HEMATOLGY

1) A 2 year old Pakistani boy has a haemoglobin of 8g/dl and an MCV of 65. The following tests are essential:

A	Serum ferritin	true	✘
B	Serum B12	false	✔
C	Serum folate	true	✘
D	Faecal occult blood	false	✔
E	Haemoglobin electrophoresis	false	✔

Comments:

In progressive iron deficiency, a sequence of biochemical and haematologic events occurs. First, the tissue iron stores represented by bone marrow haemosiderin disappear. The level of serum ferritin, an iron-storage protein, provides a relatively accurate estimate of body iron stores in the absence of inflammatory disease. Normal ranges are age dependent, and decreased levels accompany iron deficiency. Next, there is a decrease in serum iron (also age dependent), the iron-binding capacity of the serum increases, and the percent saturation falls below normal (also varies with age). When the availability of iron becomes rate limiting for haemoglobin synthesis, a moderate accumulation of heme precursors, free erythrocyte protoporphyrins (FEP), results. As the deficiency progresses, the red blood cells (RBCs) become smaller than normal and their haemoglobin content decreases. The morphologic characteristics of RBCs are best quantified by the determination of mean corpuscular haemoglobin (MCH) and mean corpuscular volume (MCV). Developmental changes in MCV require the use of age-related standards for diagnosis of microcytosis . With increasing deficiency the RBCs become deformed and misshapen and present characteristic microcytosis, hypochromia, poikilocytosis►اشكال مختلفة من الخلايا, and increased red cell distribution width (RDW). Iron deficiency is much commoner in more economically deprived communities, with up to 50% being affected in some inner city areas. Detailed investigation is therefore unnecessary in this child, unless he fails to respond to a trial of iron therapy.

2) A black West African girl aged 15 years is complaining of severe pain in both legs. The haemoglobin is 8g/dl. Sickle cell anaemia is unlikely to be the cause of her symptoms if

A	she is jaundiced	false	✔

B	she has haematuria	false	✔
C	x-ray of the spine shows osteoporosis	false	✔
D	menarche occured at 12 years	True	✔
E	the urinary osmolality is 800mosm/kg (specific gravity approximately 1022)	false	✘

Comments:
a+b-expected in sickle cell anaemia, c-x-ray usually shows fishmouth vertabrae (infarcts), d-growth + development usually impaired, e-almost all are unable to produce concentrated urine

3) Poor prognostic factors in neuroblastoma include:

A	Elevated urine catecholamines	true	✘
B	Age above 1 year	true	✔
C	Amplification of the N-Myc oncogene	false	✘
D	Stage 4S disease	false	✔
E	Stage 4 disease	false	✘

Comments:

The most important prognostic features are age and stage of disease at diagnosis. Over the age of a year, the prognosis is poorer, particularly with advanced disease. Over expression of the N-Myc oncogene and evidence of deletion of material on chromosome 1 (del 1p) is also associated with a poorer prognosis.

Staging divides tumours into 4:
I. Grossly resected tumour.
II. Localised unresectable tumour.
III. Metastases to non-contiguous ►غير متلاصقةintracavitary lymph nodes.
IV. Metastases beyond lymph nodes.

In addition, there is a stage IV, in infants with small adrenal primary with metastatic disease limited to skin, liver or bone marrow. These have been known to undergo spontaneous remission. The presence of bone involvement at this age is a poor prognostic factor.

4) Medulloblastoma:

A	Can metastasise outside the CNS.	false	✘
B	Can metastasise down the neuroaxis.	false	✘
C	Are common in Gorlin's Syndrome.	false	✘
D	Can be successfully treated with chemotherapy.	false	✔
E	Can respond to radiotherapy.	true	✔

Comments:

Medulloblastoma accounts for 20% of brain tumours. It nearly always arises in the midline of the posterior fossa. It presents with ataxia plus raised intracranial pressure. The tumour may seed throughout the CNS, and via the CSF, and up to 20% have spinal metastases at diagnosis. Treatment is with total CNS radiation after maximal surgical resection, and has a 5 year survival of 50%. Chemotherapy may be beneficial in completely resected cases and those with intraspinal metastases.

Gorlin Syndrome (nevoid basal cell carcinoma syndrome) is AD, with a defect on chromosome 9. It includes a wide spectrum of defects involving skin, eyes, CNS, endocrine system and bones.

- Skin: early onset basal cell carcinoma.
- Eyes: cataract, glaucoma, coloboma, strabismus, blindness.
- CNS: falx calcification, fits, mental retardation, partial agenesis of the corpus callosum, hydrocephalus, nerve deafness, medulloblastoma.
- Endocrine: hypogonadism, with absent or undescended testes.
- Bones: anomalous rib development, spina bifida, kyphoscoliosis.

5) The following are oncogenes:

A	The N-Myc gene	true	✔
B	The WT1 (first Wilm's tumour) gene	true	✘
C	The Retinoblastoma gene	true	✘
D	The WT2 (second Wilm's tumour) gene	true	✘
E	The BCRabI translocation (Philadelphia chromosome)	true	✘

Comments:
Oncogenes ► are endogenous human DNA sequences that arise from normal genes called proto-oncogenes. Proto-oncogenes are normally expressed in many cells, particularly during fetal development, and are thought to play an important regulatory role in cell growth and development. Alterations in the proto-oncogene can activate an oncogene, which produces unregulated gene activity, contributing directly to tumourogenesis. Oncogene alterations are important causes of:

- Rhabdomyosarcomas (ras oncogene).
- Burkitt's lymphoma (C-myc is translocated intact from its normal position on chromosome 8 to chromosome 14).
- Neuroblastoma (N-myc proto-oncogene is seen in a proportion of patients with poor prognosis).

They should be contrasted with **tumour suppressor genes**. In this situation, the genes normally down regulate cell growth, and require inactivation to allow malignant growth. Examples include retinoblastoma.

6) Overwhelming septicaemia in post-splenectomy patients:

A	Can be prevented with prophylactic penicillin.	true	✘
B	Is more common in children <5 years.	true	✔
C	Is only a significant problem for two/three years post splenectomy.	false	✔
D	Is due to hypogammaglobulinaemia.	true	✘
E	Is less common if splenectomy is for traumatic rupture.	false	✘

Comments:
Because of the risk of post-operative sepsis, splenectomy should be limited to specific indications. These include: splenic rupture, anatomic defects, haemolytic anaemia, immune cytopaenia, metabolic storage disease, secondary hypersplenism.

There is an increased risk of sudden overwhelming infection (sepsis or meningitis). The risk is increased in children under 5, and is decreased in splenectomies done for trauma, red cell membrane defects, immune cytopaenias. Encapsulated bacteria (Strep. pneumoniae, haemophilus influenzae, neisseria meningitidus, E. Coli) are commonest. The spleen is responsible for filtering the blood and for early antibody responses. There is also an increased risk of malaria.

The operation should be postponed until the patient is over 5, and pre-operatively, the child should be vaccinated with pneumovax, Hib, and meningococcal A and C

vaccines. In the case of trauma, splenic repair or partial splenectomy may be possible. Post-splenectomy penicillin reduces the risk of pneumococcal sepsis, but does not eliminate it. The appropriate duration of prophylaxis is unknown.

The following conditions commonly require splenectomy in later life:

A	Sickle cell trait	false	✔
B	Sickle cell disease	false	✔
C	Beta Thalassaemia	true	✔
D	Glucose-6-phosphate dehydrogenase deficiency	false	✔
E	Idiopathic thrombocytopenic purpura	true	✘

Comments:
Because of the risk of post-operative sepsis, splenectomy should be limited to specific indications. These include:

- Splenic rupture, anatomic defects.
- Haemolytic anaemias, immune cytopenias.
- Metabolic storage diseases.
- Secondary hypersplenism.
- Surgical indications (rare).

The major risk is infection, particularly in children less than 5 years. The risk of sepsis is slightly less in splenectomies done for trauma, red cell membrane defects, and immune cytopenias then when there is a pre-existing immune deficiency such as Wiskott-Aldrich Syndrome or reticuloendothelial blockage such as storage diseases or severe haemolytic anaemias.

Regarding Vitamin K deficiency:

A	It is commoner in breast fed babies.	true	✔

B	It causes haemolytic disease of the newborn.	true	✘
C	It should be considered if a prolonged partial thromboplastin time is found.	false	✘
D	It is associated with decreased levels of factor 5.	false	✔
E	Is usually due to decreased synthesis in the liver.	false	✔

Comments:
Vitamin K is actually from a group of vitamins (naphthoquinones). These are natural fat-soluble compounds that are stable to heat and reducing agents. They are labile to oxidising agents, acids, alkali, light. Bile salts are necessary for intestinal absorption. They are involved in the synthesis of prothrombin, and coagulation factors 2, 7, 9 and 10 and osteocalcin in addition to proteins C, S and Z. Absence results in haemorrhagic manifestations. They are found particularly in green leafy vegetables, pork and liver. Analogues may produce hyperbilirubinaemia in premature infants.

Deficiency of Vitamin K can lead to haemorrhage at a variety of sites. This may occur during the first few days (early haemorrhagic disease) or within the first 3 months of life (late haemorrhagic disease). The latter is much more serious because of the potential for intracranial bleeds, leaving 30% dead and 40% seriously handicapped. Modern formula feeds are supplemented with Vitamin K, but babies who are breast fed should definitely receive supplements. There is no definite link of intramuscular Vitamin K with childhood cancer, and the larger studies suggest that there is no link at all. Oral regimens of prophylaxis are likely to be suboptimal for compliance particularly from the third dose (in one study measured there was only 40%).

In haemophilia A

A	dental extraction bleeding can be controlled with DDAVP if factor VIII concentration is 2-5% of normal	true	✘
B	sons of an affected person will be normal	false	✘
C	there is a 30% spontaneous occurence rate	false	✘
D	hepatitis B virus is the most common cause of deranged LFTs	true	✘
E	there is a normal amount of factor VIII-related antigen	false	✘

Comments:

a-only in mild cases (5-20% activity)
b- X-linked recessive
d-hep C would be commoner in these patients
(Dr Shu Ho)

	Is one of the commonest solid tumours of childhood in equatorial Africa.	true ✔
B	Occurs in endemic and non-endemic forms.	false ✘
C	Always presents with a mass in the jaw.	false ✔
D	Usually presents with stage III or IV disease.	false ✔
E	Is highly responsive to chemotherapy.	true ✔

Comments:

The Ebstein-Barr virus is implicated in Burkitt's lymphoma, lymphoepithelioma, and with Hodgkin disease. 90-95% of Burkitt's lymphoma in Africa are EBV related, versus only 20-30% in the USA. Chronic stimulation of B lymphocytes by EBV can promote chromosomal translocations that contribute to malignant transformation. Chronic malarial infection appears to increase the risk of Burkitt's lymphoma by decreasing immune surveillance of genetically altered cells.

Burkitt's lymphoma is a small, non-cleaved cell (SNCC) type of non-Hodgkin's lymphoma (NHL). These are B cell tumours that express cell surface immunoglobulin and contain one of 3 characteristic chromosomal translocations: t(8;14), t(2;8), or t(8;22). Each involves the C-myc oncogene and an immunoglobulin gene. The endemic (African) Burkitt lymphoma is often found in the jaw, and is the most common childhood cancer in equatorial East Africa and New Guinea. The mean age of onset is 5 years. Only 20% of non-endemic (sporadic) Burkitt lymphoma cases contains EBV genomes. Prognosis is good, as for most forms of NHL.

In a blood sample from a six hour old child, you would be concerned to find:

A	White blood cell count of 18 x 10^9/L.	false ✔
B	Haemoglobin of 12.0g/dl.	true ✔
C	More lymphocytes than neutrophils.	false ✔
D	Nucleated red blood cells and reticulocytes.	true ✔

E	Low MCV.	true	✔

Comments:

The cell count changes markedly with age. In the first 24 hours after birth:

- The haemoglobin ranges from 14.5 to 22.5g/dl, and the haemtocrit from 48 to 69%.
- The MCV is much higher than in later life, ranging between 100 and 135fl.
- White cell count is extremely variable between about 9.4 and 34 x 10^9/L. Above this or below this, sepsis should be considered. Although the proportions of lymphocytes and neutrophils are relatively similar in the first few days, by early childhood, lymphocytes tend to predominate.

The following associations are well described:

A	Renal transplantation and Non-Hodgkin's lymphoma	false	✔
B	Hepatitis B and aplastic anaemia	false	✘
C	Turner's syndrome and acute myeloid leukaemia	false	✔
D	Basophilia and chronic myeloid leukaemia	true	✘
E	Crohn's disease and TB	true	✘

Comments:
Post-renal transplant complications include:

- Renal: acute tubular necrosis, acute and chronic rejection, technical urological or urovascular problems, recurrence of the original renal disease, urinoma.
- Drug toxicity (immunosuppressives, antibiotics).
- Infection (particularly viral e.g. CMV, systemic), wound or urinary tract infection.
- Bleeding.
- Pancreatitis, lymphocele, bowel obstruction.

Aplastic anaemia may be acquired or congenital.

Congenital causes:
Fanconi anaemia, reticular dysgenesis, Schwachman-Diamond Syndrome, dyskeratosis congenita, familial aplastic anaemia, preleukaemias, myodysplasia, monosomy 7, non-

haematological syndromes (Down's, Seckle, Dubowitz).
Acquired causes:

- Idiopathic
- Secondary:
    - Radiation, drugs and chemicals (either predictable or idiosyncratic).
    - Viruses: EBV, hepatitis, parvovirus, HIV.
    - Immunological diseases: eosinophilic fascitis, hypoimmunoglobulinaemia, thymoma.
    - Other: pregnancy, paroxysmal nocturnal haemoglobinuria, preleukaemia.

AML constitutes 20% of all childhood leukaemias, but is the predominant in the neonatal period. It has an increased incidence in Down's Syndrome, Fanconi anaemia, Diamond-Blackfan anaemia, Kostmann Syndrome and Bloom Syndrome. It also occurs in children treated for a previous leukaemia, with a peak incidence within 10 years of the initial malignancy. This may be related to alkylating agents, agents that inhibit DNA repair, or radiation therapy. CML is a clonal malignancy of the haematopoietic stem cell characterised by a specific location, the t(9;22) (q34;q1), known as the Philadelphia chromosome. This juxtaposition produces a fusion gene. CML is rare in children, accounting for only 3% of childhood leukaemia. In most cases there is no predisposing feature. The films shows elevated white cell counts (which may exceed 105 per mm3, with all forms of myeloid cells seen in the blood smear. Platelet count may be elevated, and the bone marrow is hypercellular. Cytogenetic and molecular studies demonstrating the Philadelphia chromosome confirm the diagnosis. Currently, there is no evidence to link Crohn's disease with TB.

A 5 year old Pakistani child who has been in the UK for one year is found to have a Hb of 7.0g/dl and an MCV of 65. The following tests are essential in his management:

A	A Microscopic stool examination	true	✘
B	Serum ferritin	false	✔
C	Haemoglobin electrophoresis	false	✔
D	Serum zinc	false	✔
E	Serum B12	false	✔

Comments:

Iron deficiency anaemia is extremely common, particularly in children from inner city and ethnic minority groups. This may relate to late weaning, or the early introduction of doorstep milk, which has a lower available amount of iron than formula or follow-on milk. In hypochromic microcytic anaemia, iron deficiency is by far the most likely cause. This, therefore, does not require further investigation, but the child should be treated with a 3 month trial of iron. If there is no response, this may be due to lack of compliance with therapy, or it may be due to haemoglobinopathy, such as thalassaemia. In the latter case, one would expect to find some abnormalities clinically such as hepatosplenomegaly or dysmorphic appearance to assist in the diagnosis. However, electrophoresis at this review stage would be justified.

Idiopathic thrombocytopenic purpura:

A	Is essentially a disease of childhood.	false	✔
B	Has a high mortality rate, even when treatment is prompt.	false	✔
C	Is associated with mucous membrane haemorrhage.	false	✘
D	Is improved by treatment with pooled gamma globulin.	false	✘
E	The mainstay of treatment is splenectomy.	false	✔

Comments:

Acute ITP is the commonest of the thrombocytopaenic purpuras of childhood. It is associated with petechiae, mucocutaneous bleeding, and occasionally haemorrhage into the tissues. There is profound deficiency of circulating platelets despite adequate number of megakaryocytes in the marrow. In 70% there may be an antecedent viral infection, and this is thought to trigger an immune mechanism causing the thrombocytopenia. Bleeding is asymmetrical, and may be most prominent over the legs. Mucous membrane haemorrhage may be prominent with bullae of the gums and lips and nose bleeds may be difficult to control. Intracranial haemorrhage occurs in fewer than 1% of cases.

There is no enlargement of liver, spleen or lymph nodes, and the acute phase usually resolves in 1-2 weeks. The thrombocytopaenia may persist. The platelet count is below 20×10^9/L, the white cell count is normal, and anaemia is not present unless significant bleeding has occurred. Bone marrow aspiration reveals increased megakaryocyte numbers. The majority of patients recover with no treatment. Platelet infusions will have only transient benefit. Gammaglobulin is followed by a sustained rise in the platelet count. Corticosteroid therapy reduces the severity and shortens the duration of the initial phase, but may mask the occasional leukaemia presenting with thrombocytopenia. Splenectomy should be reserved for chronic patients, defined as

thrombocytopenia present for more than a year, and for severe cases who do not respond to steroids.

Regarding childhood malignancies:

A	A mediastinal mass is a frequent finding in T cell Acute Lymphoblastic Leukaemia.	false	✘
B	A bone marrow biopsy should always be performed to exclude leukaemia before ITP is treated with steroids.	true	✔
C	Cranial irradiation before the age of 3 years has a high neurocognitive morbidity.	false	✘
D	Children on chemotherapy are at high risk if exposed to measles or chickenpox.	true	✔
E	The siblings of children on active treatment for cancer can be safely immunised with the combined measles, mumps and rubella vaccine (MMR).	false	✘

Comments:

A mediastinal mass is typical of T cell acute leukaemia, and can also be a manifestation of T cell non-Hodgkin's lymphoma.

Side effects of chemotherapy are extremely common and important. They include:

- Infection from immunosuppression: neutropaenia places children at risk of septicaemia, and there are specific problems with gram negative organisms, coagulase negative Staph., PCP, and disseminated fungal infections. Most viral infections are no worse than in other children, but measles and varicella may be life-threatening. Zoster immunoglobulin may be helpful in non-immune children who have been in contact with measles or varicella. Acyclovir is used to treat established varicella infection, but no active treatment is available for measles. The use of live vaccines in patients receiving chemotherapy should be avoided until at least 6 months to a year has elapsed following the completion of chemotherapy.
- Bone marrow suppression: anaemia requires transfusion, and thrombocytopenia may result in bleeding.
- Gut mucosal damage: this may increase the risk of gram negative infection, and is associated with painful mouth ulcers, which can prevent eating.

Specific side effects:
- Cardiotoxicity with Doxorubicin.

- Renal failure and deafness with Cisplatin.
- Haemorrhagic cystitis with Cyclophosphamide.
- Neuropathy with Vincristine.

Occasionally, leukaemia may present with thrombocytopenia alone. In patients presenting with a low platelet count who are thought to have ITP, a bone marrow should be done if steroids are considered, as they may suppress the leukaemia enough to delay diagnosis.

Spleen enlargement is invariably seen in:

A	Acute myeloid leukaemia	true	✘
B	Myelosclerosis	false	✔
C	Myeloproliferative disorders	false	✔
D	Idiopathic thrombocytopaenic purpura	true	✘
E	Polycythaemia rubra vera	true	✔

Comments:

A soft thin spleen may be palpable in 10% of neonates, 10% of normal children, and 5% of adolescents. In most individuals, the spleen must be 2-3 times its normal size before it is palpable.

Common causes of splenomegaly include:

- Infection:
  - Bacterial: typhoid, endocarditis, septicaemia, abscess.
  - Viral: EBV, CMV and others.
  - Protozoal: malaria, toxoplasmosis.
  - Haematological: haemolytic anaemia (congenital or acquired), extramedullary haematopoiesis: thalassaemia, osteopetrosis, myelofibrosis.
- Oncological:
  - Malignant: Leukaemia, lymphoma, metastatic disease.
  - Benign: Haemangioma, hamartoma.
- Infiltration/Storage:
  - Lipidoses: Niemann-Pick, Gaucher.
  - Muccopolysaccharidoses
  - Infiltration: histiocytosis.
- Congestion:

    - Cirrhosis or hepatic fibrosis.
    - Hepatic, portal or splenic vein obstruction.
    - Congestive heart failure.
- Cysts: - Congenital (true cysts) or acquired (pseudocysts).
- Other: - SLE, sarcoid, rheumatoid arthritis. Although splenic enlargement is seen in all these conditions, this is not invariable.

However, in polycythaemia rubra vera, the diagnostic criteria are increased total red blood cell volume, an arterial oxygen saturation of greater than or equal to 92%, and splenomegaly. The disorder in this condition is that erythroid precursors do not require erythropoietin to stimulate growth.

Regarding the red cell:

A	Carbon Dioxide binds with reduced haemoglobin.	true	✔
B	The oxygen affinity of haemoglobin is decreased in the presence of acidosis.	true	✔
C	The oxygen affinity of fetal haemoglobin is greater than adult haemoglobin.	true	✔
D	Carbonic anhydrase is present in all red cells.	false	✘
E	Most carbon dioxide in venous blood is transported bound to albumin.	false	✔

Comments:
Carbon dioxide is carried in the blood in 3 forms:

- Dissolved (10%).
- Bicarbonate, whose formation is encouraged by carbonic anhydrase present in the red cell.
- As carboamino compounds: hydrogen irons liberated from the bicarbonate reaction are bound to haemoglobin which encourages the release of oxygen, since reduced haemoglobin is less acid than the oxygenated forms.

Thus, the presence of reduced haemoglobin in the peripheral blood helps with the loading of carbon dioxide, while the oxygenation which occurs in the pulmonary capillary assists in the unloading of it. The fact that the deoxygenation of the blood increases its ability to carry carbon dioxide is often known as the Haldane effect. Fetal haemoglobin contains g polypeptide chains in place of the b-chains of Hb A. Its resistance to denaturation by strong alkali is used in its quantitations. Hb F is the predominant haemoglobin from 8 weeks gestation, and constitutes 90% of the total haemoglobin of the 6 month fetus. At birth 70% of the total is Hb F, and synthesis decreases rapidly postnatally, such that by a year, only 2% is present. Hb F has a greater oxygen affinity than Hb A, so the growing fetus is preferentially ourished by oxygen in utero.

Concerning T Lymphocytes:

A	All have CD4 receptors.	false	✔
B	They are activated in the secondary immune response.	false	✔
C	They are involved in allergic contact dermatitis.	true	✔
D	They enter lymphoid tissue through specialised venule walls.	true	✔
E	They undergo maturation in the thymus.	true	✔

Comments:

T cells are produced from precursors in the fetal liver, and begin to colonise the thymus at 8 weeks gestation (this derives from the branchial cleft and the branchial pouch). The mature T cell receptor is a heterodimer of 2 chains either a, b (common) or g, d (rare), which is co-expressed on the cell surface with CD3, a complex of 5 polypeptide chains (g,d,e,x,h). TCR gene rearrangement produces massive diversity. Positive and negative selection remove autoreactive lymphocytes. CD4 cells (helper cells) have been described as "the conductor of the immunological orchestra", since cytokine production by them orchestrates the immune response. When their function is reduced, as it progressively is in HIV infection, a discordant immune response results. CD8 cells are cytotoxic T cells.

Type IV cell-mediated or delayed type hypersensitivity, follows interaction of antigen with specifically sensitised thymus derived T lymphocytes. Contact allergy (such as poison ivy, or contact dermatitis) is the prototype of allergic disease mediated by delayed type hypersensitivity. Drug reactions with involvement of liver, lung and kidney are further examples. Tuberculin reactivity, graft vs. host disease, tissue transplant reactions, and infiltrative hypersensitivity lung diseases with granuloma formation are further examples.

The following haematological disorders are inherited as autosomal recessive conditions:

A	Antithrombin III deficiency	true	✘
B	Protein C deficiency	true	✘
C	Glucose-6-phosphate dehydrogenase deficiency	false	✔
D	Pyruvate kinase deficiency	false	✘
E	Acute intermittent porphyria	true	✘

Comments:

Anti-thrombin 3 (AT3) is a plasma inhibitor protein that blocks the enzymatic activity of some serrin proteases coagulation factors. The activity of this inhibitor in increased by heparin. AT3 is synthesised by the liver, is not Vitamin K dependent, and can be consumed during DIC. Normal newborns have a reduced activity. Congenital AT3 deficiency is an autosomal dominant. Treatment of thrombotic in these events in these patients may be difficult.

Protein C is an inhibitor that once activated inhibits clot formation and enhances fibrinolysis. It is liver synthesised and Vitamin K dependent. Protein C is converted to an active enzyme by a thrombin-thrombomodulin complex on the endothelial cell surface. Activated protein C inhibits a plasminogen activator inhibitor, which results in enhanced fibrinlysis, and, with protein S as a co-factor, inhibits the clotting of the activated factors 5 and 8 by limited proteolosis. Activated protein C thus controls the conversion of factor 10 to 10a and prothrombin to thrombin. Congenital deficiency is an autosomal dominant trait. Acquired deficiency may occur in association with infection.

Glucose-6-phosphate dehydrogenase deficiency is the most important disease of the pentose phosphate pathway, and is responsible 2 clinical syndromes: an episodic haemolytic anaemia induced by infections or certain drugs, and a spontaneous chronic non-spherocytic haemolytic anaemia. The deficiency is X-linked, and heterozygous females are resistant to falciparum infections. There are a large number of abnormal alleles causing disease of vastly different severity.

Pyruvate kinase deficiency is a rare congenital haemolytic anaemia inherited as an autosomal recessive. Generation of ATP within the red cell is impaired resulting in an abnormally high concentration of 2,3,DPG in the red cell, which inhibits the enzymes of the pentose phosphate pathway. Clinical manifestations vary from severe neonatal haemolysis, to a mild well compensated haemolysis first noted in adulthood.

Acute intermittent porphyria is an autosomal dominant disorder resulting from partial

porphobilinogen deaminase deficiency in the cytosol of all tissues including erythrocytes. Clinical expression of the disease is linked to environmental or acquired factors such as nutritional status, drugs, steroid or chemicals. The major abnormality is of the peripheral, autonomic or CNS. Major symptoms are abdominal pain, nausea, vomiting, constipation or diarrhoea. In severe cases the urine develops a port wine colour due to the high content of porphobilin, an auto-oxidation product of PBG. Hypertension and neuropathy are common, with muscle weakness, cranial nerve abnormality and seizures.

Concerning hereditary spherocytosis:

A	It is inherited as an autosomal dominant disorder.	true	✔
B	The red cells have increased osmotic resistance.	false	✔
C	Sufferers are prone to aplastic crises secondary to parvovirus infection.	true	✔
D	It is associated with macrocytosis.	false	✔
E	The cell shape returns to normal following a splenectomy.	false	✔

Comments:

Hereditary spherocytosis (HS) is a common cause of haemolysis and haemolytic anaemia, with a prevalence of 1:5000 in Northern Europeans. Patients may be asymptomatic without anaemia and minimal haemolysis, or have severe haemolysis. It is autosomal dominant, though it is occasionally transmitted as AR. 25% of patients have no family history. The abnormality is in spectrin, a major component of the cytoskeleton. This results in loss of membrane without a proportionate loss of volume, so the red cells end up as small spheres rather than biconcave discs.

There is an associated increase in cation permeability and transport, ATP utilisation, and glycolytic metabolism. The cells have decreased deformability impairing splenic passage, so the cells are prematurely destroyed. In addition to haemolysis, hypoplastic crises may be associated with parvovirus infection. This may result in profound anaemia with high output heart failure, hypoxia, cardiovascular collapse and death. In HS the haemoglobin level is usually 600g/dl, and the reticulocyte count is elevated to 6-20%. The MCV is normal, but the MCHC is increased. Spherocytes have a smaller diameter than normal cells. The diagnosis is confirmed by an osmotic fragility test. Splenectomy eliminates most of the haemolysis associated with the disorder, but carries its own risks. In mild cases, folic acid 1mg/day is administered to prevent secondary folate deficiency. For those with severe anaemia, and/or hypoplastic or aplastic crises, splenectomy is recommended after the age of 5-6 years. Vaccines for pneumococcus, meningococcus and haemophilus influenzae should be given prior to

splenectomy, and prophylactic penicillin continued for life.

In the management of acute sickle cell painful crises:

A	Patients should receive continuous oxygen and monitoring of SaO_2.	true	✔
B	Patients should receive intravenous antibiotics.	false	✘
C	Intravenous opiate analgesia should be titrated until adequate control of pain.	true	✔
D	Blood transfusions should be given.	false	✔
E	Intravenous hydroxyurea should be given.	true	✘

Comments:
Painful episodes can often be managed with oral Paracetamol -/+ codeine. Severe episodes require hospitalisation with parenteral opiates. Anti-inflammatories may decrease or eliminate the need for narcotics. Dehydration and/or acidosis should be rapidly corrected by intravenous fluids. Packed cells are specifically indicated for acute splenic sequestration and aplastic crises. The latter may require splenectomy. Intravenous antibiotics should be given to cover the possibility of haemophilus or pneumococcal infection. Chemotherapy regimens that stimulate fetal haemoglobin synthesis have been employed with beneficial effect on an experimental basis. These include hydroxyurea and hydroxybutyrate. These are given as maintenance therapy.

Prognosis in Hodgkin's Lymphoma is adversely affected by:

A	Fever	true	✔
B	Splenic involvement	true	✔
C	Bone pain with alcohol consumption	false	✔
D	Pruritis	false	✔
E	Weight loss >10% in the last 6 months	true	✔

Comments:
With modern treatment, more than 90% of patients with Hodgkin's Disease achieve initial complete remission. The likelihood of prolonged remission or cure is related to the disease stage, with most patients with stage I or II disease cured, 75% to 90% of those with stage III disease, and 60-85% of those with stage IV disease.

- Stage I: Involvement of a single lymph node region, or of a single extralymphatic organ or site.
- Stage II: Involvement of 2 or more lymphoid organs on the same side as the diaphragm, or localised involvement of an extralymphatic organ or site, and of one or more lymph node regions on the same side of the diaphragm.
- Stage III: Involvement of lymph node regions on both sides of the diaphragm which may be accompanied by localised involvement of an extra-lymphatic organ or site, or by splenic involvement.
- Stage IV: Diffuse or disseminated involvement of one or more extra-lymphatic organs or tissues, with or without associated lymph node enlargement.

Idiopathic Thrombocytopenic Purpura (ITP) in Childhood:

A	Is usually self limiting.	true	✔
B	Always requires treatment if the platelet count is less than 20 x 10^9/L.	false	✔
C	Is associated with cerebral haemorrhage in less that 1% of cases.	false	✘
D	Can be successfully treated with steroids.	false	✘
E	Can be successfully treated with intravenous immunoglobulins.	false	✘

Comments:

Acute idiopathic thrombocytopenic purpura is the most common of the thrombocytopenic purpuras of childhood. It is associated with petechiae, mucocutaneous bleeding, and occasionally haemorrhage into the tissues. There is a profound deficiency of circulating platelets despite adequate numbers of megakaryocytes in the marrow. In 70% of cases there is an antecedent disease or viral infection. ITP has an excellent prognosis even when no specific therapy is given. Within 3 months, 75% of patients recover completely, mostly within 2 months. Spontaneous haemorrhage and intracranial bleeding (<1%) are usually confined to the initial phase of disease.

Thereafter, spontaneous manifestations subside. 90% of children have a normal platelet count within a year, and relapses are unusual. FFP or platelet concentrates have transient benefit only, but should be administered when life threatening haemorrhage occurs. When the disease is mild and haemorrhages of the retina or mucus membranes are not present, no specific therapy is given. Gammaglobulin and corticosteroid may be used in severe cases. The former produces a more rapid effect, and the latter may disguise the occasional case of leukaemia presenting with

thrombocytopenia.

Poor prognostic factors in acute lymphoblastic leukaemia include:

A	Haemoglobin <6g/dl on presentation	false	✔
B	Total peripheral blood WBC greater than 100 x 10^9/L	false	✘
C	Presence of the Philadelphia Chromosome	true	✔
D	Female sex	true	✘
E	Age less than 1 year	true	✔

Comments:
Numerous clinical factors have emerged as prognostic indicators, only to loose their significance as treatment improves. Thus with modern treatment regimens the immunophenotype has largely been eliminated as a risk factor. Initial white cell count of >100 x 10^9/L(>50x10^9/L in some reports) is a poor prognostic factor, and children >10 years and younger than 1 year have an increased risk. Many chromosomal abnormalities have a reduced risk, but the presence of the Philadelphia chromosome increases it. B cell ALL has a worse prognosis. Males are more severely affected.

Which of the following is true of Factor VIII antihaemophilic globulin?

A	released mainly by megakaryocytes	true	✘
B	mediates the endothelial platelet aggregation	true	✔
C	is an essential co-factor in the activities of Factor X to Factor Xa	false	✘
D	has a half life of 36 hours	false	✘
E	deficiency is a major source of bleeding in Von Willebrand's disease	true	✔

Comments:
factor VIII antihaemophilic globulin / factor = Von Willibrand's factor It is the plasma carrier for factor VIII a-mainly from endothelium but also from megakaryocytes b-it links platelet membrane receptors to vascular subendothelium c-in association with calcium / activated factor IX d-stored blood at 4°C -> activity falls to 10% in first 3 days (Dr Shu Ho)

The following are seen in sickle-cell anaemia

A	dactylitis	true	✔
B	retardation of secondary sexual characteristics	true	✔
C	pathognomic fundal changes	false	✘
D	cardiac signs simulating mitral stenosis	true	✔
E	normal urinary concentrating ability only if the sickle-cell trait is present	true	✘

Comments:
Dactylitis - inflammation of the fingers is a feature of SCD due to expansion of bone marrow. B - a consequnce of ill health with hypogonadotrophic hypogonadism. A so-called black sunburst retinopathy is pathognomonic of sickle cell disease. Retinal vein thrmbosis is also seen. Poor urinary concentration is a feature of the disease but is unaffected with the trait.

Recognised features of sickle cell trait include:

A	Moderate anaemia	true	✘
B	Increased risk of anaesthesia	true	✔
C	Reduced renal concentrating ability in adolescence	true	✔
D	Episodic haematuria	false	✔
E	Splenomegaly	false	✘

Comments:
Heterozygous expression of the sickle haemoglobin gene (Hb AS) is usually associated with a totally benign clinical course. The haematological findings are indistinguishable from normal. About 40% of their haemoglobin consists of Hb S, and under normal circumstances this is insufficient to produce sickling. Under severe hypoxic stress, vaso-occlusive complications may occur. This may occur under anaesthesia or at high altitudes. This may result in splenic infarcts and other ischaemic sequelae. Decreased renal concentrating ability is usually present in older children and adults, and occasional gross haematuria may occur. The diagnosis is confirmed by haemoglobin electrophoresis and sickle testing.

A reduction in the absolute neutrophil count is associated with:

A	HIV infection	true	✔

B	Preeclampsia in the mother	false	✘
C	Dermatomyositis	false	✔
D	Diabetic ketoacidosis	false	✔
E	Pernicious anaemia	false	✘

Comments:

Neutropenias may be transient or chronic.

Transient causes include:

- Viral or bacterial infections (including neonatal sepsis)
- Drugs
- Malnutrition
- In the neonate it may be associated with maternal hypertension.

Chronic:

- Immune related: benign childhood autoimmune, associated with primary immune disease, neonatal alloimmune (isoimmune), and neonatal/maternal autoimmune.
- Congenital: familial benign, Chediak-Higashi Syndrome, glycogen storage disease type 1b, Shwachman-Diamond Syndrome.
- Other: related to cancer or HIV infection.

A reduction in the absolute number of neutrophil leucocyte count characteristially occurs in:

A	systemic lupus erythematosus	true	✔
B	diabetic ketoacidosis	false	✔
C	Addisonian pernicious anaemia	true	✔
D	dermatomyositis	false	✔
E	*Leptospira canicola* infection	false	✔

Comments:
A reduced neutrophil count may be feature of spesis, pernicious anaemia, SLE and is frequently due to drug therapy such as carbimazole or cytotoxics.

The following are recognised complications of treatment of acute lymphoblastic leukaemia (ALL):

A	Disproportionate short stature	false	✘
B	Renal failure	true	✔
C	Haemolytic-uraemic syndrome	false	✔
D	Neuropathy	true	✔
E	Development of secondary non-Hodgkin's lymphoma	false	✘

Comments:

Chemotherapy causes a range of side effects including:

- Bone marrow suppression: anaemia, thrombocytopenia, neutropenia.
- Immunosuppression: coagulase negative Staphylococcal infection of central venous catheters, disseminated fungal infections (Aspergillosis, Candidiasis) and pneumocysitis carinii pneumonia. Measles and varicella may be life threatening, and gram negative septicaemias may present with fever at the time of neutropenia.
- GI: anorexia, nausea and vomiting, and gut mucosal damage may result in undernutrition, and increased susceptibility to gram negative infections.
- Other: alopecia, cardiotoxicity (Doxorubicin), renal failure and deafness (Cisplatin), haemorrhagic cystitis (Cyclophosphamide), neuropathy (Vincristine).

Long term problems include:

- Specific organ dysfunction, e.g. nephrectomy for Wilm's tumour, toxicity from chemotherapy.
- Growth/endocrine problems: growth hormone deficiency from pituitary irradiation, bone growth retardation at sites of irradiation. Craniospinal irradiation may result in disproportionate short stature with relatively short trunk.
- Infertility: from gonadal irradiation or alkalating agent chemotherapy such as Cyclophosphamide or Iphosphamide.
- Neuro-psychological problems: cranial irradiation particularly below the age of 5, or brain surgery for intracranial tumour may cause these. Prolonged hospitalisation may also contribute.
- Second malignancy: secondary to irradiation or alkalating agent chemotherapy.
- Social/educational disadvantage: chronic ill health and absence from school may diminish school performance.

Childhood Non-Hodgkin's Lymphoma:

A	Is usually a high grade malignancy.	false	✘
B	Can double in size in a few days.	false	✘
C	Can be complicated by tumour lysis syndrome.	true	✔
D	Can be cured in about 50% of children using current treatment strategies.	true	✘
E	Can be associated with Epstein Barr virus infection.	true	✔

Comments:
A firm distinction between solid and haematological lymphoid malignancies is somewhat artificial. Some sub-types of ALL and NHL may represent a continuum of the same disease. In most cases of NHL the clinical features and treatment reflect the immunological organ of the malignant cells involved. T cell malignancy may present either as ALL or NHL, and both are characterised by a mediastinal mass with varying degrees of bone marrow infiltration. B cell malignancies present more commonly as NHL.

There are 3 principle presentations:

- Localised (often head and neck e.g. cervical lymphadenopathy), mainly B cell, with a good prognosis.
- Intrathoracic (anterior mediastinal mass, pleural effusion), typical of T cell disease, and treated as for ALL.
- Intra-abdominal disease (bulky gut or lymph node masses), typical of advanced B cell disease, and with a relatively poor prognosis despite very intense multiagent chemotherapy.

A 10 year old West African boy presents with Hb 8g/dl and pains in his legs. Sickle cell disease is unlikely if:

A	He is jaundiced.	false	✔
B	He has gross splenomegaly.	true	✔
C	Puberty began at 12 years.	false	✘
D	His urine osmolality is 800mosmol/L, specific gravity 1022.	true	✔
E	There is a mid systolic murmur.	true	✘

Comments:

Sickle cell anaemia is characterised by severe chronic haemolytic disease resulting from premature destruction of brittle, poorly deformable erythrocytes. Other manifestations are due to ischaemia resulting from vascular occlusion by masses of sickle cells. The clinical course is typically associated with crises.

The manifestations vary considerably with age.

- Newborns: haemolytic anaemia from 2-4 months as fetal haemoglobin is replaced by Hb S, acute sickle dactylitis (hand-foot syndrome).
- Pre-school: acute painful vaso-occlusion crises, affecting extremities.
- School children: painful crises affecting head, chest, abdomen, back, the site being typical for an any individual patient. Episodes may be precipitated by intercurrent illness.
- Late changes:
    - infarction of bone marrow or bone.
    - splenic infarction between 6 and 60 months contributing to autosplenectomy.
    - pulmonary infarcts (acute chest syndrome).
    - stroke caused by cerebrovascular occlusion -/+ hemiplegia.
    - ischaemic damage to myocardium, liver and kidneys, with progressive impairment of renal function and concentrating ability.
- Spleen changes: in young children the spleen is enlarged, with occasional acute splenic sequestration. Altered splenic function increases the risk of serious infection particularly meningitis sepsis caused by pneumococci and haemophilus influenzae (polysaccharide encapsulated organisms).

As the child ages, auto splenectomy reduces spleen size. Cardiomegaly is invariably present in older children (sickle-related cardiomyopathy), secondary haemosiderosis from increased iron absorption may damage liver, pancreas and heart, and there may be gall stone formation. Puberty is frequently delayed, and chronic leg ulcers occur in late adolescence.

Thrombocytopenia occurs in

A	pulmonary haemosiderosis	true ✘
B	cavernous haemangioma	false ✘

C	scurvy	true	✘
D	infectious mononucleosis	true	✔
E	chronic alcoholism	false	✘

Comments:

A - blood picture of iron deficiency +/-eosinophilia

C - perifollicular haemorrhage due to vascular weekness and impaired platelet function

(Dr Bob Dalton)

cavernous haemangioma - platelet sequestration
chronic alcoholism - suppression of megakaryocytes
infectious mononucleosis - immune mediated

I. **See Also**
   A. **Thrombocytopenia**
II. **Signs**
   A. Bleeding disorders
   B. **Purpura** or **Petechiae**
III. **Causes: Congenital**
   A. Glanzmann's Thrombasthenia (autosomal recessive)
      1. Platelet membrane deficiency Glycoprotein IIb, IIIa
      2. Defective binding of platelet **Fibrinogen**
      3. Decreased platelet aggregation
   B. Bernard-Soulier Disease (autosomal recessive)
      1. Platelet membrane deficiency Glycoprotein Ib
      2. **Coagulation Factor** X and Factor V deficiency
      3. Large platelets and decreased platelet aggregation
   C. Storage Pool Disease
      1. Dense granule and/or alpha granule deficiency
      2. Defective platelet release of ADP and **Serotonin**
IV. **Causes: Acquired**
   A. **Uremia**
   B. **Chronic Liver Disease**
   C. Medications
      1. **Aspirin**
      2. **Furosemide (Lasix)**
      3. **Nitrofurantoin (Furadantin)**
      4. **Heparin**
      5. Sympathetic blockers
      6. Clofibrate (Atromid-S)

7. NSAIDs

The following are poor prognostic indicators in a diagnosis of acute lymphoblastic leukaemia:

A	Female sex	false	✔
B	Age less than one year or greater than ten years	true	✔
C	Presence of Philadelphia chromosome	true	✔
D	Central nervous system involvement on presentation	false	✘
E	Thymic type (T-cell) variety of the disease	false	✔

Comments:

The prognosis in ALL is related to tumour load. The single most significant indicator is the white count. At presentation, a white count >50 x 10^9/L, with bulky organomegaly and lymphadenopathy and CNS disease, particularly in boys, is associated with a poor prognosis. The occasional patient with Philadelphia chromosome also has a poor prognosis, and B cell ALL has a poorer outlook than other phenotypes.

The following are predisposing factors for iron deficiency anaemia:

A	Drinking unmodified cow's milk	true	✔
B	Prematurity	true	✔
C	Infant of diabetic mother	false	✔
D	Intake of bottle milk	false	✔
E	Excessive tea drinking	true	✔

Comments:

The predisposing factors/causes include:

- Inadequate dietary intake of iron.
- Drinking unmodified cow's milk (doorstep milk).
- Prematurity and low birth weight.
- Food stuffs and beverages which reduce iron availability including tea.

Serum ferritin:

A	Is raised in acute rheumatoid arthritis.	false	✘
B	Stores 95% of the body's iron.	true	✘
C	Is a useful measurement of iron storage in the body.	true	✔
D	Should be measured in all cases of suspected iron deficiency.	false	✔
E	Is increased in hepatoma.	false	✔

Comments:

Iron is an essential component in the structure of haemoglobin and myoglobin for oxygen and carbon dioxide transport. It is also found in oxidative enzymes, cytochrome C and catalase. It is absorbed in the ferrous form according to body need, aided by gastric juice and Vitamin C, and hindered by fibre, phytic acid, and steatorrhoea (about 90% of intake is excreted in the stool). It is transported in the plasma in the ferric state bound to transferrin, and is stored in the liver, spleen, bone marrow and kidney as ferritin and haemosiderin. It is conserved and reused with minimal losses in the urine and sweat.

In progressive iron deficiency, a sequence of biochemical and haematological events occurs:

- First: Tissue iron stores (bone marrow haemosiderin) disappear, and serum ferritin drops. Ferritin is a relatively accurate estimate of body iron stores in the absence of inflammatory disease.
- Next: Serum iron drops, and TIBC increases, and free erythrocyte protoporphyrins begin to accumulate.
- Later: Red cells become smaller, and hypochromic with a drop in MCH and MCV. There may be poikilocytosis and increased red cell distribution width. Reticulocyte count may be normal or elevated, with nucleated red cells seen on the peripheral film. There may be thrombocytosis. The bone marrow is hypercellular with erythroid hyperplasia. Following iron therapy there is replacement of intracellular iron enzymes and a subjective improvement within 24 hours. Within 48 hours there is a bone marrow response, with reticulocytosis evident from 2 days, and peaking at about 7 days. The

haemoglobin level begins to increase from day 4 to day 30, and 3 months are required for complete repletion of iron stores.

- In most cases of suspected iron deficiency a low Hb plus microcytosis with response to iron therapy obviates confirms the diagnosis, and there is no need to measure ferritin.

In febrile neutropaenia after chemotherapy:

A	Antibiotics should be withheld until there are positive antimicrobial culture results.	false	✔
B	Antifungal treatment should be started immediately.	false	✔
C	Treatment with colony stimulating factors such as G-CSF has been shown to reduce mortality.	true	✘
D	The organisms most commonly isolated from blood cultures are coagulase negative staphylococci.	true	✔
E	Empirical antibiotic treatment should be chosen to cover such organisms as Pseudomonas.	false	✘

Comments:

Children receiving chemotherapy or wide field irradiation are immunocompromised. Chemotherapy-induced neutropenia places children at risk of septicaemia. Febrile, neutropenic children must be admitted to hospital for blood cultures and broad-spectrum antibiotics.

Particular problems include:

- Pneumocystis pneumonia.
- Disseminated fungal infection (Aspergillus, candida).
- Coagulase negative Staphylococcal infection (central catheters).
- Gram negative septicaemia.
- Viral infections, particularly measles and varicella.

Prolongation of PT, TT, and APTT in a newborn may be due to:

A	Haemorrhagic disease of the newborn.	true	✘
B	DIC.	true	✔
C	Heparin in the tube.	false	✘

D	Afibrinogenaemia.	false	✘
E	Factor XIII deficiency.	true	✘

Comments:

The prothrombin time measures factors I, II, V, VII and X (extrinsic pathway), while the APTT measures factors I, II, V, VII, IX, XI and XII (intrinsic pathway). The thrombin time is a measure of fibrinogen function and concentration. Haemorrhagic disease of the newborn is due to vitamin K deficiency and hence associated with a prolonged PT. Some laboratory APTT assays are also sensitive to the vitamin K dependent clotting factors and hence the APTT may also be prolonged. Fibrinogen is normal in neonates and hence the TT should not be prolonged. DIC and heparin affect all 3 assays. Afibrinogenaemia prevents clot formation and as all 3 assays measure time to clot formation, it will affect all 3 assays. Factor XIII deficiency is associated with abnormal clot solubility and all clotting tests are normal.

Concerning sideroblastic anaemia:

A	Ring sideroblasts are seen in the peripheral blood film.	true	✘
B	Pancreatic exocrine dysfunction may occur.	false	✘
C	It is associated with a low serum iron.	false	✔
D	It may occur with antituberculous therapy.	true	✘
E	Some cases may improve with pyridoxine.	true	✔

Comments:

The sideroblastic anaemias are a heterogeneous group of hypochromic, microcytic anaemias, probably due to abnormalities of heme metabolism. Serum iron levels are raised, and ring sideroblasts are seen in the bone marrow (nucleated red cells with perinuclear haemosiderin granules that represent iron-laden mitochondria).

Sub-types include:

- Pearson Syndrome: associated exocrine pancreatic dysfunction due to deletions in mitochondrial DNA.
- X-linked recessive: associated with splenomegaly. This may be pyridoxine sensitive or pyridoxine refractory.
- Acquired: various inflammatory and malignant processes, alcoholism.

Hodgkin's Disease:

A	Is the commonest lymphoma in the childhood.	false	✔
B	Requires a laparotomy and splenectomy for complete staging.	false	✔
C	Chemotherapy results in sterility for males.	false	✘
D	Chemotherapy results in sterility for females.	false	✔
E	Can be treated with radiotherapy alone.	false	✘

Comments:
Lymphomas account for 12% of all childhood cancers in the UK, and are the third commonest overall. Non-Hodgkin's lymphomas predominate. The age incidence of Hodgkin's is bimodal, with an early peak in the late 20's and the second peak after 50 years. There may be a familial occurrence, and EBV may be implicated in pathogenesis. The cardinal histological feature is the Reed-Sternberg cell, which has 2 nuclei, and is diagnostic of Hodgkin's Disease. Sub-types include:

- Nodular sclerosing (50%).
- Mixed cellularity (40%).
- Lymphocyte predominant (10%).
- Lymphocytic depleted (rare).

Presentation is usually with painless enlargement of lymph nodes, especially cervical. These are firm, non-tender and discrete. Mediastinal lymph node is common, producing cough or other symptoms of airway compression.
Staging:

- Stage 1: Iinvolvement of a single lymph node region or of a single extra-lymphatic organ or site.
- Stage 2: Involvement of 2 or more lymphoid regions on the same side of the diaphragm, or localised involvement of an extra-lymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm.
- Stage 3: Involvement of lymph node regions on both sides of the diaphragm -/+ localised involvement of extra-lymphatic organ or site or by splenic involvement.
- Stage 4: Diffuse of disseminated involvement of one or more extralymphatic organs or tissues -/+ associated lymph node enlargement.

Stages are further categorised as A or B based on the absence or presence respectively of systemic symptoms of fever -/+ weight loss. Both radiation and chemotherapy are highly effective. With modern treatment more than 90% of patients achieve an initial complete remission. Pelvic irradiation can cause sterility despite ovarian and testicular shielding. Second malignant tumours occur in about 10% of cases.

Regarding iron deficiency anaemia:

A	The commonest cause in children is chronic blood loss.	false	✔
B	It does not affect school progress.	false	✔
C	It commonly co-exists with thalassaemia.	false	✔
D	Cow's milk is a major source of iron for children.	true	✘
E	Lead poisoning is commonly associated with iron deficiency.	true	✔

Comments:

Iron is absorbed in the proximal small intestine, mediated partly by the duodenal protein mobilferrin. About 10% of dietary iron is absorbed, and iron is absorbed 2-3 times more efficiently from human milk than from modified cow's milk. During the first years of life, because relatively small quantities of iron-rich foods are taken, it is often difficult to attain sufficiency iron. The diet should include foods such as infant cereals or formulae that have been fortified with iron. Breast fed infants should receive iron supplements from 4 months of age. At best, the infant is in a precarious situation with respect to iron. Should the diet become inadequate, or external blood loss occur, anaemia ensues rapidly. In children with microcytic anaemia who fail to respond to iron, thalassaemia should be considered.

In this country there is an increased incidence in those from the Mediterranean and those from the Indian sub-continent. Because many such children are socio-economically disadvantaged, there may be an associated iron deficiency anaemia. Lead poisoning in this country is usually associated with eating lead paint. Since pica is associated with iron deficiency, the two often co-exist.

The following blood tests are routine in all areas of the UK:

A	Hepatitis B	false	✔
B	Maternal ABO and Rhesus blood group	true	✔
C	Rubella	false	✘
D	Alphafeta protein	false	✘
E	HIV titres	false	✔

Comments:

Blood group and antibodies for Rhesus and other red cell incompatibilities are routine as is rubella, and in may places syphilis testing. Hepatitis B testing is selective usually involving those from the Far East (China). HIV titres should only be taken after counselling and maternal consent, and is usually restricted to areas of increased prevalence such as Metropolitan London. Testing for neural tube defects using maternal alphafeta protein is routine in the UK. It is elevated in 80% of open neural tube defects and more than 90% of cases of anencephaly. Ultrasound also assists in the diagnosis of these conditions. Testing for Down's Syndrome involves obtaining maternal consent. A risk estimate can be calculated from a lowering of the maternal alphafeta protein together with measuring HCG and unconjugated oestrial (triple test), adjusted for maternal age. If the risk is high, amniocentesis and fetal chromosome analysis is offered.

The following are recognised features of sickle cell disease:

A	Dactylitis	true	✔
B	Frontal bossing of the skull	false	✘
C	Abdominal pain	true	✔
D	Chronic leg ulceration	false	✘
E	Anaemia from birth	false	✔

Comments:
Sickle cell anaemia is characterised by severe chronic haemolytic disease resulting from premature destruction of brittle, poorly deformable erythrocytes. Other manifestations are due to ischaemia resulting from vascular occlusion by masses of sickle cells. The clinical course is typically associated with crises. The manifestations vary considerably with age.

- Newborns: haemolytic anaemia from 2-4 months as fetal haemoglobin is replaced by Hb S, acute sickle dactylitis (hand-foot syndrome).
- Pre-school: acute painful vaso-occlusion crises, affecting extremities.
- School children: painful crises affecting head, chest, abdomen, back, the site being typical for an any individual patient. Episodes may be precipitated by intercurrent illness.
- Late changes:
  - infarction of bone marrow or bone.
  - splenic infarction between 6 and 60 months contributing to autosplenectomy.
  - pulmonary infarcts (acute chest syndrome).
  - stroke caused by cerebrovascular occlusion -/+ hemiplegia.

- ischaemic damage to myocardium, liver and kidneys, with progressive impairment of renal function and concentrating ability.

- Spleen changes: in young children the spleen is enlarged, with occasional acute splenic sequestration. Altered splenic function increases the risk of serious infection particularly meningitis sepsis caused by pneumococci and haemophilus influenzae (polysaccharide encapsulated organisms). As the child ages, auto splenectomy reduces spleen size.

Cardiomegaly is invariably present in older children (sickle-related cardiomyopathy), secondary haemosiderosis from increased iron absorption may damage liver, pancreas and heart, and there may be gall stone formation. Puberty is frequently delayed, and chronic leg ulcers occur in late adolescence.

Concerning Hodgkin's Disease:

A	Is diagnosed by finding Reed-Sternberg cells in biopsy specimens.	true	✔
B	Prognosis is poorer when nodular sclerosis is present.	false	✔
C	Impaired cellular immunity is present.	true	✔
D	It is associated with bone pain.	false	✘
E	It is associated with autoimmune haemolytic anaemia.	true	✔

Comments:
The age incidence of Hodgkin's Disease is bimodal, with an early peak in the 20's and a second peak after the age of 50. EBV may be implicated in pathogenesis. The cardinal histological feature is the Reed-Sternberg cell. Sub-types include: nodular sclerosing (50%), mixed cellularity (40%), lymphocyte predominant (5%), lymphocyte depleted (<10%). The commonest presentation is painless enlargement of cervical or supraclavicular lymph nodes. Nodes are firm, non-tender and discrete. Mediastinal lymph node enlargement is common, and 33% have non-specific symptoms such as fatigue, pruritis, urticaria, pain that worsens with ingestion of alcohol, lethargy, and anorexia. Unexplained fever, weight loss of at least 10% in the last 6 months, night sweats are systemic symptoms useful in staging. Rare presentations include biliary obstruction, bone marrow involvement (pancytopenia), spinal cord compression, and immune diseases such as autoimmune haemolytic anaemia, thrombocytopenia or nephrotic syndrome. Cellular immunity is impaired. Staging is important in prognostication. Treatment involves radiation and chemotherapy, and is highly effective.

Pulmonary eosinophilia is a recognised feature of:

A	Churg-Strauss Syndrome	true	✔
B	Allergic bronchopulmonary aspergillosis	true	✔
C	Malaria	false	✔
D	Hodgkin's lymphoma	true	✘
E	Polyarteritis nodosa	false	✘

Comments:

Loeffler's Syndrome is characterised by widespread transitory pulmonary infiltrations which may resemble miliary TB, and by a blood eosinophil level as high as 70%. There is usually paroxysmal cough, breathlessness, pleurisy, and little or no fever. There may be hepatosplenomegaly especially in infants, and local pneumonic consolidation may occur.

Possible underlying causes include:

- Drugs (antibiotics, crack cocaine).
- Helminthic infections: toxocara, ascaris, and strongyloides.

The differential diagnosis includes:

- Vasculidities (eosinophilic pneumonia plus polyarteritis).
- Asthma, including allergic bronchopulmonary aspergillosis.
- Filaraisis.
- Chronic eosinophilic pneumonia.

Retinoblastoma:

A	Occurs sporadically and in a familial form.	true	✔
B	Does not respond to chemotherapy or radiotherapy.	false	✔
C	Can occur as a primary tumour in the pineal gland.	false	✘
D	Can be inherited as an autosomal dominant condition with variable penetrance.	false	✘
E	Is fatal in 50% of cases in the U.K. using current treatment protocols.	false	✔

Comments:
Retinoblastoma is the commonest primary malignant intraoccular tumour of childhood occurring in 1 in 18,000 infants. Both hereditary and non-hereditary patterns occur. It is bilateral in 30%. Clinical manifestations include:

- Leukcoria: white pupillary reflex.
- Strabismus.
- Other: pseudohypopyon (tumour cells layered inferiorly in front of the iris), hyphema (blood lead in front of the iris), vitreous haemorrhage, or signs of orbital cellulitis.

The retinoblastoma gene is a recessive suppressor gene located on chromosome 13. Most tumours confined to the eye can be cured by resection. Prognosis is poor when optic nerve extension has occurred.

In polycythaemia rubra vera there may be:

A	Pruritis due to deposition of bilirubin.	false	✔
B	Increased total red cell volume.	true	✔
C	Evolution to acute leukaemia.	true	✔
D	Reduced plasma volume which contributes to the increased haemocrit.	false	✔
E	Arthropathy as a recognised complication.	true	✘

Comments:

Polycythemia rubra vera is a myeloproliferative disorder in which erythroid precursors of affected people do not require erythropoietin to stimulate growth.

Diagnostic criteria are:

- Increased total red blood cell volume.
- Arterial oxygen saturation greater than or equal to 92% (to distinguish from secondary polycythemia).
- Splenomegaly.
- There may be thrombocytosis, leukocytosis and increased leukocyte alkaline phosphotase.

Treatment includes phlebotomy -/+ antiproliferative chemotherapy.
Complications:

- Bleeding

- Thrombosis
- Malignant transformation: myelofibrosis, acute leukaemia

Prolonged survival is not unusual.

Hyperuricaemia may be a feature of:

A	Down's Syndrome.	true	✔
B	Aspirin therapy.	true	✔
C	Diabetic ketoacidosis.	false	✘
D	Chemotherapy for ALL.	false	✘
E	Cystinosis.	true	✘

Comments:
Hyperuricaemia may result from:

- Marked increases in cell number or cell destruction as in myeloproliferative disease or ALL treatment.
- Decreased renal clearance, as in salicylate therapy or Down's Syndrome.
- Raised ketone body levels, as in starvation or diabetic ketoacidosis. Prehydration is therefore used to prevent tumour lysis syndrome in the acute treatment of ALL, because of the anticipated load of uric acid from massive tumour cell destruction.

Regarding blood indices:

A	The haemoglobin concentration of a 3 month old boy is higher than a 13 year old boy.	true	✘
B	The mean corpuscular haemoglobin is low in megaloblastic anaemias.	false	✔
C	The mean corpuscular haemoglobin concentration is low in megaloblastic anaemias.	true	✘
D	The reticulocyte count increases with each year of life.	false	✔
E	Reticulocytes are similar in size to mature red blood cells.	false	✔

Comments:

The haemoglobin at birth ranges from 13.7 - 21.1g/dl, falling to 13.0 - 20g/dl at 2 weeks of age, and to between 9.5 and 14.5g/dl at 3 months. From there it rises gradually, with normal ranges between 6 months and 6 years being 10.5 - 14.0g/dl, and between 7 and 12 years being 11.0 - 16.0g/dl. Adult normal ranges for females are 12.0 - 16.0g/dl, and for males 14.0 - 18.0g/dl. The mean cell haemoglobin (MCH) is the haemoglobin divided by the red cell count. In health, this is usually between 27 and 32pg.

Any disorder which reduces red cell size reduces the amount of haemoglobin in the cell, and lowers the MCH. Likewise, disorders increasing cell size raise the value. Means corpuscular haemoglobin concentration (MCHC) equals the haemoglobin divided by the haematocrit. The normal range is 30 - 35g/dl. The MCHC is thus not the number of grams of haemoglobin in 1dl of blood, but in 1dl of pure red cells without plasma. A low MCHC is usually due to iron deficiency. The reticulocyte count in cord blood is 5%, paralleling the change from Hb F to Hb A. From 2 weeks of age it drops to 1%, and remains at this level until adulthood. Once menses start, females have a slightly higher reticulocyte count of around 1.6%. Reticulocytes are slightly larger than mature red cells because of the little remaining nuclear material.

Acute lymphoblastic leukaemia may present in the following ways:

A	Poor weight gain	true ✔
B	Haematuria	false ✘
C	Abdominal pain	true ✔
D	Chest pain	false ✘
E	Sore throat	true ✔

Comments:

Clinical presentation of ALL results from infiltration of the bone marrow or other organs with leukaemic blast cells.

They include:

- General: malaise, anorexia, lethargy.
- Bone marrow infiltration:
  - Anaemia: pallor, lethargy.
  - Neutropenia: infections.
  - Thrombocytopenia: bruising, petechiae, nose bleeds.
  - In addition, bone pain may be caused by bone marrow infiltration and may

affect anywhere in the body.

- Reticular endothelial infiltration: hepatosplenomegaly, lymphadenopathy, superior mediastinal obstruction (uncommon).
- Other organ infiltration:
  - CNS: headaches, vomiting, convulsions, nerve palsies.
  - Testes: testicular enlargement.

A 17 year old Nigerian presents with moderately enlarged spleen, haemoglobin of 7.2 g/dL, a red cell count of 3.5 x 10^{12}/L, and a reticulocyte count of 7%. The following statements are correct:

A	Recent chloramphenicol administration would be of diagnostic significance	false	✔
B	If the Coombs' test was positive, paroxysmal nocturnal haemoglobinuria is possible diagnosis	false	✔
C	Homozygous thalassaemia is possible diagnosis	false	✘
D	If Heinz bodies are present, red cell glucose 6-phosphate dehydrogenase deficiency is likely diagnosis	false	✘
E	homozygous sickle cell disease is likely diagnosis.	true	✘

Comments:
b-thalassaemia major (homozygous) thalassaemia is possible diagnosis. Splenic atrophy from splenic infarcts occurs in sickle cell disease. Chloramphenicol may cause aplastic anaemia - there will be no reticulocyte response. Heinz bodies are oxidized denatured haemoglobin. During crisis of G6PD deficiency, blood film also shows contracted and fragmented cells due to oxidant stress. PNH is not an autoimmune haemolytic anaemia, hence Coombs test is negative. It is a rare acquired defect of red cell membrane making it susceptible to lysis by complement.

Features which may be seen on the blood film of a patient with haemolysis include:

A	Polychromasia	true	✔
B	Howell Jolly bodies	true	✔
C	Elliptocytes	true	✔
D	Target cells	true	✔

E	Heinz bodies	true	✔

Comments:
The following are common abnormalities of red cell morphology:

- Polychromasia: younger cells have a bluish tinge (basophilia), and are larger than average, and may contain residual nuclear material (reticulocytes). The presence of many basophilic forms in a blood film produces a multicoloured effect known as polychromasia.
- Microcytosis indicates small red cells, anisocytosis variation in size, and macrocytosis a large size. Poikilocytosis indicates altered shape.
- Spherocytes may indicate hereditary spherocytosis, and may also be found in acquired haemolytic anaemias, while elliptocytes are found in hereditary elliptocytosis.
- Schistocytes are fragments of red cells, as seen in DIC or haemolytic uraemic syndrome.
- In splenic dysfunction: target cells and red cells containing nuclear fragments known as Howell Jolly bodies are seen. Pappenheimer bodies are iron containing inclusions, and when seen together with Howell Jolly bodies suggest previous splenectomy or reduced splenic function.
- Heinz bodies: are denatured haemoglobin which result from deficiencies of enzymes of the penthose phosphate pathway. This damages the red cell leading to haemolysis and removal of them by the spleen.

Regarding glucose-6-phosphate dehydrogenase:

A	It is an important enzyme in the kreb cycle.	false	✔
B	Deficiency is associated with an increased susceptibility to falciparum malaria infection.	false	✔
C	Deficiency may be associated with chronic haemolytic anaemia.	false	✘
D	Deficiency is inherited as an autosomal dominant.	false	✔
E	Deficiency may be associated with primiquine-induced haemolysis.	false	✘

Comments:

Glucose-6-phosphase dehydrognease (G-6-PD) is one of the enzymes in the pentose phosphate pathway (Hexose Monophosphate Shunt). The most important function of this pathway is to maintain glutathione in a reduced state as protection against oxidation of the red cell. Deficiency is X-linked, and extremely common, affecting more than 200 million people. Heterozygous females have increased resistance to

falciparum malaria, outweighing the small negative effect on hemizygous males.

Major symptoms include:

- Episodic or induced haemolytic anaemia: there is considerable variation in the defect among different racial groups, with Mediterranean whites affected more severely than Africans. Haemolysis may be precipitated by:
    1. Drugs: Antibacterials: sulfonamides, septrin, nalidixic acid, chloramphenicol, nitrofurantoin. Antimalarials: primaquine, chloroquine, quinacrine. Others: Vitamin K, methylene blue, Aspirin.
    2. Chemicals: Phenylhydrazine, benzene, naphthalene.
    3. Illness: Diabetic ketoacidosis (DKA), hepatitis.
- Chronic haemolytic anaemia: chronic non-spherocytic haemolytic anaemia is associated with profound deficiency of G-6-PD. Splenectomy is of little value in these types.

The following are recognised acute or chronic side effects of the cytotoxic drugs listed:

A	Doxorubicin - cardiomyopathy	true ✔
B	Ifosfamide - renal tubular damage	true ✔
C	Cisplatin - deafness	true ✔
D	Cyclophosphamide - haemorrhagic cystitis	true ✔
E	Vincristine - neuropathy	true ✔

Comments:
Side effects of chemotherapy may be general or specific.

GENERAL:

- Bone marrow suppression: anaemia, thrombocytopenia, neutropenia, immunosuppression, infection.
- GI upsets: anorexia, nausea, vomiting, gut mucosal damage. Undernutrition.
- Other: alopecia.

SPECIFIC:

- Doxorubicin - cardiotoxicity. · Cisplatin - renal failure and deafness.

- Cyclophosphamide - haemorrhagic cystitis.
- Vincristine - neuropathy.

Chronic intravascular haemolysis is associated with:

A	Splenomegaly.	true	✔
B	Haemosiderinuria.	true	✔
C	Increased incidence of gallstones..	true	✔
D	Reduced transferrin levels.	true	✘
E	Increased serum haptoglobins.	true	✘

Comments:

Haemolysis is defined as the premature destruction of red cells. If the rate of destruction exceeds the capacity of the marrow to produce red cells then anaemia results. The normal red cell survival is 120 days, and 1% of red cells are removed per day and replaced by the marrow. During haemolysis, the red cell survival is shortened, and there is increased marrow activity (raised reticulocyte count). Marrow output can increase 2-3 fold acutely, and 6-8 fold in long-standing cases. In chronic haemolytic anaemia, erythroid hyperplasia may be so extensive that the medullary spaces may expand at the expense of cortical bones (particularly skull and long bones). Intravascular haemolysis increases circulating haemoglobin which binds to haptoglobin reducing the circulating levels of it. There is an increase in urine haemoglobin and haemosiderin. Increased bilirubin production from heme results in increased faecal urobilinogin, which is reabsorbed and excreted in the urine.

The following drugs should be avoided in all patients with glucose-6-phosphate dehydrogenase deficiency:

A	Quinine	true	✘

B	Nitrofurantoin	true	✔
C	Sulphapyridine	true	✔
D	Chloramphenicol	true	✔
E	Chloral hydrate	false	✔

Comments:

In glucose-6-phosphate-dehydrogenase deficiency (G-6-PD) subjects are susceptible to developing acute haemolytic anaemia on taking a number of common drugs. Ingestion of fava beans may result in haemolysis in severe cases, or when they are eaten raw. G-6-PD is genetically heterogeneous. The risk from drugs therefore varies from patient to patient. There is no test available to identify potential risk in G-6-PD deficiency. The risk of severity of haemolysis is almost always dose related.

Drugs with a definite risk in most G-6-PD deficient subjects include:

- Sulphonamides and Dapsone.
- Methylene blue
- Nitrofurantoin
- Primiquine
- Quinilones (including Ciprafloxacin, Nalidixic acid)

Disseminated intravascular coagulation:

A	The diagnosis may be suggested by falling platelet count.	true	✔
B	May be diagnosed by rising fibrin degradation products (FDP).	false	✘
C	Can be treated with fresh frozen plasma.	true	✔
D	Should be treated with heparin.	false	✔
E	Is associated with sepsis.	true	✔

Comments:
Acute disseminated intravascular coagulation (DIC) causes bruising and bleeding in severely ill children. A more chronic form may present with low platelets, reduced fibrinogen, and only mild bleeding. Treatment relies on correcting the underlying cause while providing intensive care. Supportive care may be provided using FFP to replace clotting factors, and platelets. Therapy with heparin and antithrombin-3 remains controversial.

The following diseases are inherited in a sex-linked recessive manner:

A	Idiopathic thrombocytopenia	(False)
B	Haemophilia	(True)
C	Christmas disease	(True)
D	Von Willebrand's disease	(False)
E	Hereditary spherocytosis	(False)

Comments:
Idiopathic thrombocytopenia is not a genetic disorder. Haemophillia A and B (Christmas Disease) have both sex linked transmission. Von Willebrand's disease is mostly inherited in a dominant fashion, but recent case reports suggest some forms of the disease are autosomal recessive. HS is autosomal dominant.

The following are true statements about a man with haemophilia type A:

A	His mother is always a carrier	(False)
B	All his daughters are carriers	(True)
C	All his sons are normal	(True)
D	Haemarthroses are common	(True)
E	If his sister has an affected boy she must be a carrier	(True)

Comments:
Both his parents may have been unaffected/non-carrier and the disease occurs as a result of a spontaneous mutation. His daughters will inherit the abnormal gene from their father and be carriers and his sons will be unaffected. Haemarthroses are a common clinical feature. If his sister has an affected son and a brother with the condition, the disease is inherited and she must be a carrier.

A low platelet count in the newborn period occurs in babies:

A	Of mothers with idiopathic thrombocytopenic purpura	(True)
B	Suffering ABO compatibility	(False)

C	With congenital rubella	(True)
D	Of mothers given Chlorthiazide during pregnancy	(True)
E	With a large caput	(False)

Comments:
Transplacental passage of maternal anti platelet antibodies may occur in mothers with ITP. Maternal infection with TORCH organisms (Toxoplasmosis, CMV, Rubella and Herpes) can lead to severe thrombocytopenia. ABO incompatility leads to haemolysis in utero and hydrops fetalis, but not thrombocytopenia. Maternal drugs such as chlorothiazide and sulphonamides may cause thrombocytopenia in the newborn. Other causes include prematurity and sepsis. Caput is not a cause of thrombocytopenia.