د.نادر ابو الفتوح
أستاذ الباطنة بالمنصورة

Short Notes :

In

Blood

Internal medicine

5th year medical students

Mansoura University

Anaemias

Conditions in which the Hb conc. is below 12.5 gm% in males or below 12 gm% in females. Usually the count and/or the quality of the circulating RBCs is below normal.

Classification : according to the aetiology :

A) Dyshaemopoietic anaemias : the production of RBCs by the bone marrow is defective :

1. deficiency of factors necessary for the normal erythropoiesis :
   - **Iron** → iron deficiency anaemia.
   - **B12** and **folic** → megaloblastic anaemias.
   - **Vit. C** and **vit. B6** deficiency and anaemia of **protein** malnutrition.
2. deficient utilization of these factors by the bone marrow as in :
   - Anaemia of infection.
   - Anaemia of malignancy.
   - Anaemia of collagen diseases.
   - Anaemia of liver diseases.
   - Anaemia of hypothyroidism and hypopitutarism.
   - Anaemia of chronic renal failure.
3. inadequate number of the cell precursors in the bone marrow (marrow damage) :
   - hypoplastic or aplastic anaemias.
   - Leucoerythroblastic anaemias (or myelophthisic anaemia).

B) Excessive RBCs destruction = Haemolytic anaemias.

C) Blood loss : post haemorrhagical anaemia. (similar in every aspect to iron deficiency anaemia and discussed with it).

• **According to the haematological findings** (peripheral blood picture) anaemias are also classified into :

1- **Microcytic anaemia** : with RBCs less than normal in diameter and volume : seen in iron deficiency anaemia.
2- **Macrocytic anaemia** : with RBCs more than normal in diameter, characteristic of B12 and folic acid deficiency (megaloblastic anaemias) but it occurs with any brisk bone marrow reaction.
3- **Hypochromic anaemias** : with colour index below 0.9 and MCHC below 32%. Same causes as microcytic anaemias.

Symptoms and signs of anaemia (in general) :

1- **Resp. symptoms** : dyspnea and rapid breathing.
2- **Cardiovascular** :

Palpitations, dyspnea, angina and intermittent claudications or more commonly easy fatigability.

There are : pallor, tachycardia, increased arterial neck pulsations, increased pulse volume (rarely water hammer), capillary pulsations and other manifestations of hyperkinetic circulation.

There may be functional mid-systolic ejection murmurs over the pulmonary and aortic areas and very rarely even diastolic murmurs over the pulmonary, aortic or mitral areas (increased flow + diminished blood viscosity).

Both heart sounds may be accentuated and cardiac size may increase. Later on, C.H.F. may result (more in presence of associated heart disease). Oedema may occur.

3- **General symptoms** : headache, blurring, of vision, increased sensitivity to cold and later irritability.

- **Causes of pallor without anaemias** : (e.g.: in the face)
  1- Vasoconstriction as low cardiac output states (e.g.: valve lesions esp. aortic), and shock.
  2- Oedema stretching the skin as in nephrotic syndrome and myxoedema (here pallor is more than can be explained by the degree of the anaemia).
  3- Prolonged indoor life e.g.: in jail.
  4- Racial : as in Chinese and Japanese.

Iron deficiency anaemia

Causes of iron deficiency anaemia :

1) **Nutritional** : primary in :
   - females at puberty (chlorosis) (due to anorexia + menstruation + increased demands).
   - Middle aged woman (due to anorexia + menses + pregnancy and lactation).

   With a factor of deficient intake, this is called chronic nutritional hypochromic anaemia. Nutritional factors alone are not sufficient to cause iron deficiency anaemia in normal adult males.

2) Defective **absorption** of iron in :
   - Achlorohydria.
   - Malabsorption syndromes.

Iron may be given :

- **I.V. :** as saccharated iron oxide (ferronascin) or colloidal iron (colliron), 20 mg/mL, 5 mL are given every 2 – 3 days.
- **I.M. :** as iron dextran complex (imferon), 5 mL amp. containing 250 mg. of iron.

N.B.:

1- Treatment should be continued for at least 2 – 3 months after restoration of the Hb level to normal.
2- Bl. transfusion is indicated if the Hb level is below 5 gm% (40%)
3- Failure of response to iron therapy in iron deficiency :
   a. Failure to take the tablets (give parenteral iron).
   b. Wrong diagnosis (not every hypochromic anaemia is due to iron deficiency).
   c. Impairment of absorption (give parenteral iron).
   d. Persistent hge of ankylostomiasis (most important cause; give causal treatment).

Megaloblastic anaemias

Anaemia with megaloblastic bone marrow due to vit. B12 deficiency, folic acid deficiency or very rarely vit. C deficiency.

AE. & Classification :

1) Diminished intake = nutritional megaloblastic anaemia :
   1. Tropical : malnutrition + destruction of the vitamins by prolonged cooking + poor absorption due to sprue or intestinal infestations + increased requirements due to repeated pregnancies; chronic blood loss and malaria.
   2. Non-tropical : as in vegetarians.

2) Diminished absorption :
   1. Low or no intrinsic factor (vit. B12 deficiency) as in : Addisonian pernicious anaemia, following gastrectomy (patients with gastric carcinoma will not live long enough to exhaust the stores of vit. B12 and develop anaemia).
   2. Malabsoption syndrome which usually cause folic acid deficiency. Vit. B12 deficiency will result if the disease involves the ileum as in regional enteritis and T.B.
   3. Competition for vit. B12 by parasites e.g.: Diphyllobothrium latum (in Finland not in Egypt).

3) Defective utilization :
   - With folic acid antagonists e.g.: methotrexate.
   - With anticonvulsants e.g.: phenytoin and primidone.
   - With antimalarials e.g.: pyrimethamine.

Addisonian pernicious anaemia

Pathogenesis :

deficiency of the intrinsic factor of gastric juice resulting from gastric atrophy probably genetically determined or the result of autoimmune disease.

Incidence : age 40 – 70 years, both sexes, may be positive family history. Rare in colored races, more in Scandinavia and blond persons. Very few cases are recorded in Egypt.

C/P :

1- Symptoms and signs of anaemia.
2- May be S.C.D (pyramidal tract, post. Column & peripheral nerve affection). [refer to neurology for more details]

Blood picture :

1- Macrocytic anaemia with colour index above 1 with anisocytosis (RBCs of different size) and poikilocytosis (RBCs of different shapes). In severe cases megaloblasts may be seen.
2- Polymorph-nuclear leucopenia with relative lymphocytosis + shift to the right.
3- Thrombocytopenia.
4- Evidence of increased haemolysis e.g.: increased indirect reacting bilirubin.
5- Vit. B12 serum level is low (less than 80 uug/mL or even zero). Also vit. B12 content of the tissues and urine is low.

Bone marrow picture :

Megaloblastic hyperplasia with ineffective erythropoiesis and increased haemolysis of the immature cells.

Functional test meal :

Histamine fast achlorohydria and achylia gastrica.

Vit. B12 absorption tests :

Impaired absorption, storage and urinary excretion of orally administered dose of radioactive B12.

Treatment :

Vit. B12 parenterally (I.M.) in a dose of 1000 ug every week for 6 weeks and then 100 ug every week for 6 weeks and then 100 ug every 2 weeks forever.

Oral vit. B12 may be parenterally absorped if :

- given with intrinsic factor preparations as desiccated stomach or ;
- if given in big doses.

Anaemias due to **Folic acid deficiency** are characterized by :

- Absent neurological manifestations.
- No histamine fast achlorhydria and normal vit. B12 absorption tests.
- Impaired folic acid absorption tests and low serum folate.
- They respond to folic acid not vit B12.

Otherwise blood picture and bone marrow are the same.

They are treated by :

Folic acid orally, I.M., or folinic acid orally + the general measures + deal with the cause e.g.: malabsorption.

Anaemia of vit. C deficiency : may be:

1- Normocytic normochromic = defective bone marrow utilization.
2- Microcytic hypochromic = repeated hges (in scurvy).
3- Megaloblastic = very rare in infants.

Anaemia of protein malnutrition; as in Kwashiorkor.

Anaemia of **infection, rheumatoid arthritis** and **collagen diseases** :

Usually normocytic but may be hypochromic. There is hypoferraemia i.e. low serum iron + low serum TIBG. Refractory to treatment unless the infection (or the disease) is controlled. Of similar nature is; anaemia of malignancy.

Anaemia of **endocrine deficiencies** :

1- **Hypopitutarism** : hypochromic macrocytic or normocytic anaemia. Rarely hypoplastic anaemia may be present.
2- **Myxoedema** : gives hypochromic or normochromic macrocytic anaemia. Rarely pernicious anaemia may be associated.
3- **Addison's disease** : normocytic normochromic.

Anaemia of **chronic renal failure** :

Due to deficiency of nephrons = less production of erythropoietin = normocytic normochromic anaemia. Hb% fluctuates with the fluctuations of the renal function.

Hypoplastic or aplastic anaemias :

= anaemia resulting from partial or complete loss of the precursor cells of erythrocytes, leucocytes and platelets in the bone marrow. Very rarely the erythroblastic tissue is only affected.

Types :

A) **Primary** : no cause, may represent in inborn errors of metabolism. Familial cases are recorded. Some cases are associated with thymic tumors or myasthenia gravis. It may rarely precede leukemia.

B) **Secondary** or asymptomatic : to :

i. Physical agents, e.g.: radioactive materials.
ii. Poisoning by : heavy metals (gold, mercury, lead, arsenic,.... etc.), benzol derivatives (benzol) and gases (as; CO & nitric oxide).
iii. Drugs : as cytotoxic drugs, chloramphenicol, phenyl butazones, sulphonamides, tolbutamide... etc. Any drug which is a potential bone marrow toxin.
iv. Infections : as military T.B.
v. Terminally in : renal failure, leukemias, malignancies and myelofibrosis.

C/P :

The **1ry** form affects both sexes and usually before the age of 35. it may run an acute, sub-acute or chronic course. The symptoms are those of :

- Anaemia.
- Leucopnia.
- Thrombocytopenia.

Blood picture :

1- normochromic normocytic anaemia with reticulocytes 0 – 1%.
2- Leucopenia with granulocytopenia and relative lymphocytosis.
3- Thrombocytopenia.

Bone marrow :

Hypocellular or acellular. May be haemosiderosis. The peripheral picture is called pancytopenia.

Treatment :

1- Stop all drugs used by the patient (except those strictly needed).
2- Give blood transfusion of packed red cells as often as necessary.
3- Give crystalline penicilline one million 6 hourly (prophylactic).
4- Corticosteroids e.g.: prednisolone 60 mg daily for 3 weeks are given + anabolics may also be given.
5- Bone marrow transplantation may be tried if possible.

Leucoerythroblastic anaemias

Anaemia due to lack of space in the bone marrow due to encroachment on (or replacement of) the normal bone marrow tissue by an abnormal tissue.

The bone marrow in most cases is hypercellular; seen in :

a. Leukemias.
b. Lymphomas.
c. Multiple myelomatosis.
d. Bone marrow metastases.

There is pancytopenia with appearance of normoblasts in the circulation.

Haemolytic anaemias

= anaemias resulting from excessive RBCs destruction. This may be due to :

1) Intrinsic red cell defect **(corpuscular causes) :**
   1- Defect in red cell stroma and metabolism :
      i. Congenital spherocytosis.
      ii. Congenital elliptocytosis (ovalocytosis).
      iii. Paroxysmal nocturnal haemoglobinuria.
   2- Defect in heamoglobin (haemoglobinopathies) :
      i. Thalassaemia.
      ii. Sickle cell disease.
      iii. Other types.

2) Extrinsic mechanisms **(extra-corpuscular causes) :**
   1- Infections : *malaria* and black water fever, septicaemias, puerperal sepsis and *Cl. wechii* infections.
   2- Drugs : e.g.: sulpha, methyl dopa, phenacetin and rarely penicillin.
   3- Chemical poisons as lead, arsine gas and snake venoms.
   4- Rh and ABO incompatibility (iso-antibodies).
   5- Paroxysmal cold haemoglobinuria : with bilharziasis, viral pneumonia and idiopathic.
   6- Auto-immune haemolytic anaemia (auto-antibodies) :
      i. Idiopathic (of Lederer).
      ii. Symptomatic : as with lymphomas, lymphatic leukemia, myelomatosis and S.L.E.

3) Combined **intrinsic** and **extrinsic** factors :
   This includes a group of haemolytic anaemia which is due to congenital absence of certain intracellular enzymes necessary for normal RBCs metabolism. The most important is glucose-6-phosphate dehydrogenase deficiency (G6P.D. deficiency). The following conditions are due to G-6-P.D. deficiency :
   1. Drug induced haemolytic anaemia esp. : to primaquine and pamaquine.
   2. Favism.
   3. Baghdad spring anaemia.
   4. Congenital non-spherocytic haemolytic anaemia.

Characteristics of haemolytic anaemia :

1- Associated with evidence of active bone marrow esp. reticulocytosis (up to 50%) but also anisocytosis, poikilocytosis, target cells and rarely normoblasts. Clinically there is tender sternum. There is normoblastic hyperplasia of the bone marrow in the sternal puncture.

2- Associated with increased bile pigment output : hyperbilirubinaemia of the unconjugated bilirubin. No bilirubinuria (acholuric). Elevated urobilinogen in urine and stercobilinogen in stool. May be gall stones. Resistant leg ulcers may occur.

3- With intravascular haemolysis, haemoglobinuria may result.

Cong. (Hereditary) Spherocytosis

Here the red cells is smaller and spheroid. M.C.D is less that 6.3 micron with increased osmotic and mechanical fragility and excessive destruction.

Spherocytosis is " defective or absent Na^+ pump mechanism with leakage of Na^+ and water to the inside of the cell resulting in characteristics morphological change and premature destruction by the spleen.

1) May be familial.
2) **Symptoms** : start in childhood and adolescence. They are :
   - Symptoms and signs of anaemia.
   - Jaundice : it is recurrent. Sudden attacks of excessive RBCs destruction are called "haemolytic crisis". These may be precipitated by infections, surgery, exposure to cold or overexertion. The jaundice deepens with increasing pallor, fever, prostration, vomiting with pain in the loins and over the spleen and the liver.
3) **Signs** : of anaemia and may be jaundice. Spleen and liver are enlarged and may be tender during crisis.
4) **Investigations** :
   1. Peripheral blood picture : anaemia with reticulocytosis (10 – 50%).
   2. Osmotic fragility of RBCs.
   3. Evidence of haemolysis.
   4. Normoblastic hyperplasia of the bone marrow.

Complications and cause of death :

1- Severe haemolytic crisis.
2- Gall stones and cholecystitis.
3- Severe aplastic crisis

N.B. :

In the course of cong. spherocytosis temporary cessation of blood formation do occur with disappearance of the reticulocytosis, appearance of leucopenia and thrombocytopenia and increase of the anaemia. This is called "aplastic crisis".

Treatment :

1- Splenectomy in severe cases (better at 10 – 12 years age).
2- During the crisis : blood transfusion.
3- For gall stones : cholescystectomy.

Paroxysmal nocturnal haemoglobinuria :

Here the RBCs are sensitive to change of the Ph to the acid side which normally occurs at night with haemolysis.

1) it is associated with intravascular haemolysis, presence of Hb in the circulation and in the urine.
2) It is not hereditary, osmotic fragility is normal. Spherocytosis is not characteristic.
3) Chronic haemolytic anaemia and splenomegaly results.
4) Mild cases require no treatment, otherwise; corticosteroids, anticoagulants and maybe splenectomy.

Haemoglobinopathies

Def. : The presence of any type of Hb other than Hb.A.

Main types are :

1- Thalassaemia :

This disease results from an inherited defect in the rate of synthesis of one of the globin chains of Hb.A. The defect affects the α chain in α-thalassaemia and the β chains in β-thalassaemia.

It is autosomally inherited and both can occur in the heterozygous or homozygous forms.

The lack of synthesis of the polypeptide chains results in general reduction of the amount of Hb, haemolysis of the RBCs precursors in the bone marrow (ineffective erythropoiesis) with marked bone marrow expansion and compensatory continued production of Hb. F ($2\alpha + 2\gamma$ Hb., normally present in the fetal RBCs).

The disease is much more common in Mediterranean races but it occasional cases occur all over the world.

Types :

1. **Thalassaemia major** (or Cooley's anaemia) :

Here the patient is a homozygous (both his parents have thalassaemia). There is severe progressive anaemia starting early in infancy with marked pallor and slight jaundice. Spleen enlarges markedly and skeletal changes develop.

There are coarse features in his face due to the thickening of the skull bones or even Mongoloid facies.

Radiologically :

In the small long bones of the hands and feet; there is widening of the medullary cavity with spongy appearance + thinning of the cortex.

In the skull there is widening of the diploic space with radiating bony trabeculae giving hair on end appearance. The outer and inner tables are greatly thinned.

The blood picture shows :

Microcytic hypochromic anaemia with low MCH, MCV and to a little extent the MCHC.

There is marked anisocytosis and many target cells. The target cells have the appearance of the bull's eye with the Hb concentrated in the centre and in a peripheral rim with a clear zone in-between.

Also there is moderate elevation of the reticulocytic count. There may be leucocytosis or leucopenia (with hypersplenism).

Treatment :

There is no cure for thalassaemia. The only method of treatment is repeated blood transfusions. If there is marked haemolysis or hypersplenism think of splenectomy.

Later on iron overload may develop with haemosiderosis and may be heart failure. At this stage " *desferal* " an iron chelating agent is added to treatment.

2. **Thalassaemia minor** : a mild form of the disease in heterozygous individuals.

3. **Thalassaemia minima** : a mild asymptomatic form of thalassaemia in the relatives of the thalassaemic patients.

2- Sickle cell disease :

The abnormal Hb is Hb.S. in which glutamic acid is substituted by the valine at the β 6 position. The reduced form of Hb.S. precipitates inside the RBCs at the low O_2 tension of the venous blood.

The RBCs will assume a sickled shape. These sickled RBCs are mechanically fragile = haemolysis and anaemia. Also they increase the viscosity of the venous blood with circulatory stasis, multiple thromboses and infarctions in the spleen, kidneys, GIT, lungs and may be the brain and heart.

Clinically the disease is very common in Negroes and very rare in other races. It represents in two forms :

- Sickle cell anaemia :

  In homozygous individuals. Splenic enlargement occurs but the spleen may not be palpable because of multiple infarctions and fibrosis (auto-splenectomy).

  Haemolytic crisis may occur. Pulmonary hypertension may result. Vascular crisis with thrombosis and ischaemia are common. Painful crises due to small infarctions in bone also occur.

  Resistant ulcers over the lower tibia may be present (vascular). Rarely aplastic crisis as in spherocytosis may occur.

  Treatment : no cure.

  Blood transfusion if the haemolysis is severe. Hydration and may be even anticoagulants are used to prevent the vascular crisis. Folic acid is given prophylactically.

- Sickle cell trait :

  In heterozygous individuals usually there is mild or no anaemia.

3- Other haemoglobinopathies : e.g.: we have Hb.C., Hb.D., Hb.E., Hb.G.,.... etc.

Favism

Haemolytic reaction to the ingestion of broad beans (vicia faba) or the inhalation of their pollens. Seen esp. in Italians and Greeks, rarely in Egyptians. The RBCs of the affected persons are found to be deficient in the enzyme G-6-P.D.

Sometimes these reactions develop in spring due to other pollens (as the pollens of verbena hybrida in Iraq = Baghdad spring anaemia).

Auto-immune haemolytic anaemias

Here the RBCs themselves are normal but they are destroyed by circulating auto-antibodies. The antibody may be active at body temp. (warm antibody) or at lower temp. (cold antibody). The idiopathic variety present in acute, sub-acute or chronic forms.

Diagnosis : They are diagnosed by Coomb's test.

Treatment :

1. Blood transfusion : gives temporary improvement because the transfused RBCs will be haemolysed as well.
2. Steroids : 60 mg prednisone are given for at least 3 weeks in every case.
   - remission occurs in 50 – 75% of cases. If improvement results, the treatment is continued for 6 months and the dose is adjusted to the minimum that keeps the Hb. level at 10 gm%.
3. Splenectomy is done if there is no response to steroids.

Polycythaemia

= a condition in which there are more than 6.300.000 RBCs./cmm, and Hb. of more than 18 gm%.

Types :

I) **Polycythaemia rubra vera (erythraemia) :**

due to excessive erythroblastic activity of the bone marrow of unknown cause. Proliferation affects platelets and white elements as well (one form of the myelo-proliferative syndromes). Deep red replaces the yellow marrow in all bones.

C/P :

Males more, age : 35 – 65 years. It is chronic, progressive and ultimately fatal.

Symptoms :

Headache, dizziness, visual disturbances, bone pains + symptoms of enlarged spleen + symptoms of complications.

Complications :

1) Multiple thromboses (hepatic vein, portal vein, mesenteric, coronary or cerebral vessels due to increased blood viscosity).
2) May be cerebral hemorrhage. (defective platelet adhesiveness)
3) Gout in susceptible individuals. (excessive cellular destruction)
4) In 50% of cases hypertension develops (? renal)
   = polycythaemia hypertonica or Gaisbock's disease.
5) May end as myeloid leukemia (acute or chronic), myelosclerosis or hypoplasia.

Diagnosis :

1- Blood picture : increased no. of RBCs and Hb. colour index is below 1 and the RBCs may be hypochromic.
   - Leucocytosis (up to 40.000 /cmm) with shift to the left.
   - Thrombocythaemia (up to 1 – 3.000.000).
   - Slow E.S.R.

2- Sternal puncture : it will show hyperplasia of all elements (erythroid, myeloid and megakaryocytic).

Treatment :

1- Repeated venesection : 500 mL blood are withdrawn twice weekly until the count is 6.000.000 /cmm. and then every month.
   - Best in children.
   - Gives rapid result.
   - RBCs are removed intact (so no increase in uric acid, Hb or bile pigments in the body) but it is troublesome due to the increased viscosity of the blood.

2- Radioactive phosphorus (P32) : 5 – 7 millicuries IV one injection or 4 millicuries may be given after 6 months if the count is still high. The best in its result and very easy to give, but the incidence of myeloid leukemia later on is high.

3- Bone marrow irradiation.

4- Myeleran is given sometimes.

5- General measures as a diet poor in purine content and care during surgery.

II) Secondary polycythaemia (erythrocytosis) :

it is 2ry to a known condition and the increase affects the RBCs only. It may be :

1- Absolute with actual increase of the RBCs mass seen in :
   - Conditions with low O_2 tension as : congenital cyanotic heart diseases and resp. insufficiency (e.g.: emphysema) and at high altitudes (ch. Mountain sickness).
   - Renal conditions : as hypernephroma, some cases of hydronephrosis and polycystic kidney (may be due to increased production of erythropoietin).
   - Sometimes with hepatomas, uterine fibrinoids, Cushing's syndrome and infra-tentorial tumors.
   - May be due to drugs as cobalt and amphetamine (if used for long periods).

2- Relative : with no actual increase of the RBCs mass but due to diminution of the plasma volume as in dehydration, burns, shocks and crushing injuries.

Leukemia

A disease resulting from unlimited proliferation of one or more of the leucopoietic elements in the bone marrow usually associated with appearance of large no. of abnormal (immature) cells in the circulation (one form of the myeloproliferative syndromes).

Pathogenesis :

What initiates the process of abnormal proliferation in leukemia is still unknown. It may be a virus (infective theory), may be due to genetic factors (chromosomal abnormalities have been reported in some types of leukemias).

Classification :

1- Acute : when the process of proliferation involves the blast cells (very immature cells). So there are : acute myeloblastic, acute lymphoblastic and monocytic leukemia.
2- Chronic : when the process of proliferation involves the mature cells. So we have : Ch. myeloid (myelocytic) leukemia and Ch. lymphatic (lymphocytic) leukemia.

Acute leukemia

Here the blast cells proliferate excessively forming the greatest bulk of the bone marrow. This leaves no room for other elements (platelets, erythroid and myeloid cells).

Also the bone marrow function is depressed. This results in reduction of the RBCs, platelets and the normal WBCs with appearance of these blast cells in increasing no. in the peripheral blood.

Infiltrations formed of leukemic cells appear in many organs. It may even form rapidly growing tissues in the orbit, skull bones or other bones and parenchymatous organs (chloroma).

C/P :

Both sexes are affected.
Age : Acute lymphoblastic leukemia : 1 – 5 years.
Acute myeloblastic leukemia : 5 – 10 years.
Acute monocytic leukemia : young adults.
Onset : is acute but may be gradual esp. in adults.
Symptoms :

1. General : lethargy, headache, bone aches, fatigue and exertional dyspnea (anaemia).
2. Fever + sore throat and may be infections e.g.: bronchitis, bronchopneumonia. This is due to the low number of the

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mature granulocytes and diminished immunological response of the present mature cells.

3. Symptoms due to thrombocytopenia : petechiae, bleeding from the nose (epistaxis), from the gums (characteristic of monocytic leukemia), from the ears or eyes. May be melena, haematuria or haemoptysis.

Examination :

There is marked pallor + petechiae and bleeding gums (which may be swollen and spongy esp. in monocytic leukemia).

There may be generalized lymphadenopathy. Lymph nodes are small, discrete, firm and non-tender but cervical septic lymphadenitis may occur. Ulcerations of the mouth may be present. The spleen may be felt slightly enlarged in 70% of cases.

There is tenderness over the sternum.

Peripheral blood picture :

1. Normocytic normochromic anaemia.
2. Leucocytosis (up to 50.000) with about 80% of the total count formed of immature (abnormal) cells. Special studies are used to separate the 3 types of immature cells (lymphoblast, myeloblast, monocyte or monoblast) from each other. This may be difficult from the usual blood film.
3. Thrombocytopenia.
4. E.S.R. is high

Sternal puncture :

High total count and the blast cells predominate.

Complications :

1- Infections → death.
2- Hemorrhages : intracranial (esp. result in cranial nerve lesions), in the internal ear → deafness & intra-ocular → diminution or loss of vision.
3- Infiltrations in the lungs, bones or liver (i.e. the liver may be felt clinically).

N.B. :

Sometimes the leukemic process is only present in the bone marrow with no or few abnormal cells in the circulation. Even the white count may be low. This is sub-leukemic or aleukemic leukemia.

D.D. :

In absence of a blood picture and in sub-leukemic leukemia in absence of a sternal puncture, acute leukemia has to be differentiated from :

1. Other causes of fever + sore throat.
2. Other causes of fever + generalized lymphadenopathy.
3. Rheumatic fever.

Prognosis :

Acute leukemia is still considered ultimately fatal even with the present lines of treatment. This view may be questioned by certain studies done with the recent schedules of treatment.

Treatment :

1- **General lines** (good diet + symptomatic + rest).

2- **Supportive treatment :** in the form of :
   a. Blood transfusion : to correct the anaemia, leucopenia and the thrombocytopenia. So it must be of fresh blood. Even concentrated platelets, granulocytes or packed RBCs may be given according to which element is mainly deficient.
   b. Antibiotics : crystalline penicillin 1 million 4 – 6 hourly is given as prophylactic. If any infection actually occurs the proper antibiotic is given.
   c. Allopurinol is given prophylactically to prevent the development of hyperuricaemia.

3- **Specific treatment :** in the form of :
   a. Corticosteroids : as prednisolone 60 mg. daily until a remission is induced. It gives a remission in 70 – 90% of cases of acute lymphoblastic leukemia in children. In acute myeloblastic leukemia the result is only 20 – 30%. So methotrexate may be used when prednisolone fails. In both types of leukemia after induction of a remission, methotrexate is used for maintenance.
   b. Methotrexate (amethopterin) : given as 1 – 5 mg. daily orally or 20 – 60 mg. IV twice weekly. It is used for maintenance of the 1st remission in children and for the 1st relapse in adults. To induce a remission in adults, 6-mercaptopurine is used.
   c. 6-mercaptopurine : given as 2.5 mg/kg in a single dose daily. It is used to induce and keep remissions in adults and to induce a remission when there is relapse in children.
   d. Vincrestine (oncovin) : said to be the most powerful anti-leukemic agent. But it is toxic. It is given for 2nd relapses in both children and adults as 1 – 2 mg. IV weekly.

This approach in treating acute leukemia by single drugs in succession is now completely abandoned in most centers of the world.

Treatment of leukemia is now done by intensive combination programs using 4 or more drugs in big doses either combined or in very rapid alternation. Each centre in the world has its own schedule of treatment and there are many combinations.

Toxicity of these drugs :

Is mainly bone marrow depression with infection and bleeding and G.I. disturbances. Vincristine is neurotoxic (causes peripheral neuritis). Growth retardation, sterility and liver damage occur with prolonged use.

Chronic leukemia

1) Chronic myeloid leukemia :

This is the rarest type of leukemia. Here proliferation affects mainly the granulocytic series with over-production of myelocytes and mature cells in the circulation. There is encroachment on the erythroid elements. At the start; there may be over-production of platelets as well (irritation or myeloproliferation).

C/P :

The disease affects both sexes equally. It is a disease of middle and old age (30 – 60 years). It is rare in children.
Onset : is gradual. It may complicate polycythaemia rubra vera or myelofibrosis.
Symptoms :

1. Those of anaemia.
2. Those of huge splenomegaly; dragging pain, dyspepsia and may be acute pain (infarction).
3. Loss of weight, bone pains and may be priapism (persistent painful erection).

Examination :

1. Pallor & very late petechiae appear.
2. Huge splenomegaly : which is fleshy not so firm, borders rounded and may be slightly tender. The liver may also enlarge (leukemic infiltrations).
3. Generalized lymphadenopathy; only in 20% of cases and late.
4. Tenderness over the sternum is an early sign.

Complications :

Leukemic infiltrations in the brain (cranial nerve affection), meninges, eyes, internal ear and other places may occur. Herpes zoster may occur.

Blood picture :

1- Normocytic normochromic anaemia.
2- Leucocytosis (to above 300.000 /cmm.), with appearance of myelocytes (more than 10%) and myeloblasts (not more than 2%). All the granular cells are high

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(eosinophils, basophils and neutrophils). Sometimes eosinophils predominate (eosinophilic leukemia).

3- Platelets at first are high to above 500.000 /cmm. But later they are normal or even drop.

Sternal puncture :

Increase in total count with increased myelocytes, metamyelocytes and mature polymorph nuclear cells.

Prognosis :

Ultimately fatal. It may terminate as acute myeloblastic leukemia. Here the myeloblasts will be more than 2% in the peripheral blood.

Treatment :

1. The drug of choice is **myeleran** (busulphan) in a dose of 4 – 6 up to 12 mg. daily until a remission is induced and then continued indefinitely as 1 – 2 mg. for maintenance. Keep the WBCs count around 20.000 /cmm.
2. Splenic irradiation is done if the spleen is very large. It is repeated until the spleen shrinks, the WBCs count reaches 20.000, the Hb. and platelet count reaches normal levels.
3. Blood transfusion to raise the Hb. to 11 gm%.
4. Terminally with myeloblasts in the blood 6-mercaptopurine is added.

N.B. :

An abnormal chromosome called Ph. Chromosome (Philadelphia) is described in the leukemic cells in chronic myeloid leukemia in adults.

2) Chronic lymphatic leukemia :

This is the commonest type of leukemia. Proliferation affects the lymphopoietic tissue all over the body (bone marrow, lymph nodes, spleen,.... etc.). Early and for a long time no depression of the bone marrow function occurs. This results only very late in progressive cases.

C/P :

More in males. Age : old age (60 – 70 years).
Onset : insidious. Even it may be detected by chance on routine examination.
Course & prognosis : may be very long up to 20 years. May not affect the life span of the patient. It is slowely progressive.

Symptoms : General weakness, increased susceptibility to infections + enlargement of the lymph glands in different regions.

Examination : patient general condition is usually good except late in the disease. There is :

1. Generalized lymphadenopathy : which are firm, painless, discrete and usually symmetrical. May reach big sizes. Tonsils and adenoids may be enlarged.
2. Moderate splenomegaly : (in 10 – 20% of cases; it is huge) and hepatomegally.

Complications :

Leukemic infiltrations in various places e.g.: salivary and lacrimal glands (Mickulicz syndrome), intestine with malabsorption, in the bones; vertebral collapse and spinal cord compression may occur, intracranial (space occupying lesions), in the internal ear; deafness occurs... and so on.

Enlarged glands in the mediastinum may give mediastinal syndrome and in the hilum of the liver may result in obstructive jaundice.

Immunological abnormalities as auto-immune haemolytic anaemia, idiopathic thrombocytopenia may complicate the disease. Hypo-gammaglobulinaemia and infections esp. herpes zoster may occur.

Blood picture :

1- may be no anaemia. But late normocytic normochromic anaemia may occur (bone marrow depression) or autoimmune haemolytic anaemia. Thrombocytopenia is also a late feature.
2- WBCs count is not very high (up to 50.000). Rarely counts as high as 200.000 may be present. About 80% of the white count is lymphocytes. Lymphoblasts may appear terminally.

Sternal puncture : lymphocytes are increased.

Treatment :

1- Some say that non-progressive symptomless cases should be left alone.
2- The drug of choice is leukeran (chlorambucil). It is given 10 – 12 mg daily until a remission is induced and the white count is kept around 10.000. then 1 – 5 mg. of the drug is given as a maintenance treatment.
3- Local irradiation over the spleen (in huge splenomegaly) or over the enlarged glands (in the neck and mediastinum).

4- Corticosteroids are given in presence of haemolytic anaemia. Even in those cases and after special studies splenectomy may be done.
5- Blood transfusions, gamma-globulins and antibiotics are given in the presence of infection.
6- When lymphoblasts are high the treatment of acute leukemia is given.

N.B. :

As seen; acute leukemia doesn't progress to chronic leukemia but chronic leukemia usually end as acute leukemia.

Diseases of the reticulo-endothelial system

The R.E.S. is the collection of cells with the ability to phagocytose coarse particles and abstract dyes from the blood.

It is widely distributed throughout the body esp. lining the sinuses of the lymph nodes, bone marrow, spleen and liver (Kupffer cells). Also the histocytes present in the C.T. of various organs of the body and the microglia of the CNS. It includes also the monocytes of the blood (mobile cells).

Reticulosis : this term was used to mean systemic proliferation of the elements of the R.E.S. but it is no longer used. When the proliferation is neoblastic in nature and of unknown cause; these are the lymphomata.

Lymphomas : these are malignant diseases of the lympho-reticular system and include :

1- Hodgkin's disease.
2- Follicular lymphoma.
3- Lymphosarcoma.
4- Reticulum cell sarcoma.

Hodgkin's disease :

This is the commonest lymphoma. The disease usually starts in the lymph nodes where it may remain localized for sometime in a single group until finally it becomes systematized.

The normal structure of the lymph nodes is replaced by variety of different cells : reticulum cells, lymphocytes, neutrophils, eosinophils, plasma cells, histocytes, large mononuclear cells and giant cells which are called "Dorothy Reed or Reed-Sternberg cells (It has a double mirror image nuclei). This tissue pleomorphism, eosinophilia and giant cells are pathognomonic.

When the disease is early and least malignant there is lymphocytic predominance. With progress, lymphocytic depletion occurs in most malignant type.

On clinical and histological grounds we used to say that we have 4 variants of Hodgkin's disease :

1- **Hodgkin's granuloma :** (12%) :

The disease is localized to one group of lymph nodes commonly the cervical lymph nodes especially the lower deep cervical; which are enlarged, rubbery in consistency, discrete, painless and not tender. The enlargement is asymmetrical. General health of the patient is unaffected.

There is lymphocytic predominance histologically, the fibrosis is minimal with no capsular invasion. Prognosis is good. If treated it may progress to the usual type of systemic disease.

2- **Nodular sclerosing Hodgkin's disease :** (15%) :

Similar to the above but the glands re seen histologically to be divided by very thick collagen bands which separate masses of Hodgkin's tissue with mixed cellularity. Here prognosis is much better.

3- **Usual type of Hodgkin's disease (or Hodgkin's granuloma) :**

Which may start in one group and then spread with affection of other groups of lymph nodes, spleen, liver and practically every organ. The glands contain Hodgkin's tissue with mixed cellularity.

<u>The general condition of the patient suffers from</u> :

Fever, loss of weight, intense pruritis, sweating, abdominal pain, back-ache and pallor.

The fever is usually irregular or continuous. Characteristically Pel-Ebstien fever may occur (it is an intermittent fever of 2 weeks duration with rigors and sweating and afebrile periods of 2 weeks and so on..).

This type of fever occurs more when Hodgkin's disease involves the spleen and/or the abdominal lymph nodes. "Abdominal Hodgkin's" disease which may occur alone without affection of other lymph nodes.

Even the spleen may not be hugely enlarged and the case presents clinically as pyrexia of unknown origin (P.U.O.). This type may start acutely.

Pressure manifestations from the enlarged glands e.g.: mediastinal syndrome, obstructive jaundice, spinal cord compression, malabsorption syndrome.... and so on.

4- **Hodgkin's sarcoma** : least common and most malignant. Histologically there is lymphocytic depletion and invasion of the capsule. Prognosis is bad.

Now Hodgkin's disease is better **staged** as follows :

1- Hodgkin's stage I :
In which the disease is limited to one anatomical region (e.g.: one lymph gland group). There is no systemic manifestations. When it affects one extra lymphatic organ or site it is called (stage IE)

2- Hodgkin's stage II :
The disease is limited by the diaphragm to the upper or lower half of the body. If there is no systemic manifestations this is (stage IIA). If there are systemic manifestations e.g.: fever, this is (stage IIB).

3- Hodgkin's stage III :
The disease is not limited to either side of the diaphragm (present in both sides) but is still limited to the lymphatic system.

4- Hodgkin's stage IV :
The disease spreads outside the lymphatic system with affection of the bones, GIT, liver, skin and CNS.

This staging affects very much the line of treatment. That is why it is very important. Diagnostic laporotomy with splenectomy and exploration for abdominal nodal involvement and lymphangiography are done in all cases of clinical stage I and II to exclude affection of the abdominal organs which change the stage to III or IV.

Diagnosis :

1. Clinically : the disease is more common in males esp. young adults. But all ages and both sexes can be affected.
2. Blood picture : there is no specific blood picture but : moderate or severe anaemia + moderate leucocytosis or leucopenia + lymphopenia + eosinophilia and monocytosis are suggestive. E.S.R. is high.
3. Gland biopsy : shows the characteristic Hodgkin's tissue.
4. Sternal puncture : may show excess reticulum cells or giant cells.

Complications :

1- Immunological deficiency with herpes zoster, other infections and autoimmune haemolytic anaemia.
2- Amyloidosis.
3- Pressure manifestations from the enlarged glands.

D.D. :

1. From other causes of lymphadenopathy.
2. From other causes of splenomegaly.
3. From other causes of P.U.O.

Treatment :

1- For localized disease with no disturbance of the general health of the patient (stage I and II); give local extended field radiotherapy (high voltage or megavoltage radiotherapy is used).
2- For generalized disease (stage III and IV) and when there are systemic symptoms; give chemotherapy :
   a. Leukeran (in the same way as in chronic lymphatic leukemia).
   b. Nitrogen mustards : as nitromin 50 mg. IV or mustine HCl 10 mg. every 3rd day for 5 injections and then weekly.
   c. Cyclophosphamide (endoxan) : 100 – 200 mg. IV daily.
   d. Procarbazine or natulan, a hydrazine derivative given as 50 mg. tablets increasing gradually up to 200 – 300 mg. daily. Combination of more than one and up to 4 drugs as used in acute leukemia is now the standard treatment in many centres e.g.: 6 courses of MOPP (mustard, oncovin, procarbazine and prednisone). These give better results or even cure.
   e. Corticosteroids are given with pyrexia, weight loss, pruritis and haemolysis.
3- Combined chemotherapy and radiotherapy are now tried and are claimed to give optimum results.
4- Blood transfusion is done in severe anaemia, as a supportive treatment.

Hypersplenism :

Pancytopenia (anaemia + leucopenia + thrpmbocytopenia) of the peripheral blood related to hyperfunction of the spleen either by phagocytosis or by bone marrow inhibition. Some times only one of the elements in the peripheral blood is affected e.g.: anaemia alone, leucopenia alone or theombocytopenia alone. Treated by splenectomy if the patient is actually suffering from attacks of bleeding or recurrent infections.

Types :

1- 1ry : with no cause for splenic enlargement. Even the spleen may not be felt clinically.
2- 2ry : when it complicates cases of splenic enlargement.

- **Causes of tender sternum :**
  1. acute leukemia.
  2. chronic myeloid leukemia.
  3. active haemolytic anaemia.
  4. multiple myelomatosis.

Multiple myelomatosis :

Tumors of plasma cells. Usually in the bone marrow (yeloma). May come as a single tumor (solitary myeloma) or as multiple swellings (multiple myelomatosis).

Even in some cases plasma cells may reach high levels in the blood (plasma cell leukemia). The tumors affect the flat bones mostly (contain red marrow) e.g.: ribs, skull,... etc.

C/P :

Usually above the age of 50. both sexes are affected equally with the following symptoms :

- Severe bone pains.
- Spontaneous fractures (pathological fractures).
- Symptoms of anaemia and may be mild fever.
- Swellings of the ribs or skull may be seen. Even CNS manifestations due to involvement of the skull or vertebrae may occur.

Investigations :

1- blood picture : there is anaemia which is usually normocytic (leucoerythroblastic). Myeloma cells (plasma cells) may be present. Their count is high in plasma cell leukemia. Otherwise it is only high in the bone marrow.

2- Plasma proteins are high (up to 10 gm%) especially the globulins. Abnormal globulins will also appear (synthesized by the plasma cells).

3- Hypercalcaemia with normal serum P and alk. phosphatase.

4- Urine : one of the abnormal proteins will appear in urine called *Bence-Jones protein*. A white precipitate appear at 50 – 60°C while heating the urine. With further heating to near boiling the precipitate dissolves.

5- X-rays : show punched out areas (appear translucent) in the skull and ribs.

Other causes of punched out areas of translucency in the skull :

1. Multiple secondaries (from any tumor except those from cancer prostate which cause bone formation).
2. Paget's disease of bone (very rare in Egypt).
3. Histocytosis.

Complications :

1- renal failure (myeloma kidney).
2- Amyloidosis.
3- Spinal cord compression.
4- Leucoerythroblastic anaemia.

Treatment :

1. surgical excision of a solitary myeloma if accessible.
2. radiotherapy if the disease is limited to one area e.g.: lumbar vertebrae.
3. chemotherapy in multiple myelomatosis : e.g.: the best is a combination of melphalan and corticosteroids in big doses. Endoxan may also be used.

Haemorrhagic ddiseases

With injury of the vessels, bleeding stops by 3 mechanisms :

1- Contraction of the damaged capillaries, arterioles and arteries.
2- Adhesion of the platelets to the injured wall of the capillaries and to each other (platelet adhesiveness and platelet aggregation) with formation of platelet plug.
3- Coagulation of the blood forming a firm clot that closes the end of the torn vessel.

A defect in any of these mechanisms will cause abnormal bleeding. Bleeding may be spontaneous or follow minor trauma or minor procedures (e.g.: tooth extraction). It may take the form of spontaneous hges (petechiae, ecchymosis) or from the orifices (orificial hges) as haemoptysis, haematemsis, haematuria....and so on.

N.B. :

Purpura = the presence of big hges over any part of the body (better used to describe the disease).
Petechiae = small pin point well defined and non-raised purplish red spots caused by intradermal or subcutaneous hges.
Echymosis = small or big bleeding under the skin (subcutaneous).

Classification of purpuras (abnormal bleeding) :

1) Purpura due to vessel wall lesions :

1. Henoch's Schonlein purpura (allergic or anaphylactoid).
2. Waterhouse Friederichsen syndrome and most cases of septicaemia (remember S.B.E. and scarlet fever).
3. Rhc. Purpura and purpura in acute glomerulonephritis.
4. Drugs : e.g.: salicylates, phenylbutazones and other antirheumatics.. etc.

5. Miscellaneous :
   e.g.: hereditary hgic telangiectasia and von-Willebrands' disease, mechanical purpura (as in whooping cough and convulsions), senile purpura and cachectic purpura (when there is weakness and atrophy of the S.C. tissues) and also in scurvy and Cushing's syndrome.

2) **Platelet abnormalities** :

1- Thrombocytopenia :
   shown when the platelet count is less than 40.000 /cmm.
   This may be :
   i. 1ry thrombocytopenic purpura (or essential).
   ii. 2ry or symptomatic thrombocytopenic purpura; seen in : aplastic and leucoerythroblastic anaemia (with leukemias, lymphomas and myelomatosis).
   iii. Hypersplenism.
   iv. S.L.E.
   v. Drugs : e.g.: sulpha, quinine and qunidine, chloramphenicol and cytotoxic drugs.

2- Thrombocythaemia (increased platelet count) :
   which may be 1ry as a myeloproliferative syndrome or seen with chronic myeloid leukemia. Here the quality of the platelets is seen to be abnormal.

3- Abnormal quality of the platelets with a normal count = thrombasthenia :
   In platelets and vessel wall abnormalities, the bleeding is in the form of petechiae and may be orificial hges. The bleeding time is prolonged and Hess test is +ve. But the coagulation and prothrombin times are normal.

3) **Coagulation defects** :

1- Haemophilia = deficiency of factor VIII = AHG.
2- Christmas disease = deficiency of factor IX.
   Some times called haemophilia B because it is similar clinically to haemophilia but can be corrected by haemophilic plasma and not by factor IX deficient plasma.
   These two diseases are characterized by :
   - prolonged coagulation time.
   - Normal bleeding time, prothrombin time, platelet count and Hess test.

3- Hypoprothrombinaemia :
   May be congenital, due to liver disease, vit. K deficiency or result from the use of coagulants (e.g.: dindevan).
   Prothrombin time is prolonged, but the coagulation time may be normal or slightly prolonged.

4- Hypofibrinogenaemia :
May be congenital, due to liver disease or caused by the defibrination syndrome with consumption of the plasma fibrinogen as in accidental hge, intrauterine fetal death.. etc. Fibrinogen level in the plasma is found to be low (normal : 250 – 400 mg%).

Primary thrombocytopenic purpura :

Due to low level of circulating platelets of undetected aetiology.
It is either :

A) a type of 1ry Hypersplenism directed mainly against the platelets.
B) A type of autoimmune disorder with platelet agglutination and destruction. This is more accepted.

C/P :

May be acute or chronic. It occurs more in young females.

Acute :

sudden onset of generalized skin petechiae. Also seen sub-mucous. May be epistaxis, menorrhagia,... etc.
Spleen is not palpable in this acute type. Hess test is +ve.
Bleeding time is prolonged.
Coagulation and prothrombin times are normal.

Chronic :

as above but it recurs several times. Spleen starts to be palpable (but only in 1/3 of cases). The same tests are abnormal as in the acute type.

Treatment :

Give dexamethazone 6 – 8 tabs. daily for 4 weeks. Then gradually tapers the dose, if recurrence occurred after a 3rd course, splenectomy is considered.

Henoch's Schonlein purpura :

A type of allergic purpura with increased capillary fragility and capillary damage. It affects :

1. The skin : with petechiae, often symmetrical on the extremities, may be with urticaria and angineurotic oedema.
2. Joints : with tenderness and swelling.
3. Kidney : with glomerulonephritis (acute nephritis syndrome).
4. G.I.T. : with colic, haematemsis, melena or diarrhea.

Treatment :

Corticosteroids + antihistaminics.
Splenectomy is useless.

Haemophilia

A disorder of blood coagulation resulting from cong. deficiency in factor VIII (AHG). It is transmitted by recessive sex linked inheritance. So most of the sufferers are males. There may be +ve family history.

C/P :

It causes bleeding especially in the soft tissues, muscles, joints and G.I.T. usually related to trauma (even the minor trauma on ordinary life). So commonly it represents as :

1. Prolonged bleeding after circumcision, tooth extraction, and similar things.
2. Haemoarthrosis (in up to 90% of cases) with bleeding into the knees, ankles, elbows and other big joints (trauma).
   This may lead later to ankylosis and changes similar to osteoarthritis in X-ray (haemophilic arthritis).
3. Bleeding with big ecchymoses in the soft tissues may occur in different places. It may occur in the neck with suffocation, in the retroperitoneal tissues with a picture similar to acute abdomen, in the muscles with Volkmann's contracture later on.. and so on.
4. May be haematuria with renal colic (clot colic).

Treatment :

1. General management : with rest and immobilization of the bleeding part.
2. Raise the concentration of factor VIII by :
   a. Human concentrate of factor VIII if available.
   b. Fresh (and fresh frozen) plasma : 1 litre is given rapidly e.g.: in one hour with an average dose of 20 mL/kg.
   c. Animal AHG : but it is antigenic.
3. Before any surgery; plasma or better AHG is given to raise the AHG concentration.

Consumption coagulopathy or defibrination syndrome :

= Hypofibrogenaemia or afibrogenaemia resulting from rapid consumption of fibrinogen in a process of accelerated coagulation extra- or intravascular.

Extravascular consumption :

e.g.: formation of big retro-placental haematoma in accidental he.

Intravascular consumption :

When active tissue extracts enter the circulation and activate the coagulation factors with transformation of fibrinogen to fibrin.

The fibrin formed is removed at rapid speed by the active fibrinolytic system.

No thrombosis occurs and the net result will be loss of fibrinogen and abnormal bleeding.

This is seen with :

- Amniotic fluid embolism.
- Intrauterine fetal death.
- Sometimes with malignancy.
- Sometimes with some infections e.g.: malaria.
- In renal and hepatic failure.

Treatment :

Treated by fibrinogen and heparin.

Bleeding treated by anticoagulants.