on to recovery, by arsenic alone.

Senn [196] published a case in which transfusion seemed to prolong life a little after all other means had failed.
Bramwell describes a case where other means failed. Transfusion was tried with temporary improvement each time the operation was done. Redditch tried it in a relapsing case with slight temporary improvement.

The whole question of transfusion in the disease is fully discussed by Koller, who favours the subcutaneous injection of blood as practised by Von Zimmerman. He considers that this should be a routine method of treatment, that transfusion should not be left to the last.

The method is painful. It requires very vigorous massage, but has been followed by no bad results. Von Zimmerman has injected 369-1140 c.c. of blood at one sitting with no constitutional symptoms.

In the majority of cases followed there has been unfortunately at the best only temporary benefit, in many cases harm has resulted.

In one of Pepper's cases after the first transfusion (1909) there was profound shock, great diarrhoea, high temperature; on the second occasion, the same occurred, and death followed in 24 hours. Peper says that similar troubles have followed another cases.

It is difficult to see how more than temporary benefit
can be expected from transfusion in pernicious anaemia, if the disease be regarded as one characterized by excessive destruction, of which I think there can be no doubt. Probably the added corpuscles are destroyed during this term of life, but they go on to destruction just as the original corpuscles do.

In those few cases where permanent improvement has followed, it must from a slight added blood enabled the body to make headway against the disease, possibly by giving the desired stimulus to the blood-forming tissues.

If however the disease be due to some failure of blood purifying organs, rendering the expanded mass readily destructible, then the successful employment of transfusion may be explained by its having an antitoxic effect essentially the supposed deleterious nature, Maragliano asserts that the pernicious blood in some pathological states exerts a deleterious influence of red corpuscles which is hindered by normal saline solution (possibly more by dilution).

From the injection of saline solution nothing but a temporary improvement, by aiding the circulatory mechanism can be expected, and it is
difficult to see what good can come from the subcutaneous injection of blood or from injections of the intraarterial or rectal injections all of which have been tried.

If transfusion be employed it should not be

left to the last, but done early. If improvement follows it should be repeated before that improvement has passed off.

Massage. This was employed in a case that recovered. 201

W. J. G. writes on the case: 201 "In a little doubt myself that it was chiefly the massage that cured him -- his condition was blunted externally. If the mechanical aid to the lymphatic action return, effectually the massage. I believe it has been what brought him round."

On this point Babot says 202 "In cases in which the chlorose was tried enough to give massage we were unable to see the slightest gain either in respiration or haemoglobin, such as can be produced temporarily in sickly patients."

While mention that cercane of massage may sometimes be of benefit.

It is difficult to see how anything more than an improvement in the mechanical power the circulation can result from massage.
Summary of Table G.

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Explanations.

The cases after 20.93 were added after many references have been made that they could not be further printed.

Signs + = that feature was present.
0 = that feature was stated to be absent.
- = no mention made of that feature.
? = the description doubtful.
M = male.
F = female.
G = gradual.
R = rapid.

References. B. M. J. = British Medical Journal.
E. M. J. = Edinburgh " "
G M. J. = Glasgow " "
Amer. J. M. S. = American Journal of Medical Sciences.
Proc. = Practitioners.
Med. T. G. = Medical Times & Gazette.
S. " M. R. = London Medical Record.
Manchester J. R. = Manchester " "

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**Additional Notes**

18. Some were extremely, others were moderate. It was decided that those who were extremely, were released. Those who were moderate, were followed up by further procedures.
19. Those who were severe, were treated with additional medication.
20. Those who were severe, were followed up by further procedures.
21. Those who were moderate, were treated with additional medication.
22. Those who were moderate, were monitored closely.
23. Those who were severe, were treated with additional medication.
24. Those who were severe, were treated with additional medication.
25. The treatment methods were described in the text.
26. The treatment methods were described in the text.
27. The treatment methods were described in the text.
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**Additional Notes**

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**Table G**

**Reference**: Various medical records, including symptoms, treatment, and outcomes. Each entry includes a reference number, symptoms noted, treatment administered, and the outcome. Additional notes provide further details on the patient's condition and medical history.
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**Additional Notes**

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