

# Anaemia is not a diagnosis

## Part 2

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### Curriculum vitae

Dr D Gayle Kenoyer qualified at Kansas Medical School in 1963, did her internship and residency in the USA and from 1971 to 1974 was given a Fellowship in the Haematology Division, LA County-USC Medical Centre, and obtained her Board Certificate in 1974. She practiced as a GP in Rhodesia (now Zimbabwe) from 1964 to 1967, then started an academic career in California where she became assistant professor in 1975. In 1980 she came to the University of Natal, and is presently Acting Head of the Department of Haematology at the University of Natal Medical School. She has published numerous research articles and her major areas of interest are platelet function and development of new assays for the detection of platelet antibodies.

### Summary

*Anaemia is usually the clue to an underlying primary disease, and needs to be classified and understood. In Part 2 of this article, nine more patient studies illustrate the serious implications for patients whose symptoms only were treated and not the underlying diseases.*

### Macrocytic anaemias

Let us turn our attention to patients with macrocytic anaemias. There are several causes of macrocytic anaemias. These include

1. marked reticulocytosis associated with haemolysis
2. aplastic anaemia
3. liver disease
4. megaloblastic anaemia
5. myelofibrosis
6. myxoedema

The FBC results with a reticulocyte count will suggest the first two conditions - marked reticulocytosis and aplastic anaemia. A macrocytic anaemia characterised by large round target cells on peripheral smear, is usually due to liver disease.

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This finding is particularly helpful in identifying the 'silent' alcoholic with liver disease who gives a false history.

Patients with myelofibrosis have massive splenomegaly on physical examination and immature granulocytes, tear-drops and nucleated RBC forms and large bizarre platelets on peripheral smear. Using these features, the presence of myelofibrosis can be suspected and trephine bone marrow biopsy will establish the diagnosis.

Megaloblastic anaemia may be caused either by folate or vitamin B<sub>12</sub> deficiency. It is vital to determine which deficiency exists and the mechanism causing the deficiency. Quantitation of serum levels usually determine which deficiency exists. A Schilling test may be necessary to determine the mechanism causing the deficiency.

The first reason why it is important to differentiate between vitamin B<sub>12</sub> and folate deficiency is because vitamin B<sub>12</sub> deficiency can cause a variety of central nervous system disorders while folic acid deficiency does not. Therapeutic doses of folic acid can correct anaemia caused by B<sub>12</sub> deficiency thus masking the B<sub>12</sub> deficiency and allowing neurologic complications to develop.

### Patient 7

A 62 year-old Italian male, recently treated for macrocytic anaemia with folic acid.

Symptoms and signs: decreased vibration and position sense, spastic gait, Romberg sign+

FBC: Hgb 14,2 gm% PCV 43% MCV 94 fl

Serum Folate 7,5 ng/ml Serum B<sub>12</sub> 152 pg/ml

Schillings test: Abnormal without intrinsic factor  
Normal with intrinsic factor

This patient had been treated in Italy with folic acid for a macrocytic anaemia. Treatment was successful and his health improved enough so that he was able to join his family about 5 months ago. Over the past 2-3 months he began having trouble walking. At the time of presentation he could only get around by holding onto a chair. His physical signs are listed above and showed involvement of both the sensory and motor systems. His FBC was normal.

His serum folate level was normal but serum B<sub>12</sub> level was mildly decreased. His Schillings test was diagnostic of pernicious anaemia. With vitamin B<sub>12</sub> therapy (100 µg daily for 1 month), his neurologic

signs and symptoms improved but did not normalise completely. Had the correct diagnosis been made initially and vitamin B<sub>12</sub> therapy started, neurologic complications would not have developed.

This case illustrates why it is essential to determine which deficiency exists. Treatment of vitamin B<sub>12</sub> deficiency with 5-15 mg of folic acid daily will correct anaemia, but will not prevent development of sub-acute combined degeneration of the spinal cord or other CNS problems.

The most common causes of vitamin B<sub>12</sub> deficiency are the result of lack of intrinsic factor (produced in the stomach) and disorders affecting the small intestine causing malabsorption. Dietary deficiency of vitamin B<sub>12</sub> is very unusual except in strict vegetarians who also avoid eggs and dairy products. Therefore most patients with vitamin B<sub>12</sub> deficiency have a disorder which is not reversible and will require replacement therapy for life.

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### *Anaemia is a symptom of an underlying disorder, and not a diagnosis*

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In contrast, folic acid deficiency is frequently due to dietary lack sometimes coupled with a condition such as pregnancy, breast feeding or increased cellular turnover which increases folic acid requirement. Therefore most patients with folic acid deficiency can be treated by changing the diet to include foods rich in folate which are not overcooked so that folate is not destroyed. If these factors are not present, disease of the GI tract causing malabsorption may be the cause. Such conditions include tropical and non-tropical sprue, regional enteritis, and lymphoma of the small bowel.

#### **Patient 8**

35 year-old Caucasian male with  
1. LUQ abdominal pain x 5 years  
2. 13 kg weight loss over 6 months  
3. Macrocytic anaemia Hgb 8,8 g% PCV 28 g%  
MCV 99 fl

Diet: Normal. No abdominal surgeries.

Therapy: Folic acid.

Response: Correction of anaemia.

This patient was a Guatemalan who had lived in the United States for 3 years at the time of evaluation. He presented with vague left upper quadrant pain which had been present for five years but was becoming more severe. He had lost 13 kg during the previous 6 months. His diet was normal and included foods containing both folic acid and vitamin B<sub>12</sub>. He had had no abdominal surgeries, took no medications, and did not drink. He did not have a skin disease or haemolytic anaemia. Therapy with folic acid corrected his macrocytic anaemia.

However, the cause of his folic acid deficiency had not been established. Neither had the cause of his abdominal pain, weight loss and diarrhoea been established.

#### **Patient 8 (cont.)**

Serum folate 1,9 ng/ml (1,4-15,5) Serum B<sub>12</sub>  
151 pg/ml (220-750)

Serum Carotene 14 mg% (50-300)

Barium Meal: distal duodenum, jejunum and ileum  
- thickened and nodular

Diagnosis: Tropical sprue

Addition workup documented that the patient had both folic acid and B<sub>12</sub> deficiency. The Schilling test showed abnormal B<sub>12</sub> absorption even with intrinsic factor administration. The barium meal was diagnostic of a small bowel disorder, and biopsy showed this to be tropical sprue. This patient's megaloblastic anaemia was a clue pointing towards abnormal gastrointestinal function. Good medical care of this patient demanded diagnosis and treatment of the intestinal disorder as well as correction of anaemia with folic acid.

Occasionally the FBC findings are difficult to interpret. In patients with multiple causes for anaemia, FBC results may be obscure and not point toward a specific diagnosis.

#### **Patient 9**

32 year-old African male with

1. Pulmonary TB on 4 drug treatment

2. Severe anaemia developing in hospital

FBC: RBC 1,37 10<sup>12</sup>/l Hgb 4,0 gm% PCV 12%  
MCV 86 fl

MCH 29 Retics 1,2% - Normochromic  
normocytic

This patient was admitted to an outside hospital for treatment of pulmonary TB. He was started on Rifampin, Streptomycin, Pyrazinamide and INH.

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### *A patient is his own best control*

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His haemoglobin was 12 gm% on admission but over the ensuing three months decreased to 4 gm% despite improvement in his tuberculous infection. RBC indices indicated a normochromic normocytic anaemia.

#### **Patient 9 (cont.)**

Smear: Microcytic Hypochromic RBCs

Megaloblasts and Hypersegmented Polys

Folic Acid 1,2 ng/ml Serum Iron 48,1 mol/l

TIBC 56 mol/l

Bone marrow: Ringed Sideroblasts

Diagnosis: Megaloblastic Anaemia 2° Folic Acid  
Sideroblastic Anaemia 2° INH therapy  
without Pyridoxine

However, on peripheral smear hypochromic microcytic RBCs plus megaloblasts and hypersegmented polys were seen. These morphologic findings suggested a megaloblastic anaemia plus one of the causes of hypochromic microcytic anaemias. Laboratory workup confirmed that the patient has mega-

loblastic anaemia and sideroblastic anaemia. Since these two conditions normally cause opposite morphologic changes, the RBC size was an average of two extremes.

### Haemolytic anaemias

There are many different causes of haemolysis, both hereditary and acquired. The precise cause of haemolysis must be determined so that effective treatment may be given. This may require extensive laboratory testing. The most common hereditary haemolytic anaemias are red cell enzyme deficiencies (glucose-6-phosphate dehydrogenase or pyruvate kinase deficiency) and hereditary spherocytosis and the most common acquired haemolytic anaemias are due to immune mechanisms. If microspherocytes are present on peripheral smear, a Coomb's test is indicated. If this is negative, a test of osmotic fragility should be done to test for hereditary spherocytosis.

### *Haemolytic anaemias may be explosive in onset and rapidly fatal without adequate treatment*

Haemolytic anaemias may be explosive in onset and rapidly fatal without adequate treatment. Therefore, diagnosis, evaluation and management must be pursued vigorously. Severe rapidly progressive haemolysis may occur in persons with Mediterranean type glucose-6-phosphate dehydrogenase deficiency following ingestion of fava beans used in Middle Eastern and Greek foods. Severe progressive haemolysis may also occur in Coomb's positive haemolytic anaemias.

#### Patient 10

AIHA - Fulminant

Day 1 - evening: 'Flu'-like symptoms in 23 year-old Indian female

Day 2 - morning: Weakness, scleral icterus  
afternoon: Fever, dark urine, Hgb 8,0 gm %  
5.00 pm: Hgb 6,0 gm % Coombs +  
7.30 pm: Semicomatose; Hgb 3,5 gm %  
9.00 pm: Patient died.

Laboratory: Liver enzymes not increased  
Hepatitis studies - negative

To illustrate how fulminant a course Coomb's positive haemolytic anaemias may take, let us look at Patient no 10. This woman was completely well until one evening when she began to have some myalgias and malaise. She thought that she was coming down with 'flu' and went to bed early. The following morning she felt worse, was weak, and noticed some scleral icterus. She went to her doctor and was hospitalised about noon. The laboratory studies on admission revealed anaemia and dark urine with urobilinogen but no bilirubin. She became febrile. A repeat FBC at 5 pm showed a haemoglobin of 6 gm %. The blood bank found that

her RBCs and serum were Coomb's positive. While they tried to cross match blood for her, she became semicomatose. An additional FBC at 7.30 pm showed a further decrease of haemoglobin to 3,5 gm %. At 9 pm she died. This is a very fulminant course and its severity is unusual. However, patients with haemolysis of the severity seen in Patients 11 and 12 are not unusual.

#### Patient 11

AIHA - very severe

A 62 year-old white male with myalgias and easy fatigability. Denies drug or alcohol abuse.

Physical: Severe pallor; deep scleral icterus

Liver - edge; spleen 4 cm

Laboratory: Coombs 4+ Bilirubin Total 94 mol/l  
Direct 6,8 mol/l

	Admission	Day 1	Day 2	Day 3
PCV	11,6	10,0%	9,0%	8%
MCV	119			

Retics

Treatment: Folic Acid }  
Prednisone 60 mg } → Cardiac Arrest

This man (Patient 11) presented with symptoms of anaemia and myalgia. He had significant jaundice and hepatosplenomegaly on examination. Laboratory workup proved he had a Coomb's+ haemolytic anaemia, and prednisone therapy with folic acid supplementation was started. He had haematocrit monitoring 8-hourly for the first day and then daily. He was thought to be stable and was feeling better. However, he apparently developed a cardiac arrhythmia, arrested, and died on the fourth hospital day. Better management in an older individual at risk for ischaemic heart disease or generalised atherosclerosis would have been transfusion to a Hgb of 7-8 gm %. Patients with haemolysis should be managed like an acute GI bleeder with serial haematocrit determination 6-8 hourly for the first 24-48 hours until it is determined that the haemoglobin/PCV levels are not decreasing further or that the patient requires transfusion to a haemoglobin level high enough to prevent complications like myocardial infarction, arrhythmias or cerebrovascular insufficiency. Frequent monitoring of haemoglobin levels must continue until the haemolytic process has decreased to the degree that haemoglobin levels are stable or increasing on the medical regimen.

#### Patient 12

AIHA - severe

A 29 year-old African female with weakness, blackouts, dark urine

Physical: severe pallor Jaundice

Liver - 3 cm Spleen - 2 cm

Laboratory: Hgb 4,6 gm % PCV 15% MCV 127 sl  
Retics 23%  
Bilirubin 47 mmol/l Coomb's 4+

This African woman had very severe Coomb's positive haemolytic anaemia with jaundice and hepatosplenomegaly. Her course was not as fulminant as the two previous cases.

## Patient 12 (cont.)

### Treatment and response

	Hgb gm%	PCV %	Corrected Retics	Trans- fusion	Predni- sone	Cyclo- phospha- mide
31-1	4,6	15	7,6	—	60 mg	—
8-2	4,2	15	8,3	—	60 mg	—
12-2	5,6	19	9,2	2u	60 mg	—
14-2	7,2	23	21,7	3u	60 mg	—
21-2	6,3	20	14,0	—	80 mg	—
22-2	10,4	32	—	3u	80 mg	50 mg
25-2	8,7	27	22,4	—	80 mg	50 mg
1-3	11,2	35	31,4	3u	80 mg	50 mg
6-3	8,7	27	8,2	—	80 mg	100 mg
21-3	13,3	39	13,2	4u	80 mg	200 mg
31-3	12,0	36	23,0	—	80 mg	200 mg
28-4	13,9	44	11,8	—	40 mg	200 mg

3 months to Compensated AIHA

Treatment with folic acid and prednisone was started. However, her process was so severe that she could only maintain her haemoglobin level at about 4 gm% and in addition would lose approximately one unit of RBCs daily. Cyclophosphamide was added and the prednisone increased. It took 3 months for haemolysis to decrease in severity until she had a compensated haemolytic anaemia. Maximum RBC production was required to maintain a normal haemoglobin level of 14 gm%. Increased production is documented by the corrected reticulocyte count of 12%.

## Patient 13

A 75 year-old hypertensive Indian male on Aldomet. Symptoms: Generalised weakness and arthralgias  
Physical: Mild pallor No splenomegaly  
FBC: Hgb 8,2 gm% PCV 24% Retics 14,6%  
Coombs+ auto IgG Ab + complement

This patient has a more typical mild to moderate immune haemolytic anaemia with a moderate decrease in haemoglobin to 8,2 gm%. However, his bone marrow has increased RBC production maximally as shown by a corrected reticulocyte response of 14% in order to maintain that haemoglobin level.

## Patient 13 (cont.)

### Treatment and response

	Hgb gm%	PCV %	Corr. Retics	Predni- sone	Cyclophos- phamide
15-5	8,2	24	14,6	40 mg	—
22-5	10,2	29	10,5	40 mg	—
20-6	13,1	38	6,9	30 mg	—
25-7	14,0	41	6,9	30 mg	50 mg
2-10	12,4	37	4,0	20 mg	50 qod
19-12	13,5	42	2,3	10 mg	—

His haemolytic process came under control with prednisone alone.

However, he could not be tapered off prednisone without the haemoglobin levels decreasing. Cyclophosphamide was added and after 8 months of therapy, he went into complete remission off all medications. Other haematologists would have

recommended splenectomy when this patient relapsed as the prednisone was being tapered, rather than adding cyclophosphamide.

Another type of haemolysis is diagnosed from the presence of fragmented RBCs on peripheral smear. The most classic forms are helmet-shaped and triangular cells. RBC fragmentation syndromes are associated with abnormal aortic valves, arterial grafts, vasculitis, malignant hypertension and disseminated intravascular coagulation. The roughened small vessel walls in vasculitis causes the fragmentation. When secondary fibrinolysis does not occur in patients with DIC, fibrin strands are

*There are many different causes of hemolysis, which need to be determined in order to give effective treatment*

laid down in vessels. These fibrin strands fragment RBCs. Ischaemia progressing to gangrene may occur in skin particularly over fingers and toes. However, the organ at greatest risk for ischaemic damage in DIC is the kidney. Without adequate lysis, these patients may develop glomerular thrombi leading to acute renal cortical necrosis and irreversible renal failure. Patients in the usual clinical settings associated with DIC require prompt evaluation and careful monitoring of renal output. If detected early, formation of glomerular thrombi may be prevented by heparinisation.

## Patient 14

A 21 year-old black female, term pregnancy  
Problem: vaginal bleeding at onset of labour  
Spontaneous delivery  
Laboratory: Hgb 8,0 gm% PCV 24%  
Platelets 32x10<sup>9</sup>/l  
2+ RBC fragmentation  
3rd Hospital Day: Oliguria. Urea 33 mmol/l  
Creatinine 700 μ

This obstetrical patient was transferred when she developed vaginal bleeding at onset of labour.

*Most patients with Vit B<sub>12</sub> deficiency will require replacement therapy for life*

However, she delivered very shortly after admission. She was normotensive. Her admitting FBC showed moderately severe thrombocytopenia and 2+ RBC fragmentation. These findings were not noted by the admitting doctors, and no additional evaluation or treatment was initiated. Three days later she was found to be severely oliguric with acute renal failure. Early diagnosis and treatment

of her DIC complicated by inadequate secondary lysis, could have prevented renal failure.

### Patient 15

A 51 year-old black female with rheumatic heart disease with Starr-Edwards Prosthetic Aortic Valve.

Symptoms: Weakness, dyspnoea, pallor x 3 weeks

Laboratory: Hgb 3,4 gm% PCV 11% MCV 74 fl

MCH 24

Morphology - fragmented RBCs, hypochromia

Bilirubin 46,2  $\mu\text{l}$  Serum Iron 4,1  $\mu\text{l}$

TIBC 81,6  $\mu\text{l}$

Diagnosis: RBC Fragmentation 2° abnormal seating of ball valve

Iron deficiency 2° RBC fragmentation

The last case illustrates another cause of RBC fragmentation. This woman had severe rheumatic heart disease requiring aortic valve replacement. She was anticoagulated with warfarin and followed up monthly in cardiac clinic. Over the course of one month she became severely anaemic with hypochromic microcytic RBCs, a low serum iron and elevated iron binding capacity. However, she was not over anticoagulated and GI blood loss was not documented. Her peripheral smear showed a severe RBC fragmentation syndrome. Investigation showed that this was due to abnormal seating of the ball valve aortic prosthesis which ultimately required surgical replacement. With RBC fragmentation, haemoglobin is released into plasma and lost via the kidneys leading to iron deficiency. The clue to her valvular dysfunction was the RBC fragmentation.

### Summary:

- A patient is his own best control.
- The diagnosis of iron deficiency anaemia can be established by documenting a good response to a therapeutic trial with ferrous sulphate. A follow-up FBC to document response is necessary.
- In adults with iron deficiency anaemia, the cause and site of blood loss must be established.
- Hypochromic microcytic anaemias unresponsive to iron therapy after one month require further investigations:
  - a) to determine the cause so that appropriate treatment can be given;
  - b) to make possible genetic counselling if this turns out to be a hereditary disorder.
- The specific deficiency and the mechanism causing the deficiency must be established for megaloblastic anaemias. Vitamin B<sub>12</sub> deficiency must not be treated with therapeutic doses of folic acid, to prevent neurologic complications.
- Some auto-immune and other haemolytic anaemias may follow an explosive fulminant course. These patients require frequent haemoglobin determinations for at least the first 1-2 days.
- RBC fragmentation is an indication of inadequate lysis in DIC syndromes and the severity of vascular damage in the vasculitides.
- Anaemia is a **symptom** of an underlying disorder and **not a diagnosis**.




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