Anaemia is not a diagnosis

Part 1

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Summary

Anaemia can be the result of an underlying primary disease and needs to be classified and understood. By discussing a few patient studies this becomes clear. Systematic guidelines are given as to how to define and classify anaemia, as well as the treatment, and the medical implications and dangers are highlighted.

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.

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Many patients present with symptoms of generalised malaise, easy fatigability and dyspnoea on exertion. These symptoms are found to be secondary to anaemia. With correction of the anaemia, the patient becomes asymptomatic. This process is often so dramatic that we doctors begin to think of anaemia as a diagnosis. However, anaemia is **not** a diagnosis but a **symptom** of an **underlying disease.** The type of anaemia can act as a clue to the diagnosis of the primary disease. In order to be able to use anaemia as an important clue, we must classify anaemia into groups according to the pathophysiologic mechanisms causing the anaemia. Criteria for the diagnosis of anaemia, microcytosis and macrocytosis, are listed for use with the following case discussions. A diagram subdividing anaemias into groups according to the ability of the bone marrow to increase red blood cell (RBC) production (kinetics) and according to RBC morphology is also included.

How do we classify anaemias?

We must first determine whether the cause of anaemia is due to blood loss/haemolysis or due to bone marrow dysfunction. When the bone marrow is normal, it will respond to anaemia by an increase in RBC production. The reticulocyte count which has been corrected for anaemia will be $> 2\%$ when there is adequate bone marrow response to anaemia. The formula for correction of the reticulocyte count is:

$$\text{Corrected reticulocyte count} = \frac{\text{patient's value (PCV)}}{\text{normal value (PCV)}} \times \text{uncorrected reticulocyte count}$$

The parameter used may be RBC count or haemoglobin level or haematocrit.

In persons with normal RBC production, a 1% reticulocyte count represents the production of 50 000 new RBCs/μl of blood per day. This is calculated by multiplying 1% by the normal RBC count of 5 000 000/μl. When using the corrected reticulocyte count for an anaemic individual, a 3% reticulocyte

count indicates a three-fold increase in RBC production while a 0,5% reticulocyte count indicated a 50% decrease in RBC production. In Table 1, anaemias are subdivided into two groups depending on whether the corrected reticulocyte count is > 2% or < 2%. Thus they are subdivided kinetically, depending on whether or not the bone marrow is capable of increasing RBC production. (Table 1)

The anaemias are again subdivided morphologically on the basis of the size of the RBCs and their haemoglobin content. If the MCV is <80, the patient has a microcytic anaemia. If the MCV is >100, the patient has a macrocytic anaemia. If the RBCs have an MCV >80 <100, the patient has a normocytic anaemia. Using both kinetic and morphologic information, the flow sheet in Table 1 divides anaemias into 6 groups. Pathophysiologic mechanisms are indicated for the various groups.

The cause of anaemia needs to be established while it is still treatable

Anaemias on the left of the flow sheet are due to blood loss, haemolysis or splenic sequestration. Those on the right are due to inadequate bone marrow response either due to bone marrow destruction or replacement, the lack of erythropoietin or other chronic illnesses, or the lack of something required for RBC production like iron or folic acid or vitamin B_{12}. Specific causes of the anaemias in each group have been listed as well as laboratory tests which are helpful in making a specific diagnosis.

Definition of anaemia in adults

	Male	Female
RBC count	< 4,6	< 4,2
Haemoglobin	< 14 gm%	< 12 gm%
Haematocrit	< 42%	< 37%
Microcytosis	≤ 80	
Macrocytosis	≥ 100	

There is very little variation of haemoglobin and RBC count from week to week in normal individuals. Therefore a person should be his own best control. This is better than referral to a range of values determined from many normal people.

Patient 1.

A 38-year-old man, small business owner
Complaint: Vague upper abdominal pain
Physical: Mild epigastric discomfort on palpation
Barium Meal: Normal
Initial FBC: Hgb 16,5 PCV 50 MCV 91
FBC - 6 weeks later: Hgb 14,5 PCV 44 MCV 87
Discharge Diagnosis: Psychosomatic gastro-intestinal (GI) disorder

This patient is a middle-aged business man who has been under considerable pressure lately. He consulted his doctor on several occasions for abdominal discomfort. His symptoms were vague and his physical examination was unremarkable. However, because of continued complaints, he was admitted to hospital where a partial GI workup was done and was negative. The discharge diagnosis was psychophysiologic GI reaction.

By definition this patient is **not** anaemic because his discharge FBC shows his haemoglobin is 14,5 gm% and haematocrit 44%. However, the patient had a significant decrease in haemoglobin and haematocrit values and the RBC size began to increase. Therefore, this patient has good evidence of significant blood loss, even though he was not yet anaemic by our definitions. An incorrect diagnosis had been made on this patient. Interpretation of the laboratory data as indicating blood loss is strengthened when using the patient's own baseline FBC. Thus a person is his own best control.

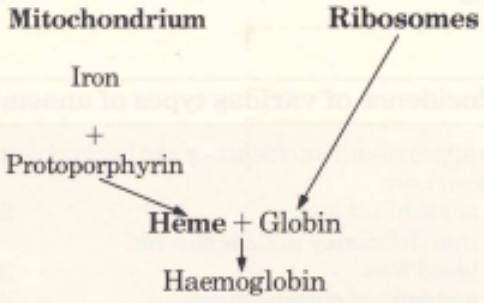
Incidence of various types of anaemia

The approximate incidence of the various causes of anaemia are

- acute blood loss	- 25%
- iron deficiency and/or chronic blood loss	- 25%
- anaemia of chronic disease	- 25%
- megaloblastic anaemia	- 8%
- haemolysis	- 8%
- bone marrow damage or renal disease	- 9%

Hypochromic, microcytic anaemias

Haemoglobin is composed of iron plus a protoporphyrin ring which combines to form heme. Four heme molecules are coupled to two alpha and two beta globin chains to form one molecule of adult A haemoglobin. Any condition which inhibits haemoglobin production causes a hypochromic microcytic anaemia.



Causes include:

1. iron deficiency anaemia
2. anaemia of chronic disease (relative iron deficiency)
3. thalassaemia (globin chain production abnormality)
4. sideroblastic anaemias (protoporphyrin production abnormality).

Iron deficiency anaemia

By far the most common cause of hypochromic microcytic anaemia is iron deficiency. The expense of laboratory tests to quantitate serum iron, TIBC and ferritin is usually unnecessary. The diagnosis can be established by use of a therapeutic trial administering a ferrous salt.

Patient 2.

A 60-year-old Caucasian male painter

Symptoms: generalised malaise for 6-8 months
Consultation with GP three times – nothing wrong

Signs: Pallor

FBC: Hgb 7,9 gm % PCV 21 % MCV 73
MCH 23 Retics 0,4 %

Treatment: Ferrous sulphate tab i tds

FBC – 1 month later: Hgb 11,4 gm % PCV 37 %
MCV 79 MCH 24

This man had not felt well for 6 to 8 months. He consulted his doctor on three occasions, only to be told there was nothing wrong.

Finally, pallor was noted and a full blood count (FBC) drawn which showed a severe hypochromic microcytic anaemia. He was started on ferrous sulphate and responded well increasing his haemoglobin and haematocrit over the next month with a corresponding increase in RBC size. The diagnosis of iron deficiency anaemia was established by the therapeutic trial.

Patient 2 (cont.)

Serum iron 5,7 (9-32) TIBC 79 (44-79)
Barium Meal: gastric ulcer

However, the cause of the chronic blood loss leading to iron deficiency had not been established. Endoscopy revealed a malignant appearing gastric ulcer. Biopsy proved this was adenocarcinoma. At laparotomy, the cancer had spread and was not resectable. Six to eight months earlier, it might have been. The most important thing for this man would have been to establish the cause of his anaemia – gastric CA – while it was resectable and curable. Correction of anaemia, while overlooking carcinoma, is not acceptable to the patient or his family.

During a therapeutic trial a maximum reticulocyte response usually occurs within 6 to 8 days after starting therapy and haemoglobin levels should increase about 1 gm/d/ per week. If this does not occur, either the person is not taking his medication, or is losing blood at a rate greater than the rate of production or the wrong diagnosis had been made. Additional valuation may then be required.

The most common cause of hypochromic microcytic anaemia is iron deficiency – and expensive laboratory tests are not necessary

Patient 3.

An Indian female with Glanzmann's thrombasthenia

Complaint: Menorrhagia and epistaxis

FBC (10-6): Hgb 9,6 PCV 28 MCV 63 MCH 21
Retics 2,1

(3-8): Hgb 7,9 PCV 25 MCV 56 MCH 17,5
Retics 6,2

Treatment: Ferrous sulphate tab i tds

This patient has a hereditary platelet disorder causing severe menorrhagia and occasional episodes of severe epistaxis. Ferrous sulphate was started. However, the haemoglobin did not increase.

Patient 3 (cont.)

Treatment: Imferon 52 m/ IV Infusion+ 2u P-RBCs

	Hgb	PCV	MCV	MCH	Retics
FBC (31-3) :	4,0	15	59	16	1,7
(14-4) :	9,6	32	85	25	9,4
(20-4) :	10,9	35	84	26	4,5

In this instance, the haemoglobin did not increase with ferrous sulphate therapy due to blood loss with an iron requirement greater than the iron absorbed. When a total dose infusion of imferon was given, there was enough iron to allow rapid RBC production with a high reticulocyte response documented at 2 weeks and a further increase in haemoglobin occurring later.

It is important to do serial studies at reasonable intervals to document response. FBCs at 1 to 2 weeks after starting iron will document beginning response as shown by the reticulocyte response and an FBC at four weeks will document increasing

haemoglobin levels and normalisation of the MCV and MCH.

Thalassaemia

We have had several patients with hypochromic microcytic anaemias referred for evaluation when there was no improvement after 6-8 months (not weeks) of iron therapy. This is a much longer therapeutic trial than is required to determine unresponsiveness to iron. In addition it can be detrimental. One of the other causes of hypochromic microcytic anaemias is thalassaemia, frequently found in the Indian population. These patients often have high iron levels. These levels will be further increased by prolonged iron therapy and may eventually lead to organ damage.

Thalassaemia:

	Normal	♂-α-Thal Carrier	β-Thal Trait	β-Thal-♂ Homozygous
RBC	4,6–6,2	5,93	4,39	1,66
Hgb♂	14–18	13,7	9,8	3,9
PCV♂	45–52	41	32	12
MCV	82–98	70	72	72
MCH	28–32	23	22	24
A_2 Hgb	3,5%	2,7	6,1	4,0
F Hgb	1,0%	0,9	4,0	2,5
Spleen		0	4 cm	12 cm
Ferritin	12–150	75	156	8400

A thalassemia carrier may have no clinical problem, but a diagnosis is necessary for genetic counselling

As you can see from the above, the severity of the anaemia with thalassaemia depends on whether the person has a heterozygous or homozygous disorder. However, even in non-anaemic carriers hypochromic microcytic indices are usually found.

Patient 4.

Thalassaemia:

	Patient, RG	Father	Mother
RBC	1,66	6,86	4,5
Hgb	3,9	14,0	11,8
PCV	12	43	36
MCV	72	62	73
A_2 Hgb	4,0	5,8	5,7
F Hgb	2,5	1,7	0,63

Although the thalassaemia carrier has no clinical problem, it is important to establish a diagnosis so that genetic counselling may be available. This may perhaps prevent the marriage of two heterozygous thalassaemia individuals and the birth of a child with homozygous thalassaemia who will have severe medical problems for life. This happened to the couple illustrated here. Neither parent was aware that he/she had thalassaemia. Their child (Patient 4) has required transfusions from early infancy.

Sideroblastic anaemias

Patient 5.

A 21-year-old African male
Complaint: Weakness and malaise, left upper quadrant (LUQ) pain
Physical: Pallor, 3 FB hepatosplenomegaly
FBC: RBC 4,58 Hgb 7,5 PCV 25 MCV 55 MCH 16 Retics 0,8%
Therapy: Ferrous sulphate tab ii daily x 2 months
IM injections (Imferon) monthly x 6 months

In normal individuals there is very little variation of haemoglobin and RBC count from week to week

Patient 5 is a person with hypochromic microcytic anaemia from another cause. This is a 21-year-old African male who was well until he was 20 when he developed weakness, malaise and left upper quadrant (LUQ) pain. On examination, he was pale and had hepatosplenomegaly. FBC documented a severe hypochromic microcytic anaemia. He was started on ferrous sulphate but did not respond and was then given IM injections which may have been Imferon, for 6 months without response. He was finally referred, after 9 months, for additional evaluation.

Patient 5 (cont.)

Serum iron 40 TIBC 37,0
Serum Ferritin > 1000
Hgb Electrophoresis AA
A_2 Hgb 2,4% Fetal Hgb = 0,8%
Bone Marrow: Ringed Sideroblasts

Additional studies showed a marked increased in body iron stores and no evidence of thalassaemia as shown by normal haemoglobin electrophoresis. Bone marrow examination proved that he had a sideroblastic anaemia which was partially responsive to pyridoxine. An etiology was not determined.

Table 1: *Approach to Anaemia*

A. Establish presence of anaemia

Data base = FBC

B. Establish category of anaemia

1. Kinetics

Effective production = RBC turnover

Total RBC production = plasma iron turnover

Pathophysiologic mechanisms

Increased production = Increased peripheral destruction or loss

Acute blood loss

Haemolytic Anaemias

RBC indices

2. RBC morphology

Differential diagnosis:

Hypochronic **Microcytic**

Macrocytic

Peripheral smear for specific RBC abnormalities

Reticulocytosis

C. Establish specific disorder

1. Special and specific tests

Targeting

1. Thalassaemia (Ineffective RBC production as well)

1. A2, F Hgb by Hgb electrophoresis

Spherocytes

1. Hereditary Spherocytosis
2. Antibody mediated haemolysis

RBC Manual, pages 42-44

1. Auto-hemolysis
2. Osmotic fragility
3. Coomb's test

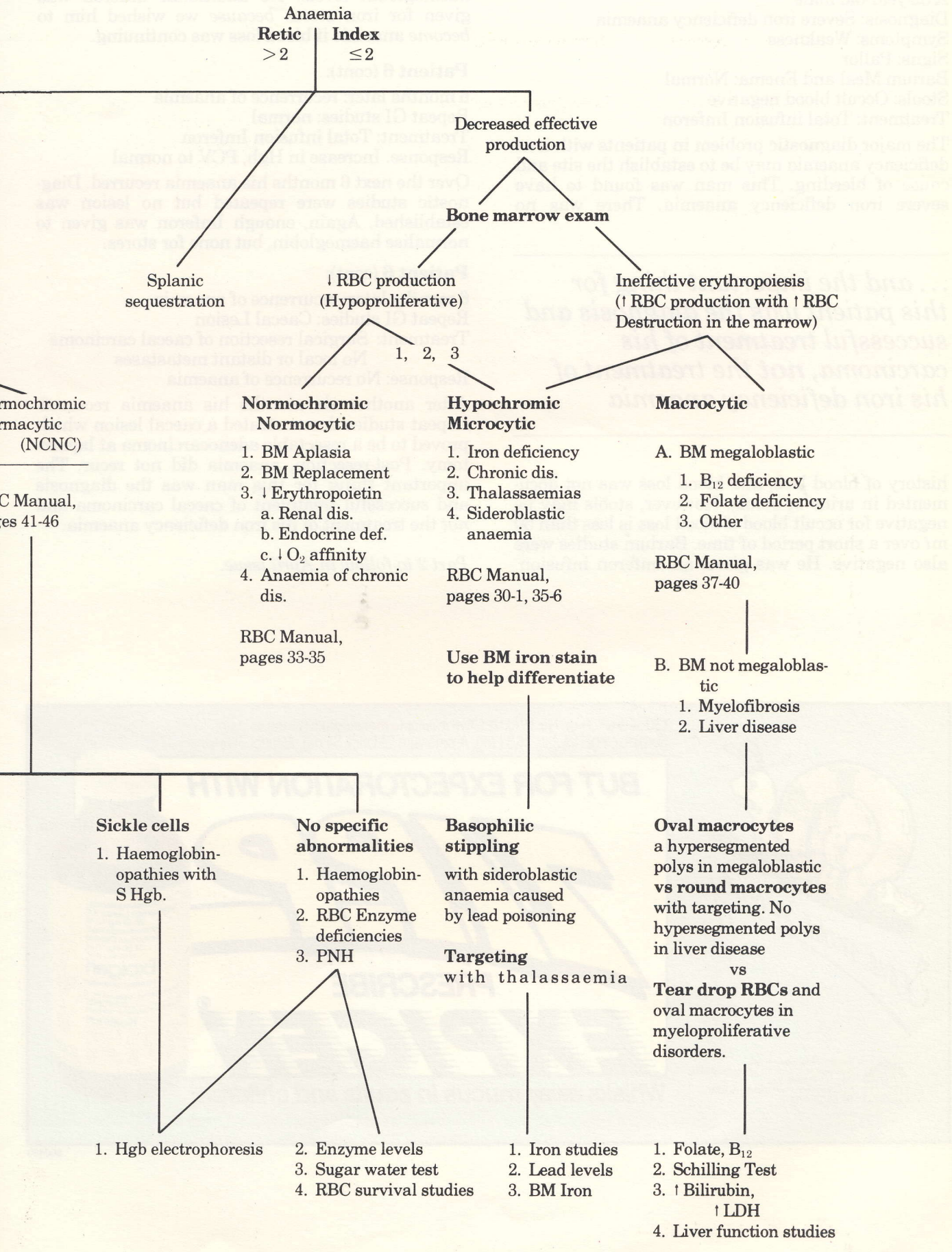
Fragmentation

1. DIC
2. Abnormal heart valves
3. Vasculitis
4. TTP
5. Sickle cell

pages 41-2

1. Clotting screen

D. G. Kenoyer, 1983


Anaemia
Retic Index
>2 ≤2
Decreased effective production
Bone marrow exam
Splanic sequestration
↓ RBC production (Hypoproliferative)
Ineffective erythropoiesis (↑ RBC production with ↑ RBC Destruction in the marrow)
1, 2, 3
rmochromic
rmacytic
(NCNC)
C Manual,
ges 41-46
Normochromic Normocytic
1. BM Aplasia
2. BM Replacement
3. ↓ Erythropoietin
a. Renal dis.
b. Endocrine def.
c. ↓ O_2 affinity
4. Anaemia of chronic dis.
RBC Manual, pages 33-35
Hypochromic Microcytic
1. Iron deficiency
2. Chronic dis.
3. Thalassaemias
4. Sideroblastic anaemia
RBC Manual, pages 30-1, 35-6
Use BM iron stain to help differentiate
Macrocytic
A. BM megaloblastic
1. B_{12} deficiency
2. Folate deficiency
3. Other
RBC Manual, pages 37-40
B. BM not megaloblastic
1. Myelofibrosis
2. Liver disease
Sickle cells
1. Haemoglobinopathies with S Hgb.
No specific abnormalities
1. Haemoglobinopathies
2. RBC Enzyme deficiencies
3. PNH
Basophilic stippling
with sideroblastic anaemia caused by lead poisoning
Targeting
with thalassaemia
Oval macrocytes
a hypersegmented polys in megaloblastic
vs round macrocytes
with targeting. No hypersegmented polys in liver disease
vs
Tear drop RBCs and oval macrocytes in myeloproliferative disorders.
1. Hgb electrophoresis
2. Enzyme levels
3. Sugar water test
4. RBC survival studies
1. Iron studies
2. Lead levels
3. BM Iron
1. Folate, B_{12}
2. Schilling Test
3. ↑ Bilirubin, ↑ LDH
4. Liver function studies

Patient 6.

A 52-year-old male
Diagnosis: Severe iron deficiency anaemia
Symptoms: Weakness
Signs: Pallor
Barium Meal and Enema: Normal
Stools: Occult blood negative
Treatment: Total infusion Imferon

The major diagnostic problem in patients with iron deficiency anaemia may be to establish the site and cause of bleeding. This man was found to have severe iron deficiency anaemia. There was no history of blood loss, and blood loss was not documented in urine or stools. However, stools may be negative for occult blood if blood loss is less than 50 m/ over a short period of time. Barium studies were also negative. He was given an Imferon infusion, giving enough iron to allow him to normalise his haemoglobin levels. No additional Imferon was given for iron stores *because* we wished him to *become* anaemic if blood loss was continuing.

*... and the important thing for this patient was the diagnosis and successful treatment of his carcinoma, **not** the treatment of his iron deficiency anaemia*

Patient 6 (cont):

6 months later: recurrence of anaemia
Repeat GI studies: normal
Treatment: Total infusion Imferon
Response: Increase in Hgb, PCV to normal

Over the next 6 months his anaemia recurred. Diagnostic studies were repeated but no lesion was established. Again, enough Imferon was given to normalise haemoglobin, but none for stores.

Patient 6 (cont):

6 months later: recurrence of anaemia
Repeat GI studies: Caecal Lesion
Treatment: Surgical resection of caecal carcinoma
No local or distant metastases
Response: No recurrence of anaemia

After another six months his anaemia recurred. Repeat studies demonstrated a caecal lesion which proved to be a resectable adenocarcinoma at laparotomy. Post-resection, anaemia did not recur. The important thing for this man was the diagnosis and successful treatment of caecal carcinoma and *not* the treatment of his iron deficiency anaemia.

Part 2 to follow in April issue.