"Pernicious Anaemia"

John Allison

1895
April 27, 1895

Dr. Allison has been in residence in this town for 5 years; during which period he has been highly respected by all the inhabitants, and
has obtained this
first will of all
with whom he
has been apprised.

William

[Signature]

[Initials]

[Signature]
Kettering Oct. 27. 1895

John Allison M.B. is Visiting Surgeon, and has been in Practice here from October 1889

John T. Stowell

a Justice of the Peace for the County of Northampton
Wallis Wells, retired schoolmaster, born at Kettering, Northamptonshire, age 51, married. On the 3rd of February 1894 he consulted me complaining of great and increasing weakness, unable for any exertion, yawning a good deal, and inclined to be drowsy.

Family History: — on the Father's side it is exceptionally good. Grandfather and Grandmother dying between 80 and 90. Father alive age 80, still in active employment as a grocer, and looks strong and well for his years. On the Mother's side, the history shows a weakness. She died in 1881 age 61 from Cardiac Weakness, and Chronic Diarrhoea. Three of her sisters are dead, one died in 1864 at Croydon, age 34 from Dysenteric Diarrhoea. Another died at the same place in 1874, age 46 from Morbus Cordis.
The third sister died at Mansfield in 1879 age 55 from Anaemia. One brother died at Kettenring in 1885 age 51 from Congestion of the Liver.

Patient has one sister and three brothers alive, who are strong and well and married. None dead. His own family consists of one son and one daughter both strong and healthy.

Personal History: He was always a weakly child which his friends attribute to a fright his mother received when pregnant. During boyhood this delicacy persisted and since he reached manhood he has never been a robust man like his brothers. He was in active employment however as a Quaker schoolmaster at Askeworth in Yorkshire up to 18 years ago, when early one morning on getting out of bed
he was seized with violent pains in both of his legs and was unable to get into bed again. He fainted several times.

The Doctor at Ackworth treated him for Suppressed Rheumatism and this diagnosis was confirmed by Dr. Allbutt of Leeds. After a time, when he became a little stronger, he was sent to Harrogate. He was laid aside from work however for three years, but slowly and gradually improved in health and gained sufficient strength to resume his work as a teacher. For eighteen months he kept at it, although during that time he was still very weak and unable to walk any distance owing to palpitation and breathlessness, which finally got worse and he was compelled to resign his position, 13½ years ago, as a Schoolmaster.

He is a life long abstainer, most temperate man in every respect.
Never been a hearty eater. Never had syphilis. He does not remember having any illness except that mentioned 18 years ago.

Present Condition: — Height 5 feet 4 inches.
Weight 7 stones 7 pounds. Sparingly made man — muscles inclined to the soft and flabby. The skin is intensely pale, with a slight yellow tinge. Face has an anxious expression. Cheek bones prominent. Not much subcutaneous fat. Sclerotics pearly white. Slight Arcus senilis in both eyes. Hands and feet are cold to the touch. Temperature normal.

Alimentary System: — Lips pale and smooth. Teeth all out. Tongue clean and quite smooth. Buccal mucous membrane, and also that of the Fauces very pale. Has occasional nausea, but never been troubled with actual vomiting. Appetite fairly good. Bowels constipated.
and they have been in this condition off and on for years. Faces are hard and dark brown.

Abdomen: — The peculiar yellowish tinge of the skin is most marked. The walls are quite flaccid.

Liver — normal

Hemopoietic System: —

Lymphatic glands and vessels normal. Spleen normal.

Blood taken from the finger flows very slowly, looks pale and watery, and does not coagulate readily.

Microscopically: The red blood corpuscles seem to be diminished in number. They are of different shapes, a number being tailed, and the others look smaller than usual. To excess of leucocytes in the field. I compared the blood with a drop of my own as I was unable to get a
A hemacytometer or a hemoglobinometer in Kettering, it was impossible for me to estimate the number of red blood corpuscles, and the percentage of hemoglobin.

Circulatory System:— When first taken ill, he suffered greatly from palpitation, breathlessness, and fainting; and for 10 years up to the present time, he has been quite free from these symptoms. But in the beginning of this year, they commenced again, and every now and again, he faints away on the least exertion— even when walking across the room.

There is slight epigastric pulsation. Impulse in 5th interspace, rather weak and jerky. Dullness of heart is slightly increased. Systolic murmurs are heard over the whole of cardiac area.
most marked over the Mitral and Pulmonary Areas, and are of a soft blowing character. Well marked Nemic bruit over the Sterno-Clavicular joint.

Pulse 88 per minute, which goes up to 100 on the slightest exertion. It is soft, easily compressible, and inclined to be jerky.

The arteries are well marked.

Respiratory System: With the exception of the breathlessness on any exertion it is perfectly normal.

Integumentary System: The skin over all the body is intensely pale, with this slight yellow tinge. It is very dry, suffers from Dandruff, hardly ever perspires. Cold at the touch, especially the hands and feet. Matrixes of Nails very pale. Very spare, little fat on the body. No Edema.
Urinary System:—  
No subjective symptoms.

Passes 39 oz. in the twenty-four hours.
Specific gravity 1016. Acid reaction.
The urine has a peculiar smell which reminded me of glycosuria.
The colour was rather high like sherry. No Albumen, Sugar, blood, or bile. There was a slight mucous cloud on allowing it to stand, upon which a deposit of amorphous urates settled, and later on a few crystals of Uric Acid.

Nervous System:—
He is a most intelligent man, bright and cheerful as a rule, yet inclined to be drowsy during the day, and has no energy to do anything.
No pains in any of the bones.
Provisional Diagnosis: - At first sight this man seemed in such a poor way, that it made me suspect that his appearance, particularly the colour of his skin and anxious expression on his face, was due to a cachexia, which one often sees in cases of Malignant Disease or Bright's Disease. So much did this impress me, that I was constrained to ask two medical men in to see the patient with me, and after the most careful examination of him, we were unable to detect any signs of Organic Disease, and our diagnosis was a case of Profound Anemia.

Treatment: - Absolute rest in bed for a week or more; and when he began to feel stronger, to get out into the fresh air, and sunshine as much as possible, as he had a fine garden behind his house.
The diet ordered was of a mixed nature, nourishing, and chiefly fluid, so as to be easily digested.

In the shape of medicine, he was given Capsule of Extract Canaara Sagrada 5 gr. one every other night to try and relieve the obstinate constipation, and the following prescription:

R. Ferri et Ammonio Atriatis 3⅓ Spirit Choloromi 3⅓ Infusi Calumba ad 3⅓

Liq. A tablespoonful in water three times a day after meals.

February 17th:— No improvement whatever. Condition of the patient the same as on the 3rd. The iron was stopped, and Liquor arsenicalis was tried. Two minimia thrice daily after meals well diluted. Even this small dose could not be borne, as it caused him colicky pains and discomfort in the stomach and bowels.
Metallic taste in the mouth, and fulness about the eyes.
February 24th:
I ordered the following pill:
R. Acid. Ascorbii gr. 1/36
              Ferri Reducet. gr. 1
Sym: one pill after food, to be increased to three pills in the day.

March 1st: - Feels better and a little stronger, and he certainly looks healthier. Pulse 88 per minute.
            Cardiac murmurs still very evident.

March 10th: - Much better, has been able to take short walks about his garden without any discomfort. The blood looks healthier under the microscope.
            Pulse 88. Cardiac murmurs not quite so intense.
            His friends took him to Cheltenham for a month, and while there
he consulted a Physician, who confirmed the Diagnosis and treatment.

April 15th:

Still improving under this treatment. Taking solid food now. pulse 80. Cardiac murmurs much less intense. He is able to go a short distance on a tricycle.

September 6th:

I had not seen him professionally since April 30th, and he tells me he had left off the pills for three months, and now he feels as bad as ever he did, if not worse. All the Anemic symptoms were more aggravated than they were in February. Fainting several times in the day, feels very weak and helpless. Pulse 92 going up to 100 on the slightest exertion. Very sleepy during the day, and yawning often. Temperature 100°.
The Colour of the skin at this time was very characteristic, and shewed the peculiar lemon tint. He had been suffering for some days previous from Diarrhoea, six or seven motions in the day, the stools being most offensive. Tongue coated, no appetite, colicky pains in the stomach and bowels, aches all over. The Urine was high coloured, very acid, specific gravity 1020. Large deposit of Urates. No Albumen, blood, sugar, or bile.

He was ordered to keep his bed, and to have a milk and farinaceous diet, and the following Medicine

_Pulse_: Bismuth: Subnutritio 3iv Spirit: Chloroformi 3 iv
_Mistura_: Cretae ad 3viii sig. A tablespoonful every three hours.
September 7th.

Feels a little better, three times to stool. Temperature 99.8°

September 10th.

Diarrhoea stopped, still very weak.

September 12th.

A drop of blood was taken from his finger to be examined and compared with my own. It presented the same peculiarities as in February—if anything a little more marked.

He was ordered the same pill as before.

October 1st.

Very much better, able to go about a little in the garden. Pulse 88—stronger. Cardiac murmur not so acute, from this time he had a better colour and gradually became a little stronger.
January 10th, 1895
I was called in to see him again on this date, and have had him under observation ever since. He informed me he had not taken pills since the beginning of December 1894. Has the same peculiar 'Lemon' tint of the skin, faints on the least exertion. Confined to bed, as he feels the cold so much. Pulse 94. Cardiac Murmurs and0 bruits as before, if anything not quite so acute as in September. Weight 7 stones 4 lb. Temperature 98.8. The condition of the patient looked so characteristic of what is described as Pernicious Anaemia, that I sent a sample of blood and urine to the Clinical Research Association, London, so as to have a proper report of the condition, and the following is the Report

"Red Blood corpuscles 2,000,000 p.e. cubic millimetre"
or forty per cent of normal

Hemoglobin 35 per cent of normal

The corpuscles were practically normal

in shape, though with some tendency
to abnormal variation from an
average in size. There was nothing
amounting to actual Poikilocytosis.

So Leucocytopsis.

The Urine passed in twenty four
hours was 37 ounces, had a peculiar
smell as before, specific gravity 1.016,
and on standing uric acid crystals
were noted.

The Report on it was as follows:

The Urine

showed the Albumin band in a
striking manner without pre-
liminary treatment. The presence
of this band in the original Urine
is strongly suggestive of Pernicious
Anemia.

Except in cases where marked Pyrexia
exists, the band is not seen in
other diseases. Its presence in a
case of Anæmia without fever is almost diagnostic of the Pernicious Anæmia form.

The usual specific gravity of Pernicious Anæmia urine is somewhat lower than that described as found in this case, usually ranging from 1.010 to 1.012 in a characteristic manner.

The point however is of much less importance than the first mentioned.

The urine was free from sugar and blood but contained a little Albumen. The nitrogenous constituents were normal in amount.

Taking all the evidence, it is extremely probable that the specimen is from a case of Pernicious Anæmia.

On this date January 10th he was put on the Milk and farinaceous diet. No Medicine except Bone Marrow Tabloids 5 grains, which I procured from Burroughs Wellcome & Co. He took one of these Tabloids three times a day.
February 5th. Does not feel any better, much the same as on Jan. 10th. Fainted twice yesterday. Pulse 94. Temperature normal. Tongue clean and smooth; mucous membranes still very pale. The skin has still the 'Lemon' Tint. Hands and feet cold. The blood, when drawn from the finger, was still watery looking, and under the microscope runs into irregular clumps, showing no tendency to form rouleaux.

The Report gives the following result:

"Red Blood Corpuscles 1,750,000 per cubic millimeter, or 35 per cent of normal.
Hemoglobin 35 per cent of normal."

"The corpuscles as before showed somewhat large differences in point of size, but there were no irregular forms, and no Leucocytosis."

The urine passed was 37 ounces in the twenty-four hours, acid reaction, specific gravity 1016. Sherry colour and had the same peculiar smell.
The Report being:

"The specimen again showed a well-marked Urobilin band, and in other respects agreed in character with that last submitted."

As the Bone Marrow Tafloids had not affected any improvement in his condition, I made arrangements to get Fresh Ox bone Marrow sent to him, 3 oz daily.

Diet as before. He was to take the bone marrow at each meal, 1 oz at breakfast and tea, made into a sandwich with toast, and at dinner the other ounce was to be mixed up with mashed potatoes.

No Medicine

February 25th: The patient says he began to feel a little better almost from the first day of taking the bone marrow. He had no difficulty in taking it raw, and now rather liked it than otherwise. He certainly
looks better and stronger, and the skin is not quite so peculiar, and over the malar bones there is a slight tinge of red. Buccal mucous membranes are not quite so pale. Appetite has improved considerably. Pulse 88. Cardiac murmurs and Systolic Bruits still very evident.

Temperature normal. Has been able to take a short walk in his garden without much discomfort. The Blood looks better when drawn from the finger.

The Report is

"Red Blood corpuscles 1900000, c.m. 38% c."
"Hemoglobin 40 per cent. of normal"

The tendency to Porphyrophyoric was perhaps somewhat greater than in previous specimens. The increase in Hemoglobin is quite certain.

The Urine passed was 33 oz. in the twenty four hours. Specific gravity 1.018. Acid reaction, not quite such peculiar smell, light sherry colour.
The Report is

"A decided change in the urine was to be observed. The urobilin band was much less obvious, and to judge from previous experience, the disappearance of the absorption band in the urine denotes that the destructive blood change was in abeyance for the time."

"The Ethereal Sulphates however were high though not markedly so. The Sulphuric acid as Ethereal Sulphate showing a ratio to the total sulphuric acid of 1:7.5; the normal ratio being 1:10. The Unoxidized Sulphur was low, but once again, not in a striking way"

As he was anxious for everything to be tried that possibly could do good. The diet was changed slightly- meat and fish being allowed occasionally. The same quantity of Fresh or Bone Marrow and in addition he was to take 2 grains of B. Naphthalin in form of a pill three times a day.
March 16th.

Greatly improved, more colour in his face, mucous membranes look redder, feels stronger, and is actually able to take short rides on his tricycle without any feeling of discomfort or fatigue. Pulse 86, strong. Cardiac murmurs not nearly so acute. Bowels are acting a little more regularly. Has gained six pounds in weight since he began the bone marrow, being now 7 stones 10 lbs. All his friends have noted the improvement.

The Blood looks decidedly better when drawn, and under the microscope shows an inclination to form irregular rouleaux.

The Report is:

"Red Blood Corpuscles. 2,250,000 a 45 p.cent."
"Hemoglobin. 48 per cent of normal."
"There is still somewhat wide variation in the size of the corpuscles, but the phenomena is less noticeable than before."

The Urine passed was 27 ounces, looked
more natural in colour, and the smell seemed quite natural, specific gravity 1.020.

He was now given, in addition to the Bone marrow, and B. Naphthol, the Arsenic pill three times a day. The diet being much the same, although taking more solid food in the shape of meat and fish.

April 2nd

A still further improvement. Pulse 82 stronger. Cardiac murmur and Stomach quiet. Almost imperceptible appetite normal, taking less liquids and more solids. Bowels regular once a day. Faces natural colour. Able to be out every day on his tricycle, and able to do some clerical work in his father's office without any fatigue. Has gained in one month 5 lbs. in weight, and is now 8 stones which he has not been for years.
The Blood looks much redder and more natural, and forms better rouleaus.

The report is:

"Red Blood corpuscles 250,000 per c.m. = 50 folded"

"Haemoglobin 48 per cent of normal"

"Condition of the blood improved in every way."

The urine is also more natural in colour and smell, 24 ounces only were passed in the twenty-four hours. Specific gravity 1020.

The same treatment was to be carried on, with the addition of more Arsenic, making six of these pills in the day.

April 16th:

The improvement in health and strength is more marked than ever. Pulse 82. Appetite normal. Bowels quite regular. The colour of the skin is now almost natural, and the part that—
shewed the peculiar lemon tint are beginning to be quite ready in appearance, notably the ears and cheeks. His own words were "I haven't felt so well and strong for years." He has gained 1 1/2 pounds since April 2nd. The improvement in the Blood is also marked—runs quite readily now when the finger is pricked and looks more natural in every way.

The Report is:

- Red blood corpuscles 2,750,000 per c.m. = 55% percent
- Hemoglobin 50% per cent of normal.

The Urine passed in the twenty four hours was 33 ounces. Specific gravity 1020. Acid reaction. Colour natural. No smell, and no deposit.

As he was able to go about now without any discomfort and fatigue, he has gone to Cheltenham for a month to see some friends. He is to keep on with the same treatment until I see him again.
I had hoped than a complete analysis of the urine passed on April 2nd from the Clinical Research Association, but they have not sent it.
Since graduating this is the second case of Pernicious Anæmia I have seen in private practice. The first was in 1887-8 when assistant to Dr. John Strachan of Dollar, who reported the case as cured by Arsenic at the British Medical Association Meeting in Glasgow 1888. The chief symptoms in this case being Diarrhoea, great and increasing weakness, and the blood changes showed the well known variation in this particular form of Anæmia. The only other case of Pernicious Anæmia I have seen was a woman in Professor Greenfield's ward in 1886, on which he gave a Clinical lecture on February 2nd 1886. This woman suffered from marked Constipation, there were numerous retinal hemorrhages besides the other well known changes.

If we accept Addison's well known description of this form of Anæmia in 1843 and later in 1855 as correct, "that it occurs without any previous..."
"loss of blood, no exhausting diarrhoea, no
Chlorosis, no purpura, no renal, splenic
miasmatic, glandular, strumous or
malignant disease." I think this
case comes under his definition.
A great variety of causes has been given
by various observers as the starting
point of this form of Anemia, such
as Mental shock, yellow fever,
intestinal worms as the Anchylostoma
Duodenale and Bothriocephalus Latex,
Rheumatism, Workers in Lead &c.
The Swiss observers notably Biermer,
Leuconew, Immerman. Guinche seem
to have missed Addison's description
as most of their cases were in women
who were either pregnant, or suffered
a great loss of blood or over lactation.
Indeed so many causes have been
given that some think the Pernicious
Anemia is not a special disease,
Guinche stating it is the product of
various morbid processes, such as, loss
of blood, continued discharge, defective
nutrition.
Coupland says it may follow severe mental shock or some violent emotion, or a profuse hemorrhage, which at the time may threaten life, leaves behind it an Anemia which never disappears and may become Pernicious, that is to say may deepen in intensity in spite of treatment. More commonly this exciting cause is added to a pre-existing and long-standing Anemia, which then takes on a fatal form, or the determining event may occur in some other exhausting discharge.

His views in Kingstone Fowler's Dictionary of Medicine 1870 are much the same, as he thinks it is still a moot point whether Pernicious Anemia is a distinct disease.

Bristowe is another who is doubtful. Hunter, Bracebridge, and others have clearly shown that it is a distinct disease both clinically and pathologically.

To doubt some of the supposed causes act as a predisposing cause to this form of
Anemia. And conditions, such as large populations, living under bad hygienic conditions, insufficient supply of food, both in quantity and quality will greatly help to bring it about. The only predisposing cause, in this case, which might be the beginning, was "suppressed Rheumatism" 18 years ago.

The family history of this man, on the Matthew side so worthy of special notice. In fact when he first consulted me, he informed me he was suffering from the "Wallis" complaint as several members of the family had suffered in the same way, getting very pale, and finally assuming a yellowish colour of the skin, which they considered was "Liver Complaint."

I have been at the trouble to get the death certificates of all those who suffered in that way, viz., Gradual and increasing weakness, becoming very pale during the last two or three
years of their lives, finally the skin assuming the peculiar yellow hue. They all seem to have suffered more or less from vomiting and diarrhea, especially the mother and brother. The mother, before her last illness consulted a Physician at Northampton who told her she was suffering from a peculiar condition of the Blood, and that it would gradually become fatal. The sister who died in 1879 at Mansfield and certified as the result of Anæmia I find the Doctor there says it was "Pernicious Anæmia." The brother who died in 1875 at Kettering from "Congestion of the Liver" seems according to what his widow tells me, to have suffered a good deal during the last year of his life from vomiting and attacks of Pyrexia.

"This history seems to point to a family weakness, which my patient might have inherited, and it
is acknowledged that heredity may play a part in anemia, especially the pernicious form. Dr. James Andrew considers in this disease there is some personal factor which allows the anemic process to become cumulative.

Hobson suggests there might be a certain weakness, hereditary or acquired, in the organs responsible for the production of fresh blood cells, whereby the resources within themselves are unduly limited. Conplanb believes heredity plays some part in disposing the organism to anemia.

Gowers suggests there is an inherent defect of vitality or of vital endurance in the blood-making tissues.

Symptoms
This man exhibited most of the symptoms of profound anemia, and with regard to those, regarded as peculiar to pernicious anemia.
I think he showed them in a marked degree with one or two exceptions.

1st. He had great and increasing weakness.

2nd. The colour of the palor was the distinct Lemon Tint.

3rd. Blood changes: The blood when drawn was pale and watery, with little tendency to coagulate, and under the microscope, the corpuscles ran into irregular clumps or masses, and made no attempt to form leukocytes. The red blood corpuscles showed many shapes and forms, which Quincke described as 'Polkytozyis'.

I was never able to detect any highly refractive bodies known as Sickhont; corpuscles which at one time were thought to be pathognomic of Periclausian Anemia, but Professor Grainger Stewart and others have shown they are not pathognomic. Oligocysthemia was well marked, although not to an excessive degree; the greatest diminution being 35 per cent of normal.
The Hemoglobin percentage was also 35 per cent. of normal.
Some writers, notably W. Hunter, attach great importance to the richness of each corpuscle in Hemoglobin, and consider it a fairly constant condition in Pernicious Anemia. Stephen Mackenzie and others say that it is by no means constant.
Quincke in his observations says the red blood corpuscles may be reduced on an average to 10 or 12 per cent of normal and the Hemoglobin never less than 20 to 40 per cent of normal.
Coupland gives the diminution of red blood corpuscles as 10.6 per cent and the Hemoglobin as 30 per cent. Hunter agrees with these observations.

In this case I have never been able to detect the condition in the red blood corpuscles described by Mackenzie and Davy, and no crystals of Hemoglobin were ever seen, which condition was first described by Copeman and Bond.
In this disease the alkalinity of the blood is greatly diminished.
The specific gravity is also lowered.

Juncque quoting a case where it was 1028.

Jones had three cases, in which it was 1032-34-40.

Copeman's two cases, 1027-1034, Fraser's, 1036

4th. Haemorrhage: - This case has never shown any haemorrhages, interstitial or subcutaneous. Biermer was the first observer to describe them in the Retina and Byrom Bramwell the first in this country.

5th. Optic Neuritis - None

6th. Pyrexia: - Immerman of Basel being the first to note this symptom. In this case there was only one rise of Temperature viz. 100° in September 1894, with that exception it has been consistently normal.

7th. Gastro intestinal symptoms: - This case never suffered from vomiting.

One attack of Diarrhea in September 1894
and with that exception, he has always suffered from Constipation.

Dr. Hale White gives some interesting facts concerning these symptoms. He found that in all the cases admitted into Guy's Hospital, 41 per cent gave a history of vomiting before admission, and 34.5 per cent a history of Diarrhea. After admission 55 per cent suffered from Vomiting, and 41 per cent from Diarrhea.

The Urine:—In this case it varied very much in quantity and colour. From 28 to 40 ounces in the twenty-four hours. The Colour sometimes very dark, like dark sherry, especially in cold weather, at other times it looked like ordinary urine. It was always acid in reaction. I never detected any Albumen, Sugar, blood or bile. Although on Jan 4, 10 of this year there was a little Albumen present.

The specific gravity varied, never below 1016, and never above 1020. While as a rule in most cases of
Pernicious Anæmia it is 1010, 1012, 1016.

A great deal of stress has been put upon the colour of the urine, notably by Hunter, who thinks the high colour of the urine is characteristic, and that it is due to a pigment described by Maemmert as Pathological Urobilin. Mott, Copeman, however have not been able to detect such a pigment in the urine of their cases of Pernicious Anæmia, and the pigment they have found in excess was Normal Urobilin. Hopkins also thinks it is normal urobilin which is the pigment that gives the dark colour to the urine. In one of the cases he examined, he thought he had found with the spectroscope Pathological Urobilin, at least the absorption bands were exactly those described by Hunter, but on further examination and treatment he found that Pathological Urobilin was a mixture of pigments viz. Normal
Urobilin and Hematoporphyrin. This case showed a well-marked Urobilinuria.

Hunter has found in the urine, especially during exacerbations of the disease, renal cells and casts containing granules of blood pigment. This pigment being in the form of fine granules, spherical shape, and fairly uniform size, varying from 1 to 2 μ.

When this blood pigment is excreted by the kidneys, he considers the Hemoglobin reaches the Kidney in a peculiar form, not being free, but in combination with the Albuminous constituents of the corpuscles or Plasma.

He further noted that in this disease there is an increased excretion of Iron in the urine. Finney had also noticed it. Iron is a constant constituent of urine in health, and the daily excretion ranges from 3 to 5.65 milligrammes. In Hunter's case the excretion of Iron once reached the large amount of 32.26 milligrammes.
Hopkins found a case where it reached 8.3 milligrammes. He agrees with Hunter that the excretion of iron is very inconstant and intermittent in this disease.

It has also been found in the urine that the excretion of Ethereal Sulphate is increased, and this excretion is entirely dependent on Intestinal conditions only. The normal ratio of Ethereal Sulphate to Ordinary Sulphate is 1:10. Hunter found in his case that the ratio was greatly disturbed, being 1:3, showing that although a small quantity of food had been taken, the quantity destroyed by putrefactive changes was three times greater than should have occurred.

In this case the ratio of Ethereal Sulphate to Ordinary Sulphate was 1:7.5.

The quantity of unoxidized sulphur compounds seem to be decreased in Perivious Anemia.
Another important and interesting condition has been found in the urine of a case of Pernicious Anæmia. The presence of Putamines Hunter separated two bodies from the urine, which resembled Cadaverine and Putrescine, and a third body belonging to the Diamine group, but which differed from the other two.

He seems to be the only observer who has discovered these Putamines in the urine of Pernicious Anæmia.

And the interesting fact is, that both Cadaverine and Putrescine are formed only by the action of Micro-organisms.

The only other condition where they have found was in a case of Cystinuria by Baumann and Udrausky.
Pathology

At one time it was thought that the only constant condition of the organs of the body found after death was profound Fatty Degeneration, and that this condition was the cause of this particular form of Anemia. Dr. Wilks in 1857 reported seven cases of Idiopathic Fatty Degeneration with profound Anemia.

Coupland also thought that this Fatty Degeneration was the only constant anatomical condition. The organs where this is found are the heart, especially the Musculi Papillares of Left Ventricle, where it shows the well known "Fatty Cal" appearance described by Guain.

The Liver, Kidneys, blood vessels all take part in this degeneration and the condition of the blood vessels explains the extravasations of blood during life as in the Retina. Shunt we now know the Fatty Degeneration to be the result of the Anemia.
The various changes in the Gastro-
Intestinal tract, such as Malignant
disease, Atrophy of Gastric glands,
acute, subacute and chronic inflam-
mations of the mucous and submucous
coats to, which have been described
by numerous observers, as being found
Post Mortem in cases of Pernicious
Anemia, are not the essential
anatomical changes in this disease,
as these lesions may occur in
people without any of the symptoms
of Pernicious Anemia, developing
during life. And many cases of
Pernicious Anemia have been
described without any of these
lesions being found Post Mortem,
and thus - agreeing with Addison's
well known description.

Changes have been described in
the Marrow of bones, Spleen, Liver,
Kidneys and Spinal Cord.
Professor Pepper of Pennsylvania in 1875 was the first to describe the marrow of the long bones being intensely red instead of yellow. He thought this caused the Pernicious Anæmia, and that it was merely the medullary form of Pseudo-Leukæmia. Cohnheim found in a case, that in all the bones, the marrow was intensely red, like what occurs in the Fetus. Microscopically, he found no fat cells, but 1. a large number of colourless corpuscles, many resembled lymph corpuscles, many had epithelial aspect, and contained one or more nuclei. 2. a large number of coloured corpuscles, the most remarkable of which contained nuclei which were coloured red like the cells. Nucleated blood corpuscles were also detected Post Mortem, in the blood taken from other parts of the body, although none were discovered in it during the last week of life. Some observers have noticed this change
while others have found no change, notably Dr. Branwell and Bradbury. Hunter observes that the changes in the bone marrow are of a twofold character, 1st, the presence of a large number of nucleated red blood corpuscles, which apparently point to some profound disorder of Haemogenesis, and 2nd, the presence of a large number of corpuscle carrying cells, cells enclosures old red corpuscles, or their pigment remains, and this points to disordered Haemolysis.

These changes are now known not to be pathognomonic of Pernicious Anæmia.

It has been found that the bone marrow contains a considerable excess of Iron, partly in diffuse and partly in granular form, but this excess is not constant. Rindfleisch has come to the conclusion that this condition of the bone marrow is due to some
obstacle in the way of the extrusion of red corpuscles from the haematoblast of the marrow, which in consequence become greatly increased in number.

**Spleen**

The condition of this organ has been found to vary a good deal. Sometimes it is greatly enlarged, weighing as much as 19 ounces in a case of Dr. Branwell, and has been recognised during life. The enlargement is often noticed during an exacerbation. While at other times it is smaller, shrunken and contracted. In the case in Professor Greenfield's Ward the Spleen only weighed 14 ounces, and could not be mapped out during life. Again it has been found to be quite normal. In its fresh state the colour also varies sometimes pale and flabby, and at other times it is a dark deep violet-red or purplish colour and greatly compares with the pale condition of other organs.
Microscopically: no changes at all have been found, and at other times nucleated red corpuscles have been found. Micro-chemically, Russell found on using solution of ferro-cyanide of potassium and weak solution of hydrochloric acid, that the spleen stained a deep blue, and he found the iron pigment chiefly in the walls of the pulp sinuses. Hunter found the blood pigment was present in large quantities in the form of minute spherical granules lying within the cells of the pulp. He attaches more importance to naked eye appearances of the spleen, than after it is hardened, because then we often fail to find any change in the spleen, and sometimes we get no reaction with the ferro-cyanide of potassium and weak hydrochloric acid. He also explains the variation in size of the spleen, when it is enlarged, there are signs of active disintegration of red blood corpuscles being in progress,
while on the other hand, two or three days afterwards, although the blood still contains remains of red blood corpuscles, and other evidences of blood destruction are numerous, the spleen may be small, shrunken, and contracted showing little evidence of being concerned in the blood destruction. Mott 44 found in one of his cases that the spleen contained a large amount of iron free in cells throughout the whole organ, and also a number of cells were of a pale orange colour which did not stain with reagents. The normal percentage of iron in spleen is 0.17.

Liver

The changes in this organ found after death are most important, and characteristic of Pernicious Anemia, on some occasions the liver is found to be enlarged and has been recognized during life. At first it was thought that the
only change was Fatty Degeneration, and this is exceptionally well marked in the centre of the lobule. The first observer to point out another and more important change was Guinée who has clearly shown that the liver in Pernicious Anaemia contained a great excess of iron. Russell found that the liver, when treated with Ferrocyanide of Potassium and weak Hydrochloric Acid, stained a deep blue in the outer middle zones of the lobule, and this staining showed there was iron present. This pigment was in the form of discrete particles or granules, and in globular masses. In the central zone there was a yellowish pigment in the cells, which did not give the Iron reaction. Hunter considers the presence of this pigment in fine granules in the liver cells, and confined to the outer two thirds of the lobule, the inner third being in a state of
Fatty Degeneration, the only constant morbid change in Pernicious Anaemia and it is now generally recognised by the profession that it is so.

The result of chemical analysis of the liver shows that there is a very large increase of iron in this disease. Grünke recording a case in which 100 parts dried liver substance gave as high a percentage as 2.1, the normal percentage of iron in the liver being 0.083. Other observers as Stekel had one in which the percentage was 0.614. Zaleski 0.624. Hunter 0.566. Stevenson 0.367.

The relation of this pigment accumulation in liver to that of spleen is greatly disturbed in this disease, and Hunter was the first to draw attention to this relationship. The liver in some cases showing a sevenfold increase of iron, unaccompanied by any increase in the spleen.
Hopkins gives the ratios in a case he examined as Liver 1:038, Spleen 0:301.

Kidneys

The changes in these organs are by no means constant. Russell found the cortical parts of the kidney stained deeply with the Ferrocyanide solution and weak Hydrochloric Acid, and on microscopic examination, the blue granules were confined to the epithelium of the Convoluted Tubules. Hunter agrees with this, and that the granules of pigment may also be in certain parts of Henle's loops where the epithelium is closely allied to that of the convoluted tubules. These granules are rarely found in the lumen of the tubules.

Spinal Cord

Lichtblau, Munich, Burr, Bowman, and others have described organic changes in the spinal cord, which
explained the nervous symptoms which were sometimes found in Pernicious Anemia. In the earlier stages, small areas of hemorrhage or extravasation of blood were found, like those seen in the retina and serous surfaces; and later Degenerations especially in the Posterior Columns of the cord.

Dr. James Taylor regards these cord changes of double origin: 1st Sclerosis resulting from hemorrhage, and 2nd Sclerosis - the result of blood stasis.

The association of these spinal cord changes with Pernicious Anemia has not been definitely proved, as these changes might be accidental; and it is well known that these changes may occur in other Anemias especially Chlorosis.

The question now arises, what is the condition in Pernicious Anemia
that leads to these changes. Is it due to defective and perverted blood formation (Hemogenesis) or is it due to excessive blood destruction (Hemolysis), or to both combined? 2.

Brakenridge's views are:
1st. That the real condition of the blood in Pernicious Anæmia is a delicacy and tendency to early death of the red corpuscles.
2nd. The probable starting point of this delicacy and feeble resistance in the red blood corpuscles is some functional weakness in the blood forming organs, which may be due to various possible causes.
3rd. The irregular shaped, and variously sized, otherwise abnormal blood corpuscles point to some such imperfect genesis.
4th. Consequently without any abnormally increased destructive force in the Portal system or organs it being a normal function of
Liver cells to destroy the red corpuscles, a greatly increased death rate of these delicate and short-lived corpuscles takes place.

Lockhart Gibson considers when more to do with defective and perverted blood production, rather than excessive blood destruction, giving as his reason that he found in the blood of a case of Pernicious Anemia cells resembling or even homogeneous with cells he described in his account of the development of blood cells in bone marrow.

No doubt the large, flabby and ill-formed macrowcles found in the blood of Pernicious Anemia cases are the result of defective and perverted blood formation.

The nucleated red corpuscles which are also found in the blood of this disease is doubtless an indication of partially
unsuccessful efforts at restoration of the normal number of corpuscles, as these nucleated corpuscles are also seen when there has been a severe haemorrhage. The red condition of the bone marrow points to the fact that it is making an effort to supply corpuscles.

Brunn, Russell, Hunter, Mott and many others, from their writings, consider that Pernicious Anaemia is essentially a disease caused by excessive Blood destruction, and that the changes in the blood forming organs viz. Hyperplasia is quite secondary.

We are chiefly indebted to W. Hunter in this country for working out the Physiology and Pathology of Blood destruction.

In health he has shown that Blood destruction takes place daily, and that it is greatest during full digestion, five or six hours after
ingestion of food, especially if it be a rich meat diet.
He describes two kinds of Blood Destructors:
1st. a slow and gradual decay of red blood corpuscles, shown by changes in colour and shape, and its resistance to the action of reagents. The Haemoglobin remains within the red blood corpuscles to the last, and becomes gradually converted into a globule of inert blood pigment retaining its size and spherical shape of the red blood corpuscle. It is to a great extent independent of cells, although the final conversion of Haemoglobin into effete pigment is the result of activity of cells. To this form he gives the name 'Passive', which is really the ultimate destiny of the red blood corpuscles which live their allotted span, and undergo a process of natural decay, and this is shown by the kind of pigment which is left behind, being of large size, and varying in shape.
It is found chiefly in the spleen, capillaries of liver, and bone marrow.

2nd. In this form he gives the name of Active Destruction, in which the haemoglobin instead of remaining within the red corpuscles escapes into the plasma and is in great part excreted by the liver as bile pigments. It differs from the Passive form in being closely dependent on the activity of cells. The chief evidence of this form is:

1st. The formation of bile pigments by the liver, to which organ the haemoglobin is mainly carried;

2nd. To a lesser and altogether subsidiary extent in health, the formation of blood pigment. The chief character of the pigment being the small uniform size and spherical shape of the individual particles. The assumption of this form by the pigment is independent of the action of cells, but the
conversion of Hemoglobin into blood pigment is as much the result of cellular activity as in Passive destruction. He has further shown the seats of blood destruction to be confined to the Portal Circulation, and its structural features are 1st Slowness of Circulation, 2nd large mass of active cells lying in close relation with the blood, 3rd Capacity for accommodating large quantities of blood.

In Pernicious Anemia the seat of blood destruction is the same as in health, being confined to the Portal circulation. This explains why in all cases the one constant anatomical change viz.: Increase of blood pigment is to be found within the liver cells and situated in the outer two-thirds of lobule. If this blood destruction should
be very excessive and the liver unable to deal with it, we then found in certain cases that the blood pigment escapes into the circulation and is finally excreted by the kidneys. Evidence of this is pigment granules in the renal cells.

Hunter by experimenting on animals found that by injecting small doses of Toluylene diamine, a poison which has a special action on the blood of the Portal Circulation, he could produce all the changes that we found in Pernicious Anemia, viz.: alteration in the shape and size of blood corpuscles etc., and the conditions found in the liver and kidneys Post Mortem. In his lectures on Hemolyzism 1872 he has further demonstrated by his experiments with Toluylene diamine that the greatest destruction of blood corpuscles takes place
1st In the Spleen; 2nd when the Spleen is removed, the Gastro-Intestinal Capillary area; 3rd Capillaries of Liver; 4th Bone Marrow.

Many observers consider Pernicious Anemia is essentially a hepatic disease, and that blood destruction takes place to a great extent in the Liver. But Hunter in these lectures considers the Liver is purely an excretory organ, and that if there is any blood destruction it is in the Capillaries of the Liver and of small extent, and not in the Liver cells.

He considers the greatest blood destruction takes place in the Spleen, after that in the Gastro-Intestinal Capillary area. The blood corpuscles being broken down in these situations, hemoglobin set free, this passes to the Liver, passes through the endothelial cells of the walls of the capillaries, and taken up
by the liver cells. The hemoglobin is here broken up to form the bile pigments, and blood pigment is left behind in the liver cells.

Russell, and others, agree that there is an antecedent blood destruction, and that this disease is not primarily a hepatic one.

Mott suggests that the excess of pigment granules in the liver cells in cases of pernicious anemia might be an exaggeration of a normal physiological process like the glycogenic function. Delapine says the liver has a ferrogenie function, the iron being stored up in the liver in such a form that it is easily reassimilated for the making of new blood corpuscles. Hunter, combat this assertion, and considers that the iron in the liver of case of pernicious anemia is not in such a state for reassimilation, and
that the iron found there is quite different to that found in the spleen and bone marrow, the two principal organs in the body where new blood corpuscles are formed.

If these observers' views are correct that in Pernicious Anaemia, excessive haemolysis is the most important process in the disease. The question arises what causes this excessive haemolysis. Hunter \textsuperscript{39} thinks it is due to a certain poison or poisons of a specific nature, probably of a cadaveric nature, which is produced in the gastro-intestinal tract, and that it is absorbed from there. This poison however being produced in excessively small quantities and not necessarily constant. He came to this conclusion from analogy afforded by the action of Toluylenediamine, which has a special action on the blood
of the Portal Circulation. That the evidences of this excessive blood destruction in Pernicious Anaemia are 1st a greatly increased excretion of urinary pigments, evidenced by the high coloured urine, no diminution in quantity and the low specific gravity. And as mentioned before, this excess of pigment has given rise to some controversy. He considering it is chiefly pathological Urobilin which he regards as a by-product, formed not only by processes of reduction or oxidation from the bile pigments within the intestinal canal, and also from the disintegration of Hemoglobin through the agency of cells. Others have only found Normal Urobilin. And Hopkins declares Pathological Urobilin is a mixture of Normal Urobilin and Hematosporphyrin. In connection with the excess of pigment in the urine - Hunter attaches a good deal of importance
to the marked 'Lemon' hue of the skin; slight degree of jaundice; increased formation of bile pigments shown by dark colour of the faeces.

2. Excretion of blood pigment in urine—found in renal cells and casts.

3. Increased excretion of Iron in Urine.

4. And Post mortem the changes already described in spleen—liver—kidneys.

In connection with the great disturbance in the ratio of Etherial Sulphate to ordinary Sulphates in the urine, and also having separated from the urine two bodies resembling Cadaverine, and Putrescine, and a third diamine body, the first two being only produced by the action of Micro-organisms.

He concludes that the exacerbations met with in Pernicious Anæmia have a relationship with the absorption of specific poisons from the Jutro-intestinal tract, and that they show a certain amount of toxic poisoning.
Mott however states that in three cases he found no relationship between the Pyrexia, diminution of red blood corpuscles, the colour of the urine, and states that many cases of Pernicious Anæmia than on Post mortem examination been found to show no affection of the Gastro-intestinal tract, and on the other hand there are many cases of Ulceration of the Gastro-intestinal tract, where there are swarms of Bacteria and yet they show no signs of Pernicious Anæmia.

Lauder Brunton suggest the cause of this blood destruction is some abnormal product of digestion, or even some digestive ferment present in the Portal Circulation which gets out in great or less quantities into the general circulation and this also causes the Pyrexia.

Destruction of white corpuscles which
their decreased number might lead us to suspect, is further evidenced, though not absolutely, by the excess of uric acid generally present in the urine; may not the Pyrexia of Pernicious Anæmia be due to the same cause?

Most of the latest editions of textbook, such as Quain's, Fagge's, Robert & agree with the view that Pernicious Anæmia is the result of excessive Hemolysis, and that the Post Mortem changes in the Liver especially support this view, and that this excessive Hemolysis is due to the absorption of a specific poison from the Gastro-Intestinal Tract, which poison is the product of certain Micro-organisms that have not, as yet, been differentiated.
Treatment

The recognised treatment of Pernicious Anæmia at the present day resolves itself into four heads viz.: 1st. Hygienic, 2nd. Dietetic, 3rd. Medicinal, 4th. Transfusion.

1st. Hygienic: — If the patients are in a very weak state when first seen, it is of the utmost importance they should have absolute rest in bed, so as to husband their strength as much as possible. The bedroom should be suitable, well ventilated and warmed, and free from any possible risks of inhaling bad smells to. Whenever they gain a little strength, and able to get out of bed, it is advisable they should get out into the open air and sunshine when the weather is suitable. This even the 2nd. and gentle exercise taken either in a carriage or bath chair.
Dietetic:—Until late years it was the custom to give a highly nutritious diet, composed chiefly of albuminuous materials, as rich soups, meat extracts etc. But if we accept the view that Pernicious Anaemia is due to excessive Haemolysis, then we ought not to give food such as a rich meat diet, as it has been shown to increase active destruction of the red blood corpuscles.

Hunter recommends a purely milk diet or a milk and farinaceous diet as likely to lessen this active destruction of red corpuscles, and thereby combat the symptoms. The case in which he tried this diet showed a decided improvement in the condition of the patient, the pallor of face improved, fell stronger, blood pigment disappeared from the urine, and the excretion of ctheral sulphate was diminished.
Alcohol in any shape does not seem to have done much good in cases of Pernicious Anemia.

Medicinal:— If there is much gastro-intestinal disturbance, we ought to try and improve this, and the milk diet is aimed at this washing out the stomach has been recommended especially in the early stages of the disease, and Tandy seems to have noticed a decided benefit from this operation.

Intestinal Lavage has also been tried, but there do not seem to have been any definite results recorded.

Constipation should be attended to at the early stages of the disease, and if drugs have not the desired effect, simple enemata from time to time will be sufficient.
Vomiting and Diarrhoea should be treated accordingly, and the preparations of Bismuth are as good as any.

Broadbent records a case (a lad of 16) in which he cured him with Phosphorus, using it because of the "favourable modification of the organic processes and leading to improved nutrition of the nervous structures." This seems to have been the only successful case treated with Phosphorus, as most observers have found it quite useless.

The preparations of Iron are of no use in this disease except maybe toward the end of a cure.

Arsenic, however, stands in a different position. Byron Braundell was the first to suggest the employment of it, and since then, ample testimony of its value has
been recorded by many observers, in fact most of the cures of Periculous Anæmia have been ascribed to its use. The Liqueur Arsenical is generally considered the most serviceable preparation. It is usual to begin with small doses — say two minims well diluted three daily after food. The dose is increased gradually, taking care to watch the effect of the Arsenic, that no Gastro-intestinal irritation is produced, as that would put back the patient considerably. Cases of palsy have been recorded where the Arsenic has been pushed too far.

Stephen Mackenzie considers the best results are obtained in Periculous Anæmia from the large doses viz.: Ten to fifteen minims thrice daily. It is supposed to have a beneficial action on the blood-forming organs, thereby improving blood formation.
Copeman and Bond have clearly demonstrated that Arsenic has the effect of stopping the formation of Haemoglobin crystals, so that it must have the effect of lessening the vulnerability of the Red blood corpuscles. Mott also states, it clears away the uric acid which occurs in the urine of cases of Pernicious Anæmia. Hunter considers that the action of Arsenic is entirely local, viz.: on the mucous membrane of the stomach and intestine, that it acts as a germicide, thereby preventing the development of Pseudomices. In some cases Arsenic cannot be borne in any shape or form, and here it might be given subcutaneously. It is as well to remember that it is not always successful in curing the disease even when well borne.

To show the efficacy of Arsenic, Padley has collected some interesting details. In 48 cases that were treated...
without Arsenic 42 died; in 22 cases treated with it 16 recovered, 2 improved, and 4 were fatal.

On the principle of Intestinal Antiseptic Hunter recommends such drugs as Beta Naphthol, Salol &c. They may be given in doses of two to five grains thrice daily after food, probably best in pill form. He considers they limit the putrefactive changes in the Intestine and so counteract the formation of the specific poison.

Gibson reported a case in which he had used Beta Naphthol with a satisfactory result. At present however it is not definitely settled that such preparations have benefitted the cases as Hale White and others have found no benefit from it.

Quinine seems to have done good in some of the Pyrexial attacks.
Oxygen Inhalations have been tried, but with doubtful benefit.

Last year Professor Fraser introduced to the notice of the Profession, the employment of Red bone Marrow in the Treatment of Pernicious Anemia. The result in his case and others who have used the bone marrow, leads us to believe that we possess in the bone marrow a powerful remedy in some of the cases of Periculous Anemia. Professor Fraser gave it in the fresh state three ounces daily.

Dr. Barr gives it in the form of a paste: three ounces bone marrow, one ounce Port Wine, one ounce Glycerine, and five drachms Gelatine. The gelatine should be soaked in sufficient water to soften it, and then should be melted with the glycerine, the mixture being kept in a mortar previously made hot with boiling water, while in another mortar...
treated in a similar manner the bone
marrow and port wine are mixed.
Then the contents of the two mortars
should be thoroughly incorporated
and allowed to settle.
The immediate improvement in
every way of the patient's condition,
in Professor Fazer's and Dr. Barris' cases, on the administration of
the bone marrow was remarkable.
It appears to be immaterial whether
it is given in powder or in the
raw state, as patients can be taught
to take it and after a time they
really seem to have no difficulty
in taking it.
Lately when going through the
Infirmary at Leicester one of the
Physicians told me he was in
the habit of putting the bone
marrow on toast and gently warm-
ing it in an oven, and that
his patients liked it in that state.
I understand it does not affect the
efficacy of the bone marrow in any way.
It has not been shown in what manner the bone marrow acts in the system after digestion unless it is by stimulating the blood forming organs, especially the bone Marrow, to better and increased blood formation.

Dr. Douglas Stanley reports a case in which he administered an extract of the Suprarenal Capsules (freshly prepared) with the result that there was a marked increase in the number of red blood corpuscles.

Systematic Massage has been recommended and Hengel thinks, when the Circulation begins to fail, that it will have more effect than medicinal treatment.

There are cases however of Pernicious Anemia, in which medicinal treatment has failed entirely, and the Transfusion of Blood has
been resorted to. During the last few years, we have had many observers who have recorded cures, or decided improvement after transfusion, while others are very sceptical of its utility, whether it be pure blood, defibrinated with phosphate of soda solution, or even common salt solution. Hunter considers that in Pernicious Anemia, transfusion of blood is contraindicated, as the condition of the blood is due to excessive hemolysis. He admits that in conditions due to failure in blood formation, as want of iron in the system, transfusion of blood possesses some hemogenic properties, as the transfused red corpuscles contain all the iron of the hemoglobin in the form it can most conveniently be stored up in the body, and be ready for new blood corpuscles. But taking all the advantages to be
gained by pure or defibrinated blood transfusion, he thinks that the same can be equally well, and be more readily obtained by transfusion of a neutral saline solution as 0.4 per cent common salt. Stengel considers the hypodermic injection of normal salt solution in large quantities - two pints to two quarts - the safest and best method. He doubts whether blood serum or blood has any great advantage over the saline solution.

Bramwell, Bradbury and others have reported failures with transfusion, but they seem to have been extreme cases.

Coupland states that in his 110 collected cases, there were twenty transfusions, all in Quincke's practice, he had five recoveries, one of which was not permanent, and that these successes were due to his having recourse to it at the early stages.
of the disease and considers by transfusion, the blood is reinforced with functionally active elements. Locke records a case where he transfused four ounces of blood and two ounces of Phosphale Soda solution with entire success. Brahenridge, however, has given a great impetus to the importance of transfusion in cases of Pernicious Anemia, which fail to respond to the ordinary medicinal treatment. And from his results one cannot help coming to the conclusion that it ought to be a recognised treatment when other things fail. Defibrinated Blood with phosphate of soda solution was used. He had nine transfusions in five cases, and had repeated transfusions in some of the cases, ranging from one to four times, and the quantity transfused was from two to six pints. With one exception they all recovered.
His idea being to transfuse a considerable amount of healthy blood which acts in a twofold manner: 1st. By immediately improving the health and resistance of blood, including the delicate red blood corpuscles which become mixed with it; and 2nd. Later, on by gradually operating beneficially on the blood forming organs through which it circulates, restoring their blood forming function to a normal condition. And if it does not cure the disease, it might give an impetus to these organs which would bring them under the influence of arsenic. His results certainly bear out his calculations.

It is needless to say if transfusion is resorted to, the operation must be done with perfect Asepsis. Dr. John Duncan recommends plenty of time to the operation, thirty minutes required to transfuse
eight ounces, one third of which should be phosphate of soda solution so as to secure perfect fluidity. He recommends the phosphate of soda solution in distilled water to be of the same specific gravity as the blood, and it should be several times well boiled, and the strength should range from 3½ to 10 per cent although the latter is rather strong.

Dr. James thinks transfusion of serum alone would be just as good as the defibrinated blood and phosphate of soda solution, as he considered what was wanted in the blood, supposing the condition of the blood in cases of Pernicious Anæmia were due to Phosphates, was some additional nourishment to allow these, time and pabulum, to follow their normal evolution.

Intra-peritoneal injections of blood have been tried especially on the
Enemas of defibrinated or blood have also been recommended, but I am not aware that either of these procedures have been very successful.

With regard to this man, a careful review of the clinical features viz:—
the great and increasing weakness, cardiac feebleness, blood changes, peculiar yellow hue of skin, character of the urine, two relapses in a year, no organic disease to be found, and the effect of treatment, all point to this being a true case of Pernicious Anaemia, as far as one can judge during life.

Although most of the writers on the Pathology of Pernicious Anaemia agree that excessive blood destruction is the principal cause of the disease, and that this is brought
about by the absorption of a specific poison, which is the product of microorganisms in the Gastro-Intestinal tract.

Still in some cases of this disease, one must come to the conclusion that excessive blood destruction alone is not the entire cause, and that defective and perverted blood formation also plays a part in some of these cases.

To my mind the majority of the recorded cases of cures of this disease by Arsenic, Bone Marrow, Transfusion &c. point to the fact that both factors are at work. No doubt excessive blood destruction is the most important element in Pernicious Anemia, which at times when a larger quantity of poison is absorbed from the Gastro-Intestinal tract than usual leads to greater destruction in the Portal Circulation, which destruction quite outruns the blood formation,
these organs not being able to supply the proper amount of blood, both in quantity and quality.

In this case, I consider both factors have been at work, only I think defective blood formation has been as much an important element as excessive blood destruction.

His personal history points to the fact, that he was always weakly as a child, and never been robust either in boyhood or manhood like the rest of his family, and since the illness mentioned eighteen years ago, he has never been the same, getting weaker and paler as time went on, on some occasions improving a little, but mon often going downhill, until at least he presented most of the symptoms regarded as characteristic of Pernicious Anaemia.

Looking also at the family history of this man on the mother's side.
The Mother herself dying at 61, three of her sisters dying at the respective ages of 34, 46, and 55, and her brother at 51, all of whom, during the last few years of their lives, were supposed to be suffering in the same way as this man, getting gradually weaker, paler, and towards the end, the skin assuming the peculiar yellow hue. The certificate of death seems to me to point to some weakness in the family, and that delicacy pointing to some defect in connection with the blood. Pernicious Anaemia at the time of their deaths not being so well known and recognised as it is now. Such a history leads one to the opinion that in this man's case, there was a hereditary tendency to defective blood formation. Associated with this, the hypothesis suggested by Dr. Gowers appears to me a very feasible one.
The failure of tissues soon after they complete their development is a well-known fact, instances of which are seen in hereditary ataxia, some late cases of Pseudo-hypertrophic Paralysis, and allied maladies. These being ascribed to an inherent defect of vital endurance on the part of the tissues concerned. This man might have had such a weakness in his blood-forming organs, never making sufficient blood either in quantity or quality, so that after he had reached manhood his blood-forming organs have gradually failed in keeping up their functional power, until at last he has developed the clinical features of Pernicious Anaemia.

It is quite conceivable in this case that primarily, blood formation was at fault, and as he got weaker the blood would be in such a delicate condition, that when there was absorption of larger quantities
than usual of the specific poison from the Gastro-Intestinal tract, which is quite likely, seeing he suffered very much from obstinate Constipation, there would be greater destruction of the delicate corpuscles in the Portal Circulation, as the symptoms showed in this case when at his worst viz.: The peculiar Lemon hue of his skin, change in the blood, condition of the urine, and the great weakness and helplessness; this destruction would completely outrun the process of blood formation, the organs not being able to meet the supply.

The effect of treatment in this case also appears to me to support the view that excessive blood destruction alone is not the entire cause of this disease. Last year, after complete failure with preparations of Iron to benefit him in any way.
The exhibition of Arsenic in the form of pill had the desired effect of improving his condition in a marked manner, no doubt by improving the blood, and blood forming organs.

I very much regret not being able to have the red blood corpuscles counted, and the percentage of Hemoglobin estimated, as well as the urine examined, when I first saw this case, as it would have made the report more complete and one would have known definitely how the Arsenic was taking effect. But it was impossible, and the only comparison I could make in regard to his blood was with a drop of my own.

Again in September, the Arsenic had the same effect, improving his general condition and tone misery way although much slower.

When seen on January 10th of this year
after he had left off the Asanie for six weeks, there must have been absorption of more poison than usual causing excessive blood destruction, which was shown by the examination of the blood and urine. The effect of treatment by the bone marrow in this case has been a decided success.

From January 10th to February 5th he had the Bone marrow infusions, but derived no benefit from them as the red corpuscles dropped from 2,000,000 to 1,730,000 per c.m. while the Hemoglobin remained at 35 per cent. The Malaria band was most marked on both occasions without any previous treatment of the urine.

From Feb. 5th to the 25th he was given 3 ounces of fresh or bone marrow in the day. No Medicine. There was an immediate improvement almost from the first day and the patient said "he felt it was doing him good."
cytophiles rose to 19,000,000 and the hemoglobin to 40 per cent. The urine did not show the urabilin band so markedly. This was interesting as the Pathologist of the Clinical Research Association wrote me to see if there was any improvement in the patient's condition generally, as well as in the blood and urine.

I consider that in such a case as this, the fresh bone marrow had a direct stimulating effect on the blood forming organs and that it could not have acted as a germicide, as the man's bowels were still constipated and there would consequently be absorption of poison from the gastro-intestinal tract. The distinct rise of 5 per cent of the hemoglobin seemed to me especially interesting, as it shows that the iron contained in the bone marrow is in the best state for assimilation to be used ultimately for the
for the formation of new red blood corpuscles.

From Feb. 23 to March 16th he was given 2 grains B. Naphthol, in pill form, three daily, in addition to the bone marrow, as I felt, being in private practice, that it was my duty to try all I could to get the man well as soon as possible. The B. Naphthol was given in the hope that it would lessen the absorption of poison, as the Urine showed on Feb. 25th that the excretion of Ethereal Sulphates was increased, the ratio being 1:95. I think the B. Naphthol might then acted in this manner, as there was a further improvement. The red corpuscles being 2,250,000 and the Hemoglobin 48 per cent.

From March 16th to April 2nd the Arsenic pill was added to the other things one thrice daily. The diet was more mixed, meat and fish occasionally. There was a still further improvement. The red corpuscles being 2,500,000 per cm.
and the Hemoglobin 48 per cent.

From April 2 to the 16th the same treatment was carried out except that he took 6 of the Arsenic pills in the day.

The red corpuscles were now 2,750,000 per cc. and the Hemoglobin 30 per cent.

That the exhibition of fresh bone marrow began the improvement in this man's health there can be no reasonable doubt, having gained 12½ pounds in weight since he first started to use it.

The B. Naphthol and Arsenic pills would also assist, and knowing that Bone Marrow and Arsenic act as stimulants of the blood forming organs, I think in this case at any rate there was primarily defective and perverted blood formation. The B. Naphthol no doubt helped to limit the putrefactive changes in the Gastro-intestinal tract, so that with the general improvement in
his health, the bowels have become quite regular, acting once a day, without any laxative medicine.

The man is still getting stronger, looking better, and has a more natural colour, and able to ordinary diet. He has gone to Cheltenham, but is to keep on with the same treatment in the hope that this improvement will be lasting.

Later on, I shall advise him to take the bone marrow one month, and the Arsenic the next month. I am quite aware in a case like this that the normal number of red blood corpuscles may never be reached, getting to a certain point and no further, owing to the inherent weakness of his blood forming organs.

I shall be quite prepared, should the bone marrow or Arsenic in turn begin to fail to do any good, to resort to Transfusion, provided
he gives his consent, which I consider would certainly be rational treatment. It will be difficult to get everything as one would like in private practice, but what I have seen of Transfusion by Dr. John Duncan and others, the operation is safe, as long as plenty of time is taken, care, watchfulness of symptoms, and perfect asepsis are employed. Failing to get blood, I should use the ordinary salt solution I drew to the point, in the hope that the transfusion would once more bring the blood forming organs into a state where the bone marrow or Arsenic would be of benefit.

Even in this case however, one is very much afraid that in the end it will follow Addison's classical description: "The disease presented in every instance the same general characters, pursued a similar course, and with scarcely a single exception was followed after a variable period by the same fatal result."
References

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71 Lancet 1881 vol. i p. 612; Brit. Med. Jour. 1890 vol. i p. 130;