Chronic Lymphocytic Leukaemia 4.02

Detailed History of Presenting Illness – Leukaemia in general

**HPI:**
- Fatigue
- Weakness
- Malaise
- Fever
- Night sweats
- Weight loss
- Jaundice
- Lymphadenopathy
- Bone pain
- Excessive bruising
- Abdominal pain/swelling/"fullness"

**PI:**
- Frequent Infections
- Past Radio/Chemotherapy
- Past Cancers

**Family/Social:**
- Leukaemia
- Smoking
- Alcohol

**CURRENT MEDICATIONS**

!! IMPORTANT: get IMMUNISATION history !!

Differential Diagnoses (DDx)
- Chronic Infection
- Non-leukaemia cancer
- Hypersplenism
- Paraneoplastic GM-CSF production
- Lymphoma
- Anaemia
- Depression

**Patient’s AGE speaks volumes:**
- The YOUNG get ALL
- The OLD get CLL + AML
- Everyone gets everything else

Pertinent findings on Examination – Leukaemia in General

**Any Leukaemia**
- Pallor or Jaundice
- **splenomegaly**
- **hepatomegaly**
- abdominal swelling.
- **Lymphadenopathy**

**Advanced: Mets ➔ Brain**
- central nervous system effects:
  - headaches
  - seizures
  - weakness
  - blurred vision
  - balance difficulties
  - vomiting

**AML Only**
- swollen, painful, and bleeding gums - mets to the oral tissue;
- pigmented (colored) rash-like spots - mets to the skin; or
- **chloromas** (granulocytic sarcomas; collections of tumorous cells within the skin or other body parts)
- ecchymoses, epistaxis, or menorrhagia

**The T-cell variety of (ALL) may cause**
the thymus to enlarge and press on the trachea
or the superior vena cava.
Tests and Investigations: Making sense of weird blood counts

FBC:
1. Look carefully. What's different? Are the...
   - WBCs Absurdly high? WHICH KIND?
   - Is there a cytopenia? Which cells are missing?

   High WBC is NOT DIAGNOSTIC

BLOOD FILM: SHOULD ALWAYS FOLLOW A SUSPICIOUS FBC
2. If the FBC is bizzarre, what do the cells look like?

   !LOOK FOR TYPICAL CELL MORPHOLOGIES!
   - Eg: BLAST CELLS DON'T BELONG IN PERIPHERAL BLOOD
   - Then order BM biopsy, as the peripheral blood is often an inaccurate reflection of what is going on

   A few stray smudge cells are NOT DIAGNOSTIC

Bone Marrow Biopsy:
3. Looking for the extent of infiltration;
   - Key word: “HOMOGENOUS HYPERCELLULARITY”
   - ASPIRATE: sucking a sample of bone marrow through a needle
   - TREPHINE: drilling a core sample of the bone marrow
   - Architecture is preserved: best for overview

   Looking for: Fat Spaces Replaced by Homogenous Cells
   - Rough Guide: 20% of cells have to be neoplastic before you call it LEUCAEMIA (and if they are)

   A marked bone marrow infiltration by an unrecognisable clone of homogenous uniform-looking cells is OBJECTIVELY DIAGNOSTIC

Lymph Node Biopsy: relevant if there is lymphadenopathy
   - BUT no bone marrow involvement (which makes one think of lymphoma)
   - Both LN and BM biopsies should be performed if lymphadenopathy is present

Immunophenotyping, Immunocytochemistry, Antigen-Expression Cytometry
4. - Is the classification of cell types according to their immunologic characteristics.
   - Keyword: “MONOCLONAL PROLIFERATION”
   - Using CD markers it is possible to track down the origin of the rogue cells to a particular known subvariety of neoplasm

   How? use PCR to look at Immunoglobulin and receptor proteins then look at PCR bands.
   - Monoclonal = one band for whole population
   - Normal (polyclonal) = smeared wide band, reflecting a variety of phenotypes

   !! BUT! ➔ MONOCLONAL does NOT mean MALIGNANT!
   - Studies refer to “transient monoclonal lymphocytosis”, talking about the over 65 year olds
   - “Watchful waiting” ensues if the number of monoclonal cells is below a threshold; for B-CLL a lymphocyte count of 10,000/mm³ was once required but today we are happy with 5000/mm³

Serum Biochemistry, LFTs, Urinalysis, UAC, etc ➔ Accessory studies
   - Major role: looking for haemolysis, liver and renal function
   - (13% of CLL gets autoimmune hemolytic anaemia ➔ !! COOMBS TESTS !!)
   - Urine cultures also looking for INFECTION which is waiting to go out of control

X-rays and Tomography
   - Imaging to see if there are
   - Enlarged lymph nodes in the chest,
   - A localized mass in the lungs,
   - Or evidence of spread to the outer bones or joints.
   - USEFUL FOR STAGING

Imaging with Radionuclides
   - If malignancy is a certainty, radionuclide studies help determine the extent of metastasis by marking tumour cells with a radioactive marker, thus singling out sites of abnormal hemopoiesis and metastatic involvement. SHOWS RADIATION ONCOLOGISTS+THERAPISTS WHAT TO SHOOT.
**How is this diagnosis made?** Clinical Pictures, painted by blood and marrow tests

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
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<tbody>
<tr>
<td>- Rapid onset symptoms</td>
<td>- Slow + progressive</td>
</tr>
<tr>
<td>- Severe marrow failure</td>
<td>- Anaemia/cytopenia precedes by years</td>
</tr>
<tr>
<td>- (pancytopenia)</td>
<td>- Marrow failure may never occur</td>
</tr>
<tr>
<td>Myeloid</td>
<td>Lymphoid</td>
</tr>
<tr>
<td>- Granulomycytosis</td>
<td>- Lymphocytosis</td>
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</tbody>
</table>

**Acute Myeloid Leukaemia:** most common leukemia in children less than 1 year of age. Second peak of incidence occurs among adults 40 years of age. Most common acute L. of adults.!!

- Enlarged spleen is seen in 50% of all AML
- BUT lymphadenopathy is Rare

Here are very large, immature myeloblasts with many nucleoli. A distinctive feature of these blasts is a linear purple "Auer rod" (arrow) composed of crystallized granules. These findings are typical for acute myelogenous leukemia (AML) that is most prevalent in young adults.

At high power, the bone marrow of a patient with acute myelogenous leukemia is seen here. There is one lone megakaryocyte at the right center.

Myeloblasts of AML have
- Little cytoplasm
- MASSIVE nuclei with prominent nucleoli
- Dispersed nuclear chromatin

**Acute Lymphoblastic Leukaemia** usually strikes children between the ages of 2 to 10. A second peak in incidence is seen in elderly patients

**FBC:**
- Total WCC usually high but May be low (“aleukaemic leukemia”)
- blast cells on film
- Hb and platelets often low
- clotting may be deranged.

**Bone marrow (BM)** heavily infiltrated with blasts-immunophenotyping and karyotyping is needed on blood and marrow.

Chest x-ray and CT needed if B or T cell phenotype for abdominal or mediastinal lymph nodes respectively.

(above: lymphoblasts of ALL; almost no cytoplasm)

The marrow between the pink bone trabeculae seen here is nearly 100% cellular, and it consists of leukemic cells of acute lymphocytic leukemia (ALL) that have virtually replaced or suppressed normal hematopoiesis.

Auer rods are elongated, bluish-red rods composed of fused lysosomal granules. **Seen an AUER ROD → its AML FOR SURE.**
Chronic Myelogenous Leukaemia  
**Peak Incidence at ages 30 to 50 years old**

- FBC: Increased WCC  
  (mainly neutrophils and myelocytes plus excess basophils and eosinophils)
- Platelets may be raised and clumped.
- ESR low in absence of secondary infection.
- LDH and urate levels increased.
- **BM- gross hypercellularity**

A peripheral blood smear in a patient with CML. Often, the numbers of basophils and eosinophils, as well as bands and more immature myeloid cells (metamyelocytes and myelocytes) are increased. Unlike AML, there are not many blasts with CML. There are numerous granulocytic forms seen here, including immature myeloid cells and band neutrophils. A useful test to help distinguish this disease is the leukocyte alkaline phosphatase (LAP) score, which should be low with CML and high with a leukemoid reaction to infection.

Chronic Lymphocytic Leukaemia is the most common type of leukemia usually occurs in older patients; it is rare in patients less than 40 years of age.

- **FBC: Lymphocytosis > 5 x 10⁹ /L with mature appearance**  
  - 90% of the time its B-cell dominant
  - (a % of cells more friable leads to smear cells - a mutation of actin and spectrin)
  - anaemia, thrombocytopenia + neutropenia usually absent in early stage CLL;
  - autoimmune haemolysis +/- thrombocytopenia can occur at any stage.
- **Bone Marrow**: lymphocytosis >25% with characteristic immunophenotypic marker pattern.
- **Trephine biopsy - infiltration prognostically informative**: nodular (favourable) or diffuse (unfavourable)

**Chronic phase** (Mild, indolent course)
1. Excessive Granulocyte (Neutrophils) proliferation

**Blastic phase** (Malignant, leukemic course)
2. Increased blasts and Promyelocytes

**Below:** These mature lymphocytes are increased markedly in number.

**Below:** A smear (“smudge”) cell at high mag

**Below:** Smudge cells

**Below:** Nodular infiltration (low mag)

**Below:** Diffuse infiltration
**PROGRESSION of CLL = NEWLY DISCOVERED MOST COMMONLY DETECTED ON ROUTINE BLOOD TEST**

- organomegaly,
- pancytopenia,
- anaemia,
- lymphadenopathy

**ASSORTED HEMATOLOGICAL NEOPLASTIC CONDITIONS:**

**Large granular lymphocyte leukaemia:**
HB and platelets normal,
mild anaemia may be present.
Mild - mod lymphocytosis with large cells (abundant cytoplasm and distinct granules)

**Hairy cell leukaemia:**
Hairy cells are characterized by their fine, irregular pseudopods and immature nuclear features. They are seen only in hairy cell leukemia.

**Non Hodgkins lymphoma**
Normocytic normochromic anaemia common,
leucoerythroblastic film with BM infiltration +/- pancytopenia.

**Hodgkins:**
Painless supradiaphragmatic lymph node enlargement,
FBC may be normocytic, normochromic anaemia,
reactive leucocytosis, eosinophilia and/or reactive mild thrombocytosis.

**Reed-Sternberg cells:** PATHOGNOMIC for H’s L

<table>
<thead>
<tr>
<th>DIFFERENCE BETWEEN HODGKINS AND NON-HODGKINS</th>
</tr>
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<tbody>
<tr>
<td><strong>Hodgkins= T cell</strong></td>
</tr>
<tr>
<td>Localised process</td>
</tr>
<tr>
<td>Neoplastic cells &lt;1% of mass</td>
</tr>
<tr>
<td>Most of mass = inflammatory</td>
</tr>
<tr>
<td>exudate stimulated by cytokines</td>
</tr>
<tr>
<td>significant narrow involvement</td>
</tr>
<tr>
<td>prone to viral infection (+myco, fungal, protozoan)</td>
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**summary of abnormalities that can be seen in FBCs and blood films**

**Recovering bone marrow** following chemotherapy: patient may show symptoms of a viral infection etc, low WCC, myelocytes and metamyelocytes, normal RBC and platelets.

**Reactive Film or Features:** features suggesting that the observed changes are secondary to an external process and not due to a primary haematological disorder. Includes 9eft shift, reactive lymphocytes, toxic features

**Left Shift** - presence of immature neutrophil precursors. A "mild" left shift with the presence of "band or stab" forms and occasional myelocytes, often accompanied by toxic granulation, is a common consequence of sepsis. A more pronounced left shift, eg with promyelocytes and/or blasts are more likely to denote a leucoerythroblastic blood film or leukaemia.

**Toxic Changes** - characteristic of bacterial infection. Can include the following; heavy dark staining granules (=toxic granulation), vacuolation, Dohle bodies (cytoplasmic RNA)

**Megaloblastic Film or Features** - the presence of larger red (macrocytosis) and white cells. The neutrophils may demonstrate nuclear hypersegmentation (right shift)

**Reactive Lymphocytes** - atypical cellular forms classically seen in viral infections (eg EBV). Distinguish from lymphoblasts.

**Leukaemoid Reaction** - reactive and excessive leucocytosis usually characterised by the presence of immature cells (blasts, promyelocytes, myelocytes) in the peripheral blood. Associated disorders - chronic infections, severe haemolysis and metastatic cancers. Needs to be distinguished from true leukaemia

**Pancytopenia** - anaemia, leucopenia and thrombocytopenia.

**Blasts/Blast Cells** - the most primitive recognisable haemopoietic precursor cell recognisable by light microscopy. Typically have large nuclei with little cytoplasm (high nuclear:cytoplasmic ratio) and nucleoli - Myeloblasts/Monoblasts/Lymphoblasts

**Leucoerythroblastic Film or Feature** - the constellation of features that suggests marrow infiltration or replacement. Defined as the presence of immature white cells, immature (nucleated) red cells and Poikilocytosis characterised by fragmented cells and tear drop forms. Megakaryocyte fragment may also be present and there are often 1-3 cytoplasias. (see myeloproliferative film)
Circulating Plasma Cells - rarely seen in normals. Present in plasma cell leukaemia (>2x10^9/l) and to a lesser extent myeloma and other lymphoproliferative diseases. Also occasionally seen in reactive states.

Circulating Lymphoma Cells - abnormal lymphoid cells seen in the blood of patients with lymphoproliferative diseases (also called "blood spill")

Smear/Smudge Cells - characteristic of chronic lymphocytic leukaemia. Bare and smeared nuclei that have been damaged in the process of film spreading.

Myeloproliferative Film or Features - those that suggest the presence of an underlying (chronic) myeloproliferative disease or disorder. May include: thrombocytosis, and large platelets, neutrophilia and left shift in neutrophil lineage, eosinophilia, basophilia, and red cell changes such as tear drop poikilocytes and circulating nucleated red blood cells. Frequently have leucocrythroblastic characters.

### Staging:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absolute lymphocytosis &gt;15x10^9</td>
</tr>
<tr>
<td>I</td>
<td>0 + enlarged lymph nodes (adenopathy)</td>
</tr>
</tbody>
</table>
| II    | 0 + enlarged liver and/or spleen  
|       | + adenopathy |
| III   | 0 + anaemia  
|       | + adenopathy  
|       | + organomegaly |
| IV    | 0 + thrombocytopenia (platelets <100x10^9/l)  
|       | + adenopathy  
|       | + organomegaly |

### Disease Definition of CLL:
neoplasm of monoclonal B cells

### Management of CLL:

Contrary to popular belief, MOST ILLNESSES HAVE NO CURE.

→ **NO CURE:** same lifespan, treatment or not

<table>
<thead>
<tr>
<th>CURABLE</th>
<th>INCURABLE</th>
</tr>
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<tbody>
<tr>
<td>AML + ALL</td>
<td>CLL</td>
</tr>
<tr>
<td>CML</td>
<td>Indolent non Hodgkins lymphoma (sometimes called low grade)</td>
</tr>
<tr>
<td>Large cell non Hodgkins lymphoma</td>
<td>Hodgkins lymphoma</td>
</tr>
</tbody>
</table>

**CURABLE:**
Means that
- intensive chemo IMMEDIATELY FOLLOWING DIAGNOSIS has positive effect  
  (while the patient is still healthy and the cells are not resistant)

**INCURABLE:**
FOR THE INCURABLES, intensive chemo means a slightly longer remission  
BUT!! Recurring disease will be MORE AGGRESSIVE

Thus, patients will still die at the same rate no matter the treatment:

**THEREFORE** : give
- single chemo drugs orally to control symptoms  
- radiation to affected sites  
- watchful waiting

EVENTUALLY the disease will become resistant to this half-assed treatment and thus AGGRESSIVE CHEMO WILL BECOME NECESSARY IN THE END.
CHEMOTHERAPY:
If it's being administered to CLL, its
- Usually **ORAL**
- Usually **ALKYLATING AGENTS**:
  Disrupt DNA synthesis by covalently bonding to **nucleophilic sites**
  eg guanine therefore → cross-linking
  **THUS** apoptosis occurs
  - **EXAMPLES**:
    - **NITROGEN MUSTARDS**
      - Cyclophosphamide
      - Chlorambucil
      - Melphan
      - Cisplatin
      - Carboplatin

Avoid QOL-bolloxing side effects - its already shit enough.

**CHEMO IS MYELOSUPPRESSIVE** therefore → pancytopenia; therefore → infection
Consider antiviral and antibacterial drugs - infection is often **FATAL**.

**RULES OF THUMB**: **ALL CHEMO CAUSES ANOREXIA, NAUSEA and VOMITING**
AND myelosuppression, EXCEPT bleomycin, vincristin, 5FU
AND hair loss, EXCEPT carboplatin, mitoxantrone, 5FU

5FU is a radiosensitizer!
**Prognosis**

Childhood ALL; greater than 98% remission, 75-80% cure.  
Adult ALL; 75% remission rate, cure 30%.  
Adult AML; 65% remission rate, 30-40% cure.  
CML – new treatments targeting the product of the Philadelphia chromosome mean that cure rates are now unknown.  
CLL – the only way to cure it is with a bone marrow transplant and full-body irradiation  

**Epidemiology**

**ALL**  
- Almost always a disease of CHILDREN  

**AML**  
- Most common Acute Leukemia of adults  

**CLL**  
- Most common Leukemia in the United States  
- Elderly patients (usually over age 50 years)  
- More common in men  
- Rare in Asian patients  

**CML**  
- Common in Atomic bomb survivors  
- Peak Incidence at ages 30 to 50 years old  

**Basic Sciences and Comparative Diseases**

**BONE MARROW FAILURE + STEM CELL TRANSPLANT**

**Consequences of bone marrow failure:**

Damage to  
- erythropoiesis,  
- granulopoiesis,  
- megakaryopoiesis, and  
- lymphopoiesis  

has the following consequences:

<table>
<thead>
<tr>
<th>Cell Lineage</th>
<th>Mature Cell</th>
<th>Deficiency State</th>
<th>Physiological Consequences</th>
<th>Clinical Symptoms &amp; Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythroid</strong></td>
<td>Red blood cell</td>
<td>Anaemia</td>
<td>Reduced oxygen carrying capacity</td>
<td>Pallor, fatigue, dyspnoea</td>
</tr>
<tr>
<td><strong>Myeloid</strong></td>
<td>Neutrophil</td>
<td>Neutropenia</td>
<td>Impaired phagocytosis</td>
<td>Fever, infections, mouth ulcers</td>
</tr>
<tr>
<td><strong>Megakaryocytic</strong></td>
<td>Platelet</td>
<td>Thrombocytopenia</td>
<td>Bleeding</td>
<td>Bruising, petechiae, bleeding</td>
</tr>
<tr>
<td><strong>Lymphoid</strong></td>
<td>Lymphocyte</td>
<td>Lymphopenia</td>
<td>Immuno-deficiency</td>
<td>Infections</td>
</tr>
</tbody>
</table>

**Causes of bone marrow failure**

A wide variety of disease processes can result in damage to bone marrow function. Infiltration of bone marrow can be caused by:

- Haematological malignancy: leukaemia, lymphoma, myeloma, myeloproliferative disorders, myelodysplasia  
- Solid tumours: especially breast and prostate cancer  
- Fibrosis, for example from radiation damage or infections, especially tuberculosis  
- Storage disorders eg Gaucher's disease  
- Nutritional, particularly megaloblastic anaemia due to vitamin B₁₂ (pernicious anaemia) or folic acid deficiency  
- Virus, eg parvovirus, hepatitis viruses  
- Drugs, including anti-cancer drugs, propothiouracil, chloramphenicol  
- Stem cell defects/damage as in aplastic anaemia
Other consequences of bone marrow infiltration
Pathological processes involving the bone marrow can also extend to affect cortical bone, resulting in
- bone pain,
- skeletal demineralization,
- osteopenia,
- pathological fractures,
- hypercalcaemia.

Relevant anatomy: LYMPHADENOPATHY
= NODES BIGGER THAN 1cm
0.5 for Epitrochlear
1.5 for Inguinal

HISTORY:
- duration of enlargement
- previous episodes
- associated symptoms:
  - fever
  - night sweats
  - weight loss
  - pruritus (itching)
  - myalgia
  - arthralgia
  - bone pain
  - limp
  - overseas travel
  - recently arrived migrants (within one to two years)
  - pet exposure
  - medications

!! LISTEN CAREFULLY TO THE MOTHER !!
In kids MAJOR CAUSE IS INFECTION –80%
In adults, think NEOPLASM

PHYSICAL:
Determine:
- regional versus general lymphadenopathy
- mediastinal or abdominal masses
- hepatomegaly and/or splenomegaly
- anaemia and bleeding.

CAUSE STILL OBSCURE? REVIEW IN 2 WEEKS
OR: give antibiotics and hope its infection (!! STUPID !!)
IF: nodes still large after 6 wks
OR: notes are getting bigger in 2-3 wks
THEN INVESTIGATE:
- FBC + Blood Film
- Mantoux test
- Chest Xray
- LFTs
- SEROLOGY for Epsteen Barr Virus, cytomegalovirus and HIV

STILL UNCERTAIN?
- Lymph node biopsy is suspect lymphoma
- bone marrow aspirate if suspect leukaemia
Aetiology: MECHANISM of Chronic Lymphocytic Leukaemia

**MATURE B CELLS**

- **Increase in BCL2 (contra-apoptotic)**
- **Increase in BCL2 to BAX ratio**
  (BAX is pro-apoptotic)
- **DECREASE in level of FAS**
  (FAS triggers Caspase apoptosis)
- **INCREASED levels of IL-4**
  (B-cell maturation is stimulated)

**CYTOGENIC ABNORMALITIES**

- Trisomy 12
- Deletions at 13q14

**LYMPHOCYTOSIS**

- **B-cells ARRESTED in G1 or G0 phase of the cell cycle**

**UNRESPONSIVE TO ANTIGENS:**
Due to downregulation of CD28 co-stimulatory molecule -> HUMOURAL immune suppression

**HUMOURAL immune suppression**

- **INFILTRATING BONE MARROW**
  - anaemia
  - cytopenia
  - BM failure,

**HYPOGLOBULINAEMIA**
Because no new Ig molecules are being produced by the defective B cells

**EXTRAMEDULLARY HEMOPOIESIS**
In the spleen

**INFILTRATE SPLEEN**
- splenomegaly

**INFILTRATE NODES**
- lymphadenopathy

**BM FAILURE:**
Means T-cell cytopenia
THUS: no IL-10
THUS: NO APOPTOTIC SIGNALS being sent

**HYPOGLOBULINAEMIA**
Because no new Ig molecules are being produced by the defective B cells

**IMMUNE DYSREGULATION**
Leads to autoimmune disease, some of which is due to the defective clone of B cells producing self-sensitive antibodies

**AUTOIMMUNE HEMOLYTIC ANAEMIA**
Dx with Coombs test
Cell biology

**CLL markers on B cells:**

- **CD 5** (normally a T cell marker)
- **CD 22**
- **CD 19** (85% of B cells in CLL have this marker)
- **Surface Ig**

**Smudge Cells:**
- Break down and smudge on blood film studies because their phospholipid membrane is weak, as it is used for metabolism. Thus, it breaks and spills cellular contents onto the slide.

**Spherocytosis:**
- Occurs in CLL because of actin and spectrin malfunction (i.e. molecular cytoskeleton is dysfunctional)
- THUS: phospholipid bi-layer degrades slowly, causing the cell to contract into a ball (like a droplet of fat in a soup)

**Polychromasia:**
- Is a blue colouration of immature RBCs, because they still have RIBOSOMES which stain blue

Genetics

**Remember Mutation?...**

**Inversion**
- Gene is reversed (most often on X chromosome)

**Deletion or Insertion**
- Of a whole chunk of DNA or of a whole gene

**Translocation**
- Chromosomes swap a gene fragment

**POINT MUTATION: of one base pair**

- **Frame shift**
  - Deleted base pair; all amino acids are therefore wrong from that point (each being made of 3 coding base pairs)

- **Missense**
  - wrong base pair replacing the right one; one amino acid is wrong (sometimes base pair is synonymous, and no phenotype change occurs because there are numerous base pair combinations which code for the same amino acid)

- **Nonsense**
  - when the wrong base pair is inserted, and the whole 3-bp sequence is read as a stop codon

- **Splice Site Mutation**
  - loss or addition of a new, WRONG splice site;
  - THUS → wrong mRNA (reads from the wrong point in the code)
  - → wrong protein
**Immunology: LEUCOCYTES**
The NORMALS: in MILLION PER LITRE

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Normal Range</th>
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<tbody>
<tr>
<td>Neutrophil</td>
<td>2.00 → 7.5</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>0.04 → 0.4</td>
</tr>
<tr>
<td>Basophil</td>
<td>0.01 → 0.1</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.2 → 0.8</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.5 → 4.0</td>
</tr>
</tbody>
</table>

**NEUTROPHILS:**
Produced in bone marrow
Serum half-life 6-7hrs
Migrate into tissues through post-capillary venules

**MACROPHAGES:**
Produced in bone marrow
Serum half-life 3 days
Migrate into tissues through post-capillary venules
**Differentiate** into tissue-specific varieties

**MEANS OF ATTACK:**
Neutrophils and Macrophages attach themselves to their victim and fuse their granules. Then, a **Respiratory burst** follows where they disgorge great volumes of superoxide and H₂O₂

MACROPHAGES ALSO PRESENT ANTIGEN

**AUTOIMMUNE HAEMATOLOGICAL DISORDERS**

Immune system targeting normal tissue:
- **Red blood cells** (autoimmune haemolytic anaemia)
- **White blood cells** (autoimmune neutropenia)
- **Platelets** (autoimmune thrombocytopenia)
- **Coagulation proteins** (coagulation inhibitors)
- Phospholipids involved in coagulation (lupus anticoagulant, anti-cardiolipin antibodies)
- And other haematological components

Non-haematological tissues:
- eg. destruction of gastric parietal cells in pernicious anaemia

**Autoimmune haematopathology** may form part of a wider spectrum of autoimmune disease including such diseases as
- vitiligo,
- diabetes,
- thyroid disease,
- systemic lupus

**PATHOLOGY is usually due to a destruction of a normal cell type**
- in **autoimmune haemolytic anaemia** the antibody coats red cells. The antigen is thought to be a widely expressed protein which is part of the Rh blood group. The disorder is characterised prinicipally by the **anaemia which results**.
- In **autoimmune thrombocytopenia**, the antibody coats platelets and the disease is manifested by the resultant reduction in platelet count and the associated increase in bleeding.
- In **lupus anticoagulant**, an autoantibody to **phospholipid** accelerates clotting and predisposes to thrombosis.

In a small number of patients with B-lymphocyte lymphoproliferative disorders, the **malignant clone of cells may produce an antibody** with specificity for an antigen expressed by a component of the haematological system. Autoimmune haemolytic anaemia or autoimmune thrombocytopenia can result. In some such cases, a **paraprotein may be produced** and may be detected in the serum by protein electrophoresis and immuno-electrophoresis.
Microbiology: Opportunistic Infection in Immune Suppression
Lack of mature leucocytes = immune suppression

PRIMARY: genetic spontaneous
SECONDARY: acquired

OPPORTUNISTIC PATHOGENS: cannot invade unless defences are down

DEFICITS:

**B CELLS:** humoral immunity impairment (!! CLL !!)
- sinusitis,
- otitis media,
- bacterial pneumonia
- infections of the skin.
- Organisms involved are typically **polysaccharide-encapsulated pyogenic organisms**, such as
  - Strep. pneumoniae,
  - H. Influenzae type b,
  - Strep. pyogenes,
  - Moraxella catarrhalis.

**Also frequent are**
- Staph. aureus,
- Giardia lamblia
- Campylobacter jejuni

**T CELLS:** intracellular defences
- fungi (mucosal Candida),
- viruses (cytomegalovirus, zoster, Herpes simplex),
- protozoa (Pneumocystis),
- Listeria and others.
These types of infections are common in AIDS, which is the prototype for deficiencies in this arm of the immune system.

**PHAGOCYTE DEFECTS:** decline in number or function.
- high-grade bacterial infections such as Staph. aureus,
- **gram-negative bacteria**
  - E. coli,
  - P. mirabilis,
  - Serratia marcescens,
  - Pseudomonas aeruginosa
- **Fungi**
  - invasive Aspergillus
  - systemic candidiasis.

**COMPLEMENT DEFECTS:**
- Neisseria meningitidis and gonorrhoeae (when any of the components from C5-9 are involved),
- gram-negative bacteria and pyogenic organisms with deficiency in the early components of the complement cascade.

**Common Opportunistic Infections**
- Pneumocystis carinii pneumonia (PCP)
- Cryptococcal meningitis
- Candidiasis.
- CMV infection
**Pharmacology of Antiviral Drugs and Corticosteroids**  
*Why?* Viral infections strike the immunocompromised  
Autoimmune hemolytic anaemia is treated with corticosteroids

**Antiviral Drugs:**
Either prevent entry into host cell or inhibit viral nucleic acid synthesis

<table>
<thead>
<tr>
<th>Antiviral drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>INHIBIT PENETRATION</td>
</tr>
<tr>
<td>amantadine</td>
</tr>
<tr>
<td>γ -globulin</td>
</tr>
<tr>
<td>INHIBIT NUCLEIC ACID</td>
</tr>
<tr>
<td>SYNTHESIS</td>
</tr>
<tr>
<td>acyclovir</td>
</tr>
<tr>
<td>ganciclovir</td>
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<tr>
<td>idoxuridine</td>
</tr>
<tr>
<td>tribuvirin</td>
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<tr>
<td>foscarinet</td>
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<tr>
<td>zidovudine</td>
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<tr>
<td>PROTEASE INHIBITORS</td>
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<td>saquinavir</td>
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<tr>
<td>ritonavir</td>
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**Corticosteroids: glucocorticoids:**

In CLL: 2 modes of action
1. **INHIBIT ANTIBODY SYNTHESIS** by faulty B cells
2. **INHIBIT PHAGOCYTOSIS** of antibody-coated RBCs by macrophages

**GLUCOCORTICOID TX: OBSERVE HEMOGLOBIN!!**
When back to normal, taper dose down to **20mg/day**