Adverse effects of Chemotherapy Lecture: 1

- Chemotherapy employs systemically administered **drugs that directly damage cellular DNA (and RNA).**
- **It kills cells by promoting apoptosis** and sometimes **frank necrosis**.
- **There is a narrow therapeutic window between effective treatment of the cancer and normal tissue toxicity**, because the drugs are not cancer specific (unlike some of the biological agents), and the increased proliferation in cancers is not much greater than in normal tissues.
- **The dose and schedule of the chemotherapy is limited by the normal tissue tolerance,** especially in those **more proliferative tissues of the bone** marrow and gastrointestinal tract mucosa.
- **All tissues can be affected**, however, depending upon the **pharmacokinetics** of the **drug and affinity** for particular tissues (e.g. heavy metal compounds for kidneys and nerves).

- **The therapeutic effect on the cancer** is achieved by a **variety of mechanisms** , most of the drugs have been derived in the past by empirical testing of many different compounds, e.g. ***alkylating agents, the new molecular biology is leading to targeting of particular genetic defects in the cancer***.

- **Toxicity to normal tissue** can be **limited by supplying growth factors** such as **granulocyte colony-stimulating factor (G-CSF**) or by the **infusion of stem cell preparations to diminish myelotoxicity**.

- The use of **more specific biological agents** with relatively **weak pro-apoptotic effects in combination with the general cytotoxics** will also improve the therapeutic ratio.

- **Most tumours rapidly develop resistance to single agents** given on their own.
  For this reason the **principle of intermittent combination chemotherapy** was developed.
  Several drugs are combined together, chosen on the ***basis of differing mechanisms of action and non-overlapping toxicities***.
  These drugs are given ***over a period of a few days followed by a rest of a few weeks, during which time the normal tissues have the opportunity for regrowth***.
  If the normal tissues are more proficient at DNA repair than the cancer cells, it ***may be possible to deplete the tumour while allowing the restoration of normal tissues between chemotherapy cycles***.

- With a **chemosensitive tumour**, relatively small increases in dose may have a large effect on tumour cell kill.

Classification of cytotoxic drugs

Table 9-8. Chemotherapy: some cytotoxic drugs

DNA damaging

Free radicals - alkylators, e.g. cyclophosphamide

DNA cross-linking - platinum, e.g. cisplatin, carboplatin, oxaliplatin

Antimetabolites

Thymidine synthesis, e.g. 5-fluorouracil, methotrexate, cytarabine and mercaptopurine

DNA repair inhibitors

Topoisomerase inhibitors - epipodophyllotoxins, e.g. etoposide; campothecins, e.g. irinotecan

DNA intercalation - anthracyclines, e.g. doxorubicin

Antitubulin

Tubulin binding - alkaloids, e.g. vincristine, vinorelbine

Taxanes - e.g. paclitaxel, docetaxel

DNA damaging

Alkylating agents

- Alkylating agents act by covalently binding alkyl groups, and their major effect is to **cross-link DNA strands, interfering with DNA synthesis and causing strand breaks**.
- **Melphalan** is one of the original nitrogen mustards and is used in multiple myeloma.
- **Chlorambucil** is used in Hodgkin's lymphoma and chronic lymphocytic leukaemia.
- **cyclophosphamide and ifosfamide**, as well as the **nitrosoureas, carmustine** (BCNU) **lomustine** (CCNU) and **busulfan** used in chronic myeloid leukaemia.
- **Tetrazines** also alkylate DNA; **dacarbazine** is used in malignant melanoma and **temozolomide** in malignant gliomas.

Platinum compounds

- **Cisplatin, carboplatin** and **oxaliplatin** cause interstrand cross-links of DNA and are often regarded as **non-classical alkylating agents**.
- They have transformed the treatment of testicular cancer and have a major role against many other tumours, including lung, ovarian and head and neck cancer.
- Toxicity, as for other heavy metals, includes renal and peripheral nerve damage.

Antimetabolites

- Antimetabolites are usually **structural analogues of naturally occurring** metabolites that interfere with normal synthesis of nucleic acids by falsely **substituting purines and pyrimidines** in metabolic pathways.
- **Antimetabolites can be divided into**:

- ***Folic acid antagonist***, e.g. methotrexate. This is structurally very similar to folic acid and binds preferentially to dihydrofolate reductase, the enzyme responsible for the conversion of folic acid to folinic acid. It is used widely in the treatment of solid tumours and haematological malignancies. Folinic acid is often given to 'rescue' normal tissues from the effects of methotrexate.
- ***Pyrimidine antagonists***. 5-Fluorouracil (5-FU) consists of a uracil molecule with a substituted fluorine atom. It acts by blocking the enzyme thymidylate synthase, which is essential for pyrimidine synthesis. 5-Fluorouracil has a major role in the treatment of solid tumours, particularly gastrointestinal cancers. Capecitabine is metabolized to 5-FU, and is useful in colorectal cancer. Tegafur with uracil is used with calcium folinate in metastatic colorectal cancer.
- ***Arabinosides*** **inhibit** DNA synthesis by inhibiting DNA polymerase. Cytosine arabinoside (cytarabine) is used almost exclusively in the treatment of acute myeloid leukaemia where it remains the backbone of therapy, while its analogue gemcitabine is proving useful in a number of solid cancers such as lung and ovary. Fludarabine is used in the treatment of B cell chronic lymphocytic leukaemia; it is also used in reduced intensity stem cell transplantation because of its immunosuppressive effect.
- ***Purine antagonists***, e.g. 6-mercaptopurine and 6-tioguanine, which are both used almost exclusively in the treatment of acute leukaemia.

DNA repair inhibitors

Epipodophyllotoxins

These are semisynthetic derivatives of **podophyllotoxin**, which is an extract from the mandrake plant. Etoposide is a drug used in a wide range of cancers and works by maintaining DNA strand breaks by acting on the enzyme topoisomerase II. Topoisomerase I inhibitors such as irinotecan and topotecan have also proved active against a variety of solid tumours. Both these enzymes allow unwinding and uncoiling of supercoiled DNA.

Cytotoxic antibiotics

These drugs such as **doxorubicin and bleomycin** act by intercalating adjoining nucleotide pairs on the same strand of DNA and by inhibiting DNA repair. They have a wide spectrum of activity in haematological and solid tumours. Doxorubicin is one of the most widely used of all cytotoxic drugs but has cumulative toxicity to the myocardium, while bleomycin has particular toxicity for the lungs. Pegylated liposomal doxorubicin is used as second-line treatment for advanced ovarian cancer with reduction of cardiotoxicity, but infusion reactions occur.

Antitubulin agents

Vinca alkaloids

Drugs such as **vincristine, vinblastine and vinorelbine** act by binding to tubulin and inhibiting microtubule formation. They are used in the treatment of haematological and non-haematological cancers. They are associated with neurotoxicity due to their anti-microtubule effect and must never be given intrathecally.

Taxanes

Paclitaxel is isolated from the bark of the western yew. **Docetaxel** is a semisynthetic

taxane. They bind to tubulin dimers and prevent their assembly into microtubules. They are active drugs against many cancers such as ovarian, breast and lung cancer. Taxanes can cause neurotoxicity and hypersensitivity reactions and patients should be premedicated with steroids, H_1 and H_2 histamine antagonists prior to treatment.

Table 9-10. Some chemotherapy regimens

Hodgkin's lymphoma	ABVD	Doxorubicin, bleomycin, vinblastine, dacarbazine
	BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone
Non-Hodgkin's lymphoma	CHOP	Cyclophosphamide, hydroxy-doxorubicin, vincristine, prednisolone
Breast	CMF	Cyclophosphamide, methotrexate, 5-fluorouracil
	AC	Doxorubicin, cyclophosphamide
	MM	Mitoxantrone, methotrexate
Lung	PE	Cisplatin, etoposide
	MIC	Mitomycin, ifosfamide, cisplatin
Stomach	ECF	Epirubicin, cisplatin, 5-fluorouracil

Side-effects of chemotherapy

- Chemotherapy carries many potentially **serious side-effects** and should be used only by trained practitioners.
- The **four most common side-effects** are ***vomiting, hair loss, tiredness and myelosuppression***.
- Side-effects are much more **directly dose related than anticancer effects** and it has been the practice to give drugs at doses close to their maximum tolerated dose, although this is not always necessary to achieve their maximum anticancer effect.
- Common **combination chemotherapeutic** regimens are shown in.

Table 9-9. Side-effects of chemotherapy

Common

Nausea and vomiting

Hair loss

Myelosuppression

Mucositis

Fatigue

Drug-specific

Cardiotoxicity, e.g. anthracyclines

Pulmonary toxicity, e.g. bleomycin

Neurotoxicity, e.g. cisplatinum, vinca alkaloids, taxanes

Nephrotoxicity, e.g. cisplatinum

Skin plantar-palmar dermatitis, e.g. 5-fluorouracil

Sterility, e.g. alkylating agents

Secondary malignancy, e.g. alkylating agents, epipodophyllotoxins

- The most frequent adverse effects of cytotoxic chemotherapy are:

Immediate effects:

– Nausea and vomiting (e.g. cisplatin,cyclophosphamide);

– Drug extravasation (e.g. vinca alkaloids,anthracyclines, e.g. doxorubicin).

Delayed effects:

– Bone marrow suppression – all drugs;
– Infection;
– Alopecia;
– Drug-specific organ toxicities (e.g. skin and Pulmonary – bleomycin; cardiotoxicity – doxorubicin);
– Psychiatric-cognitive morbidity;
– Teratogenesis.

Late effects:

– Gonadal failure/dysfunction;
– Leukaemogenesis/myelodysplasia;
– Development of secondary cancer.

Nausea and vomiting

- The severity of this common side-effect **varies with the cytotoxic** and it can be eliminated in 75% of patients by using modern antiemetics.
- Nausea and vomiting are particular **problems with platinum analogues** and with **doxorubicin**.
- A stepped policy with **antiemetics** such as ***metoclopramide and domperidone or 5-HT_3 serotonin antagonists (e.g. ondansetron, granisetron) combined with dexamethasone*** should be used to match the emetogenic potential of the chemotherapy.
- **Aprepitant**, a **neurokinin receptor antagonist** is helpful in preventing acute and delayed nausea and vomiting associated with **cisplatin-based** chemotherapy. It is used ***with dexamethasone and a 5-HT_3 antagonist***.

High Emetic Risk (> 90% frequency of emesis)	
Cisplatin Cyclophosphamide > 1500 mg/m2	
Moderate Emetic Risk (30%–90% frequency of emesis)	
Melphalan Irinotecan	
Minimal Emetic Risk (< 10% frequency of emesis)	
Vincristine Asparaginase	

Hair loss

- Many but not all cytotoxic drugs are capable of causing hair loss.
- **Scalp cooling** can sometimes be used to reduce hair loss but in general this side-effect can only be avoided by selection of drugs where this is possible.
- Hair always **regrows on completion of chemotherapy**.

Bone marrow suppression and immunosuppression

- Suppression of the production of **red blood cells, white blood cells and platelets** occurs with most cytotoxic drugs and is a **dose-related phenomenon**.

- Severely **myelosuppressive chemotherapy** may be required if treatment is to be given with curative intent despite the potential for rare but **fatal infection or bleeding**.
- **Anaemia and thrombocytopenia** are managed by ***erythropoetin or red cell or platelet transfusions.***

- **Neutropenic** patients are at **high risk of bacterial and fungal infection**, often from **enteric bowel flora**.
- Those with a **fever > 37°C** and less than 0.5×10^9 neutrophils/L are ***managed by the immediate introduction of broad-spectrum antibiotics intravenously for the treatment of infection*** (Box 9.3).
- Initial empirical therapy should be reviewed following microbiological results.
- ***Haemopoietic growth factors and peripheral blood stem cells can reduce*** the duration of neutropenia significantly, benefiting patients at high risk of infectious complications.

***Box 9.3* Febrile neutropenia treatment**

- **Resuscitation with intravenous fluids to restore circulatory** function, e.g. urine output, followed by cultures of blood, urine, sputum and stool and empirical antibiotics:

- Commonly used antibiotics should include **activity against pseudomonas**, e.g. ceftazidime or ticarcillin with gentamicin
- May require antibiotics **against *Staph***. *aureus* especially with indwelling venous access lines, e.g. flucloxacillin or vancomycin.
- If the patient **deteriorates clinically and/or temperature still** elevated after 48 hours, change antibiotics according to culture results or empirically increase Gram-negative and Gram-positive cover.

- Consider adding **treatment for opportunistic infections** if fever not responding to broad-spectrum antibiotics, e.g. **amphotericin B liposomal amphotericin B** or voriconazole (latter two are very expensive) or caspofungin - **fungus high-**dose co-trimoxazole - pneumocystis clarithromycin - mycoplasma.

Mucositis

- This common side-effect of chemotherapy reflects the **sensitivity of the mucosa to antimitotic agents**.
- It causes severe pain and problems with swallowing.
- **Treatment is with antiseptic and anticandidal mouthwash** and, if severe, fluid and antibiotic support, as the mouth is a portal for entry of enteric organisms.
- A recent study has shown a **keratinocyte growth factor** to be helpful (**palifermin**).

Cardiotoxicity

- This is a rare side-effect of chemotherapy, usually associated with

anthracyclines such as doxorubicin.

- It is **dose-related** and can largely be prevented by restricting the cumulative total dose of anthracyclines within the safe range (equivalent to 450 mg/m^2 body surface area cumulative doxorubicin dose).

Neurotoxicity

- This occurs predominantly with the **plant alkaloids, vinca, taxanes and platinum analogues (but not carboplatin**).
- It is **dose-related** and cumulative.
- **Chemotherapy is usually stopped** before the development of a significant polyneuropathy, which once established is only partially reversible.
- **Vincristine must *never* be given intrathecally** as the neurological damage is progressive and fatal.

Nephrotoxicity

- **Cisplatin (but not oxaliplatin or carboplatin), methotrexate and ifosfamide** can potentially cause renal damage.

This can usually be prevented by maintaining an adequate diuresis during treatment.

Sterility

- Some anticancer drugs, particularly **alkylating agents, may cause sterility**, which may be **irreversible**.
- In **males** the **storage of sperm prior to chemotherapy** should be offered to the patient when chemotherapy is given with curative intent.
- In **females** it may be possible **to collect oocytes to be fertilized** in vitro and cryopreserved as embryos.
- **Cryopreservation of ovarian tissue** and retrieval of viable oocytes for subsequent fertilization is still experimental.

Secondary malignancies

- Anticancer drugs have **mutagenic potential** and the development of secondary malignancies, **predominantly acute leukaemia**, is an uncommon but particularly unwelcome long-term side-effect in patients otherwise cured of their primary malignancies.
- The **alkylating agents and epipodophyllotoxins** are particularly implicated in this complication.

Drug resistance

- **Some tumours have an inherently low level of resistance** to currently available treatment and are often cured.
- These include **gonadal germ cell tumours, Hodgkin's lymphoma and childhood acute leukaemia**.
- Solid tumours such as **small-cell lung cancer** initially appear to be chemosensitive, with the majority of patients responding, but most patients eventually relapse with resistant disease.
- In other tumours such as **melanoma the disease is largely chemoresistant from the start.**

- Resistance to cytotoxic drugs is **often multiple and is then known as multidrug resistance (MDR)**, e.g. resistance to doxorubicin is often associated with resistance to vinca alkaloids and epipodophyllotoxins,

High-dose therapy

- Most anticancer drugs **have a sigmoid dose-response relationship** which suggests that, up to a point, a higher dose of a cytotoxic drug will induce a greater response.
- However, **increasing cytotoxic drug doses is often not possible**, owing to toxicity.
- For many chemotherapeutic agents the toxicity which ***limits the dose is bone marrow failure, and infusion of stem cells is necessary to restore the*** lymphohaemopoietic system.

Leukemia (18-19) **Lec:3**

Leukemias are hematologic malignancies that are derived from cytogenic alterations in hematopoietic (blood forming) cells (1).

The major types of leukemia

1. Acute lymphoblastic (lymphocytic) leukemia (ALL)
2. Acute myelogenous leukemia
3. Chronic myelogenous leukemia (CML)
4. chronic lymphocytic leukemia (CLL)

The suffix-cytic and -blastic refer to mature and immature cells, respectively (4).

Epidemiology

Leukaemias are uncommon malignancies; anyhow leukaemias and lymphomas are the commonest forms of haematological malignancy (4).
With the exception of ALL (common in childhood), other types of leukaemias are more common in the elderly (4) and their incidence increase with age (2,7).
CLL is the most common form of adult leukaemia (4).

Etiology of leukemia

Most cases of leukemia arise with no clear cause (7).
Chemotherapeutic agents may cause acute leukemia especially AML (1,2,7)
Radiation and some toxins (benzene or pesticides) are leukemogenic (2, 7)
Note: Radiation increase all forms of leukemia other than CLL (4).The etiology of CLL is unknown, but hereditary factors may have a role (2).

Pathophysiology of all types of leukemia

leukemia characterized by excessive production of immature (blast cells) (in acute leukemia) or malignant mature (incompetent) (in chronic leukemia) hematopoietic cells (1, 2,4) which eventually replaces normal bone marrow and leads to the failure of normal hematopoiesis and appearance in peripheral blood as well as infiltration of other organs (extramedullary=outside bone marrow) (2,6,7).
Overactivity of the tyrosine kinase results in the uncontrolled growth characteristic of leukaemic cells (4). Ph chromosome is seen in over 90% of CML cases (4).

Clinical presentation of leukemia

Sign and symptoms at presentation for patients with acute leukemia

•Typically, patients with acute leukemia have non-specific symptoms (fatigue, pallor and fever) with no obvious distress for 1 to 3 months before presentation (2).

Patients with acute leukemia may present with malaise and weakness (due to anemia); bleeding due to thrombocytopenia (2); fever and high susceptibility to infection (due to neutropenia) and weight loss (2).

Sign and symptoms for chronic leukemia

Many patients with chronic leukemia are asymptomatic and diagnosed by chance through doing routine blood tests (4).

At time of presentation patients with chronic leukemia rarely present with hemorrhage or symptoms of infection because neutropenia and thromobocytopenia are uncommon at presentation (4).

Patients with CML and CLL commonly present with B symptoms (non-specific symptoms), weight loss , fever and night sweats and fatigue with malaise (2, 4).

Specific sign and symptoms
Lymphoadenopathy is common in lymphocytic leukemia (ALL and CLL) (2,4).
Splenomegaly is usual (more common) in chronic leukemia. It is severe in CML may even cause abdominal pain and moderate in CLL (4).

Specific sign and symptoms for ALL
Bone pain are not as common in AML as in ALL (2,4). CNS involvement (may be associated with headache, vomiting and irritable behavior) is common at diagnosis of ALL (2,4).

Specific sign and symptoms for AML
Disseminated intravascular coagulation is associated with generalized bleeding (2).
Chloromas (localized leukemic deposits named after their color) may be seen, especially in the periorbital regions and as skin infiltrates in AML patients (2).
Gum hypertrophy is indicative of AML M4 and AML M5 subtypes (2).

Laboratory Tests
Complete blood count with differential should be performed for all types of leukemia (2).
RBC: Anemia is normochromic and normocytic (6). Anemia is more severe in acute than in chronic leukemia (4).
Platelets: mainly decreased in acute leukemia (4). Platelet count may be normal at presentation in CML and CLL (7).
WBC: In acute leukemia WBC count may be normal, decreased, or high (2). In CML WBC is more than 100000/cc3, in CLL (particularly lymphocytes elevated) and WBC is also elevated but to a lesser extent than that in CML (4). Even patients with elevated WBC counts can be considered functionally neutropenic (6).

Uric acid: may be elevated because of rapid cellular turnover and is more common in patients presenting with elevated WBC count and with ALL (6).
Electrolytes: potassium and phosphate may be elevated with a compensatory decrease in calcium, more common with ALL (6).

Coagulation defect (more common with AML): elevated prothrombin time, partial thromboplastin time, D-dimers; hypofibrinogenemia (6).

Other Tests for diagnosing leukemia
In acute leukaemia, leukaemic blast cells are usually seen on the peripheral blood film (4). Bone marrow aspirate and biopsy are usually necessary to confirm the diagnosis of leukemia (1,6, 7).
•The WHO classification defines acute leukemias as more than 19% blasts in the marrow or blood **(6).** Bone marrow must have at least 30% lymphocytes for diagnosis CLL (2).

•The bone marrow aspiration is analyzed with fluorescence in situ hybridization (FISH) (molecular test) to determine the presence of the Ph chromosome (common in CML). Quantitative RT-PCR is also performed (for peripheral blood) to assess the baseline BCR-ABL transcript levels (2,6).
At diagnosis, a Lumbar Puncture is performed to determine if CNS leukemia is present (2).

Leukemia classification and prognostic features
Classification of ALL (based on)

1. Risk of relapse (low, intermediate, high, or very high) (1,4).
2. Cytogenetic variables (e.g. Philadelphia chromosome) (1,4).
3. Immunophenotyping (Analysis of the cell marker feature= surface antigen expression= antibody cluster determinants (CD)) by flow cytometry establish three types of ALL, pre-B, mature B, and T-cell precursor ALL (2).

Poor prognostic factors for ALL patients
High WBC count (more than 50,000/cc^3) at presentation; age (<1 year or >9 years); hypodiploidy (less than 44 chromosomes), presence of certain cytogenetic abnormalities (eg, Philadelphia chromosome positive [Ph+]) and certain ALL types (T cell, mature B cell and Null B cell) (1,2,6);

Treatment of leukemia
Patients with acute leukemia are treated in the hospital inpatient setting (4) because of aggressive nature of induction therapy that can cause severe myelosupression (2) while those with chronic leukemia can be treated in outpatient setting (4).

Desired Outcome for acute leukemia treatment
The primary objective in treating patients with acute leukemia is to achieve a continuous complete remission (CCR)(remission and prevent relapse) (2).

Complete Remission is defined as the absence of all clinical evidence of leukemia with the restoration of normal hematopoiesis (2). (I.e, normal bone marrow specimen (<5% blasts) and normal peripheral blood sample (Platelet count >100,000 cells/mcL and neutrophil count >1,000 cells/mcL) (1,7).

Non Pharmacological Therapy of acute leukemia
It is important to ensure healthy life style for the patients through provide supportive care and intervention and counseling related to nutrition, smoking cessation, and exercise as a part of their active treatment (2).

Pharmacologic Therapy: ALL
Therapy for ALL is divided into many phases: (a) Induction (remission induction) (b) postinduction (postremission) and (c) maintenance therapy. CNS prophylaxis is a mandatory component of ALL treatment regimens and is administered longitudinally during all phases of treatment (3,6).

Most patients receive a total duration of 2.5 (2-3) years of therapy (1,6).
Tyrosine kinase inhibitors such as imatinib or dasatinib should be used in all phases of treatment in combination with chemotherapy for patients older than 15 years who have positive Ph chromosome as it improve remission rate and overall survival (5,6)

Induction phase (Remission induction)
Treatment in this phase is designed to induce complete remission (1). Induction phase typically lasts 28 days (1cycle) (3).

Failure to achieve Early response to treatment (delayed remission), measured morphologically (by microscope) by either clearance of blasts from peripheral blood or bone marrow on day 7 to 14 of therapy is highly predictive of later disease recurrence (1,2).

After an induction chemotherapy course (i.e. On day 29), bone marrow should be examined if there is a morphologic remission (2,3), to detect occult residual disease (also termed minimal residual disease or MRD, which usually occur even after achieving complete remission (4). If MRD is less that 0.01% (which indicate adequate response to chemotherapy, but it is not indicate a cure). Patient will be ready to begin consolidation (2,3), otherwise there is a need to repeat induction therapy!!!

Note: MRD can be measured by flow cytometry or polymerase chain reaction (100 times more sensitive the morphological examination (6).

Induction therapy for children consist of vincristine, a glucocorticoid (dexamethasone or prednisone), and pegaspargase. Many treatment protocols include anthracycline (daunorubicin or doxorubicin) in induction (four-drug induction) which is used for children at high risk of relapse (based on prognostic variables) and in ALL adult patients (2, 3,6).

If complete remission is not achieved with three agents by the end of induction, patients are treated with additional agents (e.g., an additional 2–4 weeks of daunorubicin and prednisone) (3).

If two cycles of therapy fail to induce CR in ALL, an alternative drug regimen can be used. If this is unsuccessful, it is unlikely that CR will be achieved (4). The subsequent duration of the first remission is closely linked to survival (4).

Notes about ALL chemotherapeutic agents
Dexamethasone is now being used in most standard-risk protocols (it is not preferred to be used with intensive chemotherapy that induce myelosupression) because of its longer duration of action and higher CSF penetration compared to prednisone however prednisolone is preferred for those older than 10 years because of less risk of mood alteration, hyperglycemia, myopathy, infection and osteonecrosis(3, 6).

The prednisone or dexamethasone dose is not routinely tapered at the end of induction treatment (3).

• Asparaginase toxicity includes severe, sometimes fatal pancreatitis and frequent hypersensitivity Reactions (1) Premedication does not prevent subsequent reactions. Delayed hypersensitivity reactions (less anaphylactic reactions) can occur with intramuscular administration (1,3).

Asparginase can result in inhibition of the synthesis of various clotting factors occasionally leading to cerebral hemorrhage or infarction (3).

Pegaspargase is peglyated E.Coli asparginase with long t1/2(6) It has same side effects to asparginase but it appears to be safe in patients with prior reactions to asparaginase products (1,6).

CNS Prophylaxis
Patients with ALL are at a high risk of developing CNS iniltration. Cytotoxic drugs penetrate poorly into the CNS. For this reason, all patients with ALL receive CNS prophylaxis. Cranial irradiation, intrathecal methotrexate or high-dose systemic methotrexate can be used in isolation or in combination as part of the treatment schedules for both adults and children (4). Dose of IT chemotherapy should be based on patient age not on body surface area (3). IT chemotherapy should be diluted with preservative free diluents to prevent paraplegia (3).

Postinduction (postremission)
It is important for relapse prevention (3). It consists from several cycles of intensive chemotherapy that are given every 4 to 6 weeks (2). This phase is typically last about 6 months (8).

The duration and intensity of the postinduction phase of therapy is based on prognostic features of the leukemia (3). More aggressive regimens are recommended in children and in T cell ALL (2).

Post induction phase in children usually include consolidation, delayed intensification and interim maintainace therapy (1,3,6).
Patients with T-cell leukemia also receive Nelarabine during consolidation phase and throughout the remainder of their treatment course (6).

Post-remission consolidation therapy may comprise
1. Chemotherapy (for children patients with low risk of relapse = MRD negative =less than 0.01%) and for adults with low risk of relapse if allogenic HSCT is not available= no HLA matched donor) (4,5,6,7)

2. Combination of chemotherapy and allogenic bone marrow transplantation (for high risk or MRD+ patients) (4,5,6,7).

Standard consolidation chemotherapy usually consists of vincristine, mercaptopurine, and intrathecal methotrexate (6). Consolidation usually last 4 weeks (6).

Children who are slow early responders to induction treatment or have high-risk disease may benefit from intensified consolidation (aggressive) that includes the addition of pegaspargase, cyclophosphamide, and low-dose cytarabine to standard therapy (6).

Reinduction (Delayed Intensification and Interim Maintenance)
One or two delayed intensification phases separated by low-intensity interim maintenance cycles can be added to maintain remission and to decrease cumulative toxicity (6).

Delayed intensification therapy usually consists of repetition of the initial remission induction therapy (or sometimes non cross resistance agents) administered approximately 3 months after remission (2,6).

Interim maintenance usually consists of dexamethasone, vincristine, weekly methotrexate, mercaptopurine, and intrathecal methotrexate (6).

Maintenance
Less intensive therapy lasting approximately 2 years designed to sustain (prolong) the complete remission achieved by induction therapy (1).
Maintenance therapy (orally) consists of weekly methotrexate ($20mg/m^2$) and daily mercaptopurine($50\text{-}75mg/m^2$), with or without monthly pulses of vincristine and a corticosteroid (6), these pluses can offer lower bone marrow and testicular relapse rate even in standard risk patients(3). Infrequent intravenous and CNS therapy usually given during maintainace phase (3).

Adjusting 6MP and MTX doses
Improved outcome is associated with adjusting MTX and 6-mercaptopurine doses to the limits of individual tolerance based on absolute neutrophil count (2).to be kept in a range of 300-2000cel/ μL(3).

Relapsed ALL
Relapse is the recurrence of leukemic cells at any site (bone marrow commonest site, whereas extramedullary sites such as testicle or CNS are less common) after remission has been achieved (2).

Agents used in salvage regimens are similar to those used in intensive induction regimen for high-risk ALL (4 induction agents) (3).
This is accompanied by radiation therapy to sites of local relapse (e.g., testis, CNS) and IT chemotherapy (3).

Allogeneic bone marrow transplantation can be considered in patients with intermediate – high risk only after a second remission has been achieved (1). Because HSCT is associated with less relapse but more morbidity and mortality compared to chemotherapy (2,3).

Clofarabine, a purine antimetabolite, is an option for patients with second or later relapses, but the duration of response is less than 6 months (6).

Nelarabine is an option for relapsed T-cell ALL, especially if the patient had not previously received nelarabine as part of their initial therapy (6).

Blinatumomab approved for use in relapsed/refractory B-ALL and used as a bridge to transplantation (5,7).

Treatment of AML
Treatment of AML is conventionally divided into two phases: induction and postremission therapy (2,6).

A. Remission Induction

Most patients with AML are treated with a combination of an anthracycline (daunorubicin or idarubicin) plus cytarabine, either alone (backbone of AML induction therapy) or in combination with other agents like etoposide (2, 7). Most patients achieve a CR after 1 or 2 courses of chemotherapy. Patients who require additional chemotherapy to achieve a CR have been reported to have a poor prognosis (6).
Gemtuzumab ozogamicin, a humanized anti-CD33 antibody, improve the outcome of patients younger than 60 years old when added to conventional 7 + 3 chemotherapy (2). Concerns have been raised about possible toxicity in the form of veno-occlusive disease of the liver, and the dosing schedule is not yet optimized (4).

Older patients with AML who are not candidates (intolerate because of side effects) for traditional chemotherapy may be given 5-azacitidine, decitabine, or clofarabine initially with acceptable outcomes (1,7).

Bortezomib, a proteasome inhibitor, has shown to selectively reduce the leukemic stem cells that are a cause of resistance for AML (2).

B. Postremission Chemotherapy
Aim to maintain remission and prevent relapse (1)
Only patients who achieve remission by induction therapy are shifted to this phase, while those who don't achieve remission are considered refractory and given salvage therapy (4).
Postremission therapy can include either consolidation chemotherapy (6) or hematopoietic stem cell transplantation (HSCT) as alternative approach (4, 6).

Four courses of chemotherapy are required (1,2). Regimens usually include high-dose cytarabine (>1g/m2/day) alone or in combination with other agents (e.g., anthracycline, etoposide) (1).

Hematopoietic stem Cell Transplant (HSCT)
Because improvement in chemotherapy agents and many serious side effects even mortality for allogenic HSCT, allo-HSCT is often reserved for patients (after 1st remission) that are considered high risk and have HLA-matched sibling (2,4).

Allo-HSCT provides the best chance of cure and thus preferred in patients who relapse or are refractory to therapy (1,7).

Myeloablative (high dose chemotherapy before transplantation) allogeneic HSCT is generally restricted to patients younger than 60 years of age, and non myloablative allogenic HSCT for those older than 60 years (6).

CNS Therapy
Adequate CNS prophylaxis is an essential component of therapy for patients with risk of CNS disease (patients with hyperleukocytosis; (FAB M4 or M5); young age patient) (2,4). In most cases, IT cytarabine with or without methotrexate and systemic high-dose cytarabine provide effective treatment (CNS disease at diagnosis can be cured with IT therapy alone) (2).

Maintenance Therapy

It has not been shown to improve survival in adult AML with the exception of the APL subtype (1)

Relapsed AML

There is no standard therapy for relapse, most studies have shown that high-dose cytarabine-containing regimens have considerable activity in obtaining a second remission (2).

The targeted immunotherapy agent gemtuzumab has induced remissions who have recurrent CD33+ AML alone or in combination with standard chemotherapy (2).

After a patient has achieved a second remission with conventional chemotherapy, allo-HSCT is the therapy of choice (2).

Treatment of acute promyelocytic leukemia (APL)

Induction includes tretinoin and an anthracycline; consolidation therapy consists of two to three cycles of anthracycline-based therapy; maintenance consists of pulse doses of tretinoin, mercaptopurine, and methotrexate for 2 years (6).

Arsenic trioxide can be used for patients in APL subtype patients refractory to or have relapsed (1).

B. Care for acute leukemia treatment complication

1. Infection prevention after Myelosupression treatment

The induction therapy for AML is more myelosupressive (extremely) than that for ALL which may necessitate the use of hematopoietic growth factors (2,4).

Many pediatric institutions recommend antifungal prophylaxis (eg. voriconazole) to decrease risk of life threatening disseminated fungal infections (2).

For patients undergoing allogeneic HSCT, antifungal prophylaxis is strongly recommended until at least day 75 after transplantation (5).

Trimethoprim–sulfamethoxazole is started in all patients with any acute leukemia for the prevention of *Pneumocystis jiroveci* pneumonia (PJP). Patients normally continue this therapy for 6 months after completion of treatment (2).

Treatment of infection in neutropenic patients discussed in lecture 2.

CML

Clinical course of CML

It is a triphasic disease (has three phases) based on % of myeloblasts in peripheral blood or bone marrow: initial chronic phase (blasts less than 10%) (Treatment used to alleviate symptoms and reduce WBC count), accelerated phase (disease is progressing and becomes more aggressive with worsening symptoms), and blast crisis (blasts more than 20%) which resembles acute leukemia, and immediate aggressive treatment (similar to that of acute leukemia) is required (1,2,4,7).

In accelerated and blast phases, progressive anemia and thrombocytopenia occur (7).

Treatment of CML

Desired Outcome

An early goal of therapy is to achieve hematological remission (normalize peripheral blood counts) (1,2).

Most important goal is a cure from CML which can only be achieved through complete cytogenetic response (eradicate all the Ph positive clones) (1,2) or by monitoring molecular response (ideal) (6)

Molecular responses are determined by quantitative PCR (RT-PCR) of peripheral blood, which is more sensitive than methods used to measure cytogenetic responses (6). Molecular response defined as a 3-log reduction of the bcr-abl transcript (7) while complete molecular response is the absence of BCR-ABL transcripts (6).

Non pharmacological treatment

Allogeneic stem cell transplant is the only curative therapy for CML, however it may be associated with early mortality so it is reserved for patients (only if a suitable donor is available) a. who progress after treatment with tyrosine kinase-based therapy (TKI resistance) b. present in blast crises phase (2,6).

Imatinib has been used in patients who have residual disease after allogeneic HSCT (6).

General Approach to Treatment

Nearly all patients with CML are initially (in chronic phase) treated with a first line tyrosine kinase inhibitor (TKI) (imatinib, nilotinib or dasatinib) which don't cure CML but are able to produce long-term disease control in the majority of patients (2). Dasatinib and nilotinib are comparable to, if not better than, imatinib in achieving faster and deeper cytogenetic and molecular responses. Thus fewer patients will progress to progressive and blast phases (2).

Choice among these agents is depend on patient age, comorbid disease and drug safety profile (2).

Patients with complete molecular responses lasting more than 2 years can stop drug therapy without disease recurrence (7)

The loss of hematologic or cytogenetic responses at any time should be considered a treatment failure warranting a change in therapy (6).

Newer TKIs (bosutinib and ponatinib) or omacetaxine may be options for patients who fail to respond or do not tolerate initial TKI therapy (2).

Patients with advanced-stage disease (accelerated phase or blast crisis) should ultimately be considered for allogeneic stem cell transplantation. If TKI used, they should be used in doses higher than that used in chronic phase (7).

Monitoring response to therapy (1st line TKI)

1. Evaluate hematological remission after 3 months (2.6)
2. Evaluate cytogenetic remission: Partial response should occur after 6 months and complete response after 12 months (2.6)
3. Evaluate for major molecular response after 18 month (6)

If hematological or cytogenic remission (2) or even molecular response (7) is not achieved then assess medication adherence, Consider mutational analysis, and Consider changing TKI to dasatinib, nilotinib or bosutinib based on mutation test result (2)

Additional options include:

Ponatinib if T315I mutation;

Omacetaxine, allogeneic stem cell transplantation (and clinical trials) are options for patients that do not respond to a TKI (2) or progress while on therapy (7).

Pharmacologic Therapy

Tyrosine kinase inhibitors

Advanced-Generation TKIs include Dasatinib, nilotinib, bosutinib, and ponatinib. They may overcome imatinib resistance or intolerance because they are 10-325 times more potent than imatinib(2).
Only ponatinib (3rd generation) can overcome the *T315I* mutation (2).

Side effect of TKI
Common side effects of all TKI (myelosupression, rash, fluid retention and GIT side effects), however nilotinib with no or little GIT side effects (2,6).

The myelosuppression typically occurs within the first 4 weeks of therapy and is more common in patients with advanced disease (6)
Appropriate initial management of myelosuppression is to interrupt imatinib treatment not to reduce dose which may provoke drug resistance (6).

A significant and potentially severe side effect of pleural effusions has been reported with the use of imatinib and dasatinib but not with the use of nilotinib (2). Edema and plural effusions can be managed by dasatinib drug holiday, diuretics, or short courses of steroids (6).

Congestive heart failure is a rare but serious side effect to imatinib and requires careful monitoring in patients with preexisting cardiac conditions (2).

Other specific side effects include QT prolongation (dasatinib and nilotinib) and increases in indirect bilirubin (nilotinib) (2).

The side effects of bosutinib appear to be less severe and less common than many of the other TKIs (2).

Ponatinib may cause thromboembolism so it should be used only in patients harboring the *T315I* mutation or have failed multiple prior TKIs. Rare yet serious adverse effects include liver failure and death (2).

Route of administration and DDI (2)
All given orally with many drug interactions due to metabolism by CYP450 3A4
Omacetaxine: given by subcutaneous injection twice daily. Drug interaction: P-glycoprotein substrate

Patient education about TKI usage
Dasatinib avoid medications that alter gastric pH (eg, H2 antagonists and PPIs) because exhibits pH-dependent absorption (2).

Dasatinib and Nilotinib: Avoid concomitant medications that prolong the QT-interval (correct K, Mg level if they are low before start use) (2)
Imatinib and Bosutinib take with food (2); Nilotinib take on empty stomach (2)
It is recommended that patients on imatinib to avoid (2) or to limit their use of acetaminophen to 1,300 mg daily (6).

Omacetaxine Mepesuccinate
Omacetaxine is a subcutaneous injection (twice daily) indicated for patients in chronic or accelerated phase CML who are resistant or intolerant to two or more TKIs. It may

be used in patients with the *T315I* mutation. Side effects: myelosupression, hyperglycemia and rarely but serious cerebral hemorrhage (2).

CLL

Clinical course of CLL

CLL can have a variable clinical course. Low-risk disease is asymptomatic. Intermediate risk is associated with lymphadenopathy. High-risk patients with anemia. Median survival is less in high risk patients (2).

About 4% of patients with CLL will undergo transformation of their disease to an aggressive non-Hodgkin lymphoma (diffuse large B cell), which is termed as Richter's syndrome (6).

Desired Outcomes for treating CLL

It is an indolent non curable disease, so treatment should be only initiated when patients have symptoms with aim to palliate symptoms and optimize remission duration while minimizing the burden of treatment-related adverse effects (2, 6).

Nonpharmacologic Therapy

Asymptomatic early stage CLL (especially elderly people) can be observed (watch and wait) without treatment until evidence of disease progression (2).

Splenic complications may necessitate splenectomy or splenic irradiation (4).

Allogeneic HSCT is the only curative treatment for CLL (1). It is an option for younger patients with aggressive disease who have failed prior therapies (2).

Pharmacologic Therapy

Numerous agents can be used as initial therapy in the treatment of symptomatic or advanced CLL. There are no preferred chemotherapy regimens (2).

Indications for treatment initiation include significant anemia or thrombocytopenia, progressive disease demonstrated by lymphadenopathy, hepatomegaly, splenomegaly, a lymphocyte doubling time of less than 6 months, persistent B-symptoms, threatened end-organ function, and recurrent infection (1).

General notes about CLL treatment

Chemoimmunotherapy (chemotherapy + anti CD20) that is fludarabine based (such as fludarabine, cyclophosphamide and rituximab; FCR) is commonly used as first-line therapy for younger patients(less than 70) with symptomatic CLL (2).

First-line therapy for patients ≥70 years of age or younger with significant comorbidities generally includes the following regimen which have less side effects than FCR regimen (1,6,7) but may be less effective than FCR (4).

1. Chlorambucil with prednisone (1) (chlorambucil low cost ease of administration and less side effects (2)) or
2. Anti CD20 such as rituximab and ofatumumab (1,6) Or
3. Bendamustine (alkylating agent) combination with rituximab (BR) (1,6,7)

Patients on fludarabine should be given antibacterial and antiviral prophylaxis because of myelosuppression and prolonged immunosuppression (2).

Fludarabine is effective in chlorambucil resistant disease (2).

Monoclonal Antibodies
They include anti CD20 (expressed in B cell only) (Rituximab, Ofatumumab and obinutuzumab) (2).

Ofatumumab and obinutuzumab are used in combination with chlormabucil, while rituximab is used in combination with fludarabine, or bendamustine or lenalidomide (2).

Ofatumumab is used as initial therapy with chlorambucil if fludarabine regimen is inaproperiate (6). It is also approved in CLL patients who fail fludarabine and alemtuzumab (2).
Obinutizumab can cause TLS (2). It is more effective than rituximab and chlorambucil but with more severe side effects (neutropenia and infusion reaction) (6).

Alemtuzumab (Campath) is anti CD52 (expressed in B and Tcell) may be used as single agent or combination therapy in the treatment of CLL (2). It is used for both frontline and salvage treatment of CLL (in fludarabine-resistant disease, in patients with the deletion of 17p) (2,6).

Alemtuzumab also suppresses the T cells, resulting in prolonged immunosuppression. Patients should receive trimethoprim–sulfamethoxazole and acyclovir or an equivalent antiviral to prevent infections (2).
The most common side effects of all these monoclonal antibodies include infusion reactions (2). Subcutaneous but not IV route of administrations for alemtuzumab is associated no infusion reaction (2).

Small-Molecule Inhibitors (new novel oral therapies)
Novel agents such as ibrutinib (**Bruton's tyrosine kinase inhibitor)** and idelalisib (first line for patients with 17p-deletion) (targets phosphatidylinositol-3-kinase) provide an oral option for the treatment of CLL especially for relapsed disease (6).

Supportive care for CLL
Patients with recurrent bacterial infections and hypogammaglobulinemia benefit from prophylactic infusions of gamma globulin (7).

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5. NCCN Guidelines Version 2.2015 Acute Lymphoblastic Leukemia
6. Pharmacotherapy pathophysiologic approach 2017
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Further reading

Poor Prognostic Factors in newly diagnosed AML

1. Age (older than 60 with poor prognosis) because of comorbid disease (2)
2. Certain AML subtype (2) Acute promyelocytic leukemia (7).
3. Presence of extramedullary disease (6).
4. Presence of certain cytogenetic and molecular abnormalities (6).
5. Ethnicity (African Americans children have worse outcome than whites)(2)
6. Body mass index affect prognosis in children (only normal weight have good prognosis) (2).

Midostaurin is a multi-targeted FLT3 inhibitor and has been shown to improve survival in the subgroup of patients with FLT3-mutated AML (4).

CLL Poor Prognostic Factors (2,6)

Mainly based on Rai's or Binet's criteria.

1. **Presence of lymphoadenopathy, splenomegaly or hepatomegaly**
2. Lymphocytosis with accompanying: Anemia (hemoglobin ≤ 11.0 g/dL) and Thrombocytopenia (platelets < 100 × 103/mm3)

Recently added criteria

3. Biological markers (Cytogenetics) such as deletions of chromosomes 17p and 11q
4. Molecular markers ZAP-70 mutation and CD38 antigen expression

Some studies suggest that high-dose methotrexate and cytarabine alternating with fractionated cyclophosphamide plus vincristine, doxorubicin, and dexamethasone (hyperCVAD) may improve response and survival in adults (older than 40 years) with ALL (6). Hyper CVAD + rituximab should be used in adults with ALL PH- CD20 + (5,6).

Ibrutinib is approved for treatment of patients with 17p-deletion (as first line) and for patients with relapsed disease who have received at least one prior therapy (6).

Idelalisib may be used in combination with rituximab for relapsed or refractory disease and as first line therapy when concomitant medical conditions preclude the use of systemic chemotherapy such as GFR below 60 or severe neutropenia or severe thrombocytopenia (6).

Both agents metabolized by CYP450 (6).

TherapeuticsII

Lecture 4

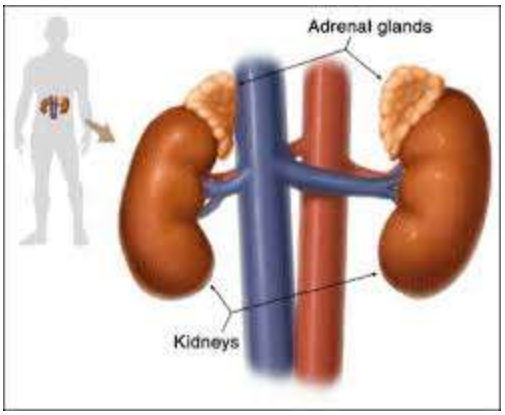
Adrenal Gland Disorders

Adrenal glands play essential roles in regulating:

1- water and electrolyte homeostasis,
2- blood pressure,
3- carbohydrate and fat metabolism,
4- physiologic response to stress, and
5- sexual development and differentiation.

Anatomy and Physiology of the Adrenal Glands

Each adrenal gland consists of two functionally distinct endocrine parts: the **cortex** and **medulla**. The cortex consists of three concentric zones: The outer glomerulosa secretes the mineralocorticoid **aldosterone**, the intermediate fasciculata secretes **cortisol** (hydrocortisone), and the inner reticularis secretes **androgens** [androstenedione&dehydroepiandrosterone (DHEA)]. The endocrine cells of the adrenal medulla are the chromaffin cells, which are part of the sympathetic nervous system and produce the catecholamine epinephrine.



Cortisol secretion follows a **circadian** rhythm, beginning to rise at 4 am &peaking around 6 to 8 am. Thereafter, cortisol levels decreasethroughout the day,approach 50% of the peak value by 4 pm,and reach their nadir around midnight. Thenormal rateof cortisol production is about 8 to 15 mg/day. Cortisol is converted in the liver to an **inactive** metabolite known as **cortisone**, while androstenedione and DHEA are converted in the peripheral tissues, largely to testosterone and estrogen.

Adrenal hormone production is controlled by the **hypothalamus** and **pituitary**. **Corticotropin-releasing hormone** (CRH) is secreted by the hypothalamus and stimulates secretion of **corticotrophin[adrenocorticotrophic hormone (ACTH)**] from the anterior lobe of the

pituitary gland. ACTH in turn stimulates the adrenal cortex to produce cortisol. When sufficient or excessive cortisol levels are reached, a negative feedback is exerted on the secretion of CRH and ACTH, thereby decreasing overall cortisol production.
The most common conditions associated with adrenal gland dysfunction: glucocorticoid insufficiency (e.g., Addison's disease) and glucocorticoid excess (Cushing's syndrome)

Glucocorticoid insufficiency

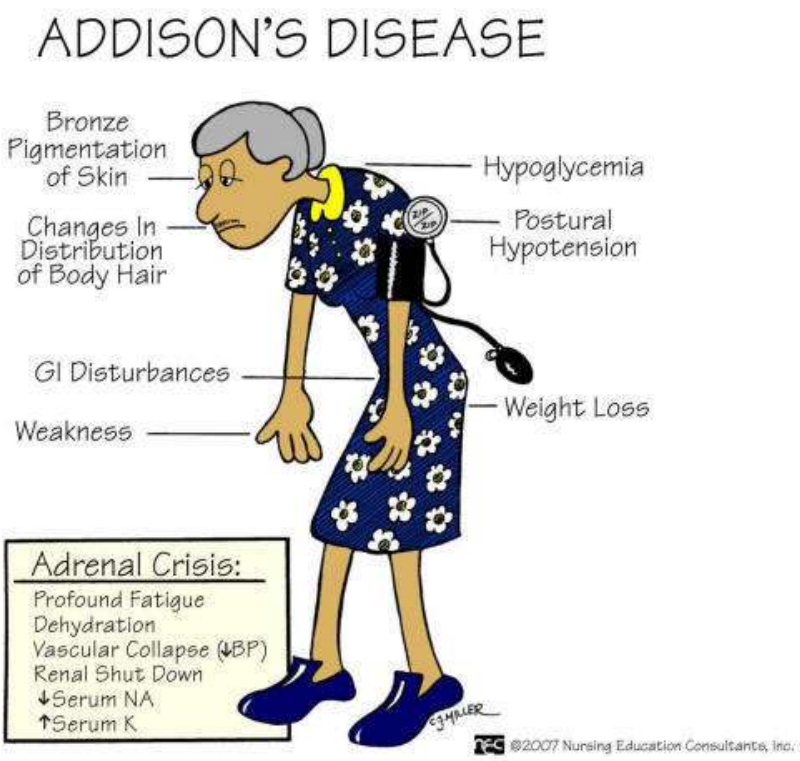
Primary adrenal insufficiency**(Addison's disease)** occurs when the defect is in the adrenal cortex itself; this disease**affects cortisol mainly**, but affects mineralocosticoid& androgens to a lesser extent. The serum levels of both CRH & ACTH increase in a compensatory manner.
Autoimmune dysfunction is responsible for 80% to 90% of cases in developed countries,whereas **tuberculosis** is the predominant cause in developing countries. Medications that inhibit cortisol synthesis (eg, ketoconazole) or accelerate cortisol metabolism (phenytoin, rifampin, phenobarbital) can also cause **primary** adrenalinsufficiency.
Secondary adrenal insufficiency occurs as a result of a **pituitary** gland disorder, whereby decreased production and secretion of ACTH leads to a decrease in cortisol synthesis. **Tertiary** adrenal insufficiency is a disorder of the **hypothalamus** that results in decreased production and release of CRH. ***Aldosterone*** *production is* ***unaffected*** *in the secondary and tertiary forms of the disease*. Chronic adrenal insufficiency often has a good prognosis if diagnosed early and treated appropriately.
Acute adrenal insufficiency (i.e., **adrenal crisis or addisonian crisis**) results from the body's inability to sufficiently increase endogenous cortisol during periods of excessive physiologic stress.Adrenal crisis can occur when patients with chronic adrenal insufficiency do not receive adequate glucocorticoid replacement during stressful conditions such as surgery, infection, acute illness, invasive medical procedures, or trauma.

Clinical presentation:

The clinical manifestations are observed when destruction of the cortex exceeds 90%. Weight loss, **dehydration**, **hyponatremia**, hyperkalemia, and elevated blood urea nitrogen are common in Addison disease. Hyperpigmentation is common in Addison disease and may involve exposed and non-exposed parts of the body. *Hyperpigmentation is usually* ***not seen*** *in secondary adrenal insufficiency because of* ***low amounts*** *of melanocyte-stimulating hormone.*

Diagnosis

The short cosyntropin stimulation test can be used to assess patients with suspected hypocortisolism. An increase to a cortisol level of 18 mcg/dL or more rules out adrenal insufficiency. Other tests include insulin hypoglycemia test & CRH stimulation test



Treatment

Goals of Treatment: Limit morbidity and mortality, return the patient to a normal functional state, and prevent episodes of acute adrenal insufficiency

Pharmacotherapy

Hydrocortisone,prednisone& prednisoloneare the glucocorticoids of choice, administered **twice daily** at the **lowest** effective dose to mimic the normal **diurnal** adrenal rhythm of cortisol production.

Recommended starting total daily doses are hydrocortisone 15 - 25 mg daily, which is approximately equivalent to prednisone 2.5 - 5 mg. **Two thirds** of the dose is given in the **morning**, and **one third** is given 6 to 8 hours later. The patient's symptoms can be monitored every 6 to 8 weeks to assess the response to proper glucocorticoidreplacement.**Fludrocortisone acetate** 0.05 to 0.2 mg orally once daily can be used to replace mineralocorticoid loss.

During times of severephysical stress (eg, febrile illnesses and after accidents), patients should be instructedto **double** their daily **dose** until recovery to eliminate the risk of adrenal crisis.

Treatment of secondary adrenal insufficiency is identical to primary disease treatment,with the exception that **mineralocorticoid replacement is usually not necessary**.

TABLE 18–2	Relative Potencies of Glucocorticoids			
Glucocorticoid	Anti-inflammatory Potency	Equivalent Potency (mg)	Approximate Half-Life (min)	Sodium-retaining Potency
Cortisone	0.8	25	30	2
Hydrocortisone	1	20	90	2
Prednisone	3.5	5	60	1
Prednisolone	4	5	200	1
Triamcinolone	5	4	300	0
Methylprednisolone	5	4	180	0
Betamethasone	25	0.6	100–300	0
Dexamethasone	30	0.75	100–300	0

Pharmacotherapy of acute adrenal insufficiency

Acute adrenal insufficiency representsa true endocrine **emergency**.Surgery, infection, and trauma are potential stressful**predisposing**events.The most common cause of adrenal crisis is abrupt withdrawal of exogenous glucocorticoids in patients receiving chronic treatment that resulted in hypothalamic pituitary-adrenal-axis suppression.

Hydrocortisone given **parenterally** is the treatment of **choice** because of its **combined** glucocorticoid and mineralocorticoid activity.The starting dose is 100 mg IVby rapid infusion, followed by a continuous infusion (usually 10 mg/h) **or** the recommended dose is administered via IV intermittent boluses of 50 – 100 mg / 6 hours usually for 24-48 hours. If the patient is stable, **oral** hydrocortisone started at **50 mg every 6hours**, followed by tapering to the individual's chronic replacement needs.

Fluid replacement often is required and can be accomplished with IV glucose-saline (**dextrose 5% in normal saline**) to support blood pressure.If hyperkalemia is present after the hydrocortisone maintenance phase, additional **fludrocortisone acetate** 0.1 mg daily.

Patients with adrenal insufficiency should carry a card or wear necklacethat containsinformation about their condition. They should also have easy access toinjectable hydrocortisone or glucocorticoid suppositories in case of an emergency orduring times of physical stress, such as febrile illness or injury.

Cushing syndrome

Cushing syndrome results from effects of **supraphysiologic** glucocorticoid levelsoriginating from either

1- **exogenous administration** or
2- **endogenous overproduction**

The endogenous overproduction results from either elevated levels of ACTH (**ACTH dependent**) or from abnormaladrenocortical tissues (**ACTH-independent**).

ACTH **dependent** Cushing syndrome (80% of all Cushing syndrome cases) is usuallycaused by overproduction of ACTH by the pituitary gland, causing adrenal hyperplasia.**Pituitary adenomas** account for ~85% of these cases (**Cushing disease**).
Ectopic ACTH-secreting tumors cause theremaining **20% of ACTH-dependent** cases.Ectopic ACTH syndrome refers to excessive ACTH production resulting from an endocrine or nonendocrine tumor, usually of the pancreas, thyroid, or lung (eg,small-cell lung cancer).
ACTH-**independent** Cushing syndrome is usually caused by adrenal adenomas and adrenal carcinomas.

Clinical presentation:

The **most common** findings in Cushing syndrome are central obesity, facial rounding (moon facies) & fat accumulation in the dorsocervical area (buffalo hump).
Other findings may include myopathy, abdominal striae, hypertension, glucose intolerance, psychiatric changes, gonadal dysfunction, and (amenorrhea and hirsutism) in women. Up to 60% of patients develop Cushing-induced **osteoporosis**.

Diagnosis:

Hypercortisolism can be established with a 24-hour urinary free cortisol (UFC), and/or low-dose dexamethasone suppression test (DST).
Other tests to determine **etiology** are plasma ACTH test; (adrenal, chest, or abdominal) CT scans and CRH stimulation test.

Treatment:

Goals of therapy include return the patient to a normal functional state by removing the source of hypercortisolismby removing the source of hypercortisolism while minimizingpituitary or adrenal deficiencies.

Non-pharmacological therapy:

Treatment of choice for both ACTH-dependent & independent Cushing syndrome is **surgical** resection of offending **tumors**. Transsphenoidal resection of the pituitary tumor is recommended.
Pituitary irradiation provides clinical improvement in about 50% of patients within 3 to 5 years, but pituitary hormone deficiencies (hypopituitarism) can occur.
Laparoscopic **adrenalectomy** may be preferred in patients with unilateral adrenal adenomas or for whom transsphenoidal surgery or pituitary radiotherapy have failed or cannot be used.

Pharmacotherapy:

Pharmacotherapy is generally used as:

1- Secondary treatment in preoperative patients, or
2- Adjunctive therapy in postoperative patients awaiting response.
3- Rarely, monotherapy is used as a palliative treatment when surgery is not indicated.

The therapeutic agents include:

1- Steroidogenic inhibitors

a- **Metyrapone** inhibits 11 β-hydroxylase, thereby inhibiting cortisol synthesis. Initially, patients can demonstrate increased plasma ACTH concentrations because of a sudden drop in cortisol. This can increase androgenic and mineralocorticoid hormones, resulting in hypertension, acne, and hirsutism. Other side effects include vertigo, headache, abdominal discomfort, and allergic rash. Metyrapone is currently available through the manufacturer only for compassionate use

b- **Ketoconazole** inhibits hepatic 11 β-hydroxylase& 17 α-hydroxylase. It is effective in lowering serum cortisol levels after several weeks of therapy. It also has **antiandrogenic**activity, which may be beneficial in women but can cause gynecomastia and decreased libido in men. The most common adverse effects are reversible elevation of hepatic transaminases. Ketoconazole may be used concomitantly with metyrapone to achieve synergistic reduction in cortisol levels; in addition, ketoconazole's antiandrogenic actions may offset the androgenic potential of metyrapone.

c- **Etomidate** is an imidazole derivative similar to ketoconazole that inhibits 11β-hydroxylase. Because it is only available in a **parenteral** formulation, use is limited to patients with acute hypercortisolemia requiring **emergency** treatment.

d- **Aminoglutethimide** inhibits cortisol synthesis and should be coadministered with another steroidogenesis inhibitor (usually metyrapone) due to **high relapse rates** with aminoglutethimidemonotherapy.

2- Adrenolytic agents

Mitotane is a **cytotoxic** drug that inhibits the 11-hydroxylation &**reduces synthesis** of cortisol. It takes weeks to months to exert beneficial effects. Mitotane damages cells within the zonafasciculata and reticularis. Nausea & diarrhea are common at doses greater than 2 g/day and can be avoided by gradually increasing the dose and/or administering it with food.

3- **Neuromodulators of ACTH release**

ACTH secretion is **mediated by neurotransmitters** such as serotonin, acetylcholine and catecholamines. Consequently, agents that target these transmitters have been proposed for treatment of Cushing disease, including cyproheptadine, bromocriptine, cabergoline, octreotide& rosiglitazone.

a- **Cyproheptadine**can decrease ACTH secretion in some patients. However, sedation and weight gain significantly limit its use.
b- **Pasireotide**is a somatostatin analogue that activates somatostatin receptors, thereby inhibiting ACTH secretion. It is approved for treatment of adults for whom pituitary surgery is not an option or has not been curative.

4-Glucocorticoid Receptor Blocking agents:

Mifepristone (RU-486) is a progesterone- and glucocorticoid-receptor antagonistthat inhibits dexamethasone suppression and increases endogenous cortisol andACTH levels in **normal subjects**.

Evidence suggests that mifepristone is highly effectivein **reversing** the manifestations of **hypercortisolism**. Its use for treatment ofCushing syndrome remains investigational.

Pheochromocytoma

Pheochromocytoma is a rare, **catecholamine-secreting tumor** derived from chromaffin cells.

Typically, there is elevation in the secretion of norepinephrine and epinephrine. Dopamine is found to be produced by some tumors. Because of excessive catecholamine secretion, pheochromocytomas may precipitate life-threatening **hypertension** or cardiac **arrhythmias**.If pheochromocytoma is found, it is potentially curable.

About **85%** of pheochromocytomas are located **within the adrenal glands**.When tumors arise outside of the adrenal gland, they are termed extra-adrenal pheochromocytomas, or **paragangliomas**.Common locations for extra-adrenal pheochromocytomas include bladder wall, heart& mediastinum.Approximately 10% of pheochromocytomas and 35% of extra-adrenal pheochromocytomas are malignant.

Clinical presentation

Headache, diaphoresis, palpitations, tremor, nausea, anxiety, epigastric pain, constipation & weight loss.

Diagnosis

Pheochromocytoma is diagnosed by measuring elevated levels of **metanephrines** (catecholamine metabolites) in blood or urine. CT scanning or MRI is performedtospecify the location of the tumor.

Treatment

Surgical resection of the tumor is the treatment of choice for pheochromocytoma and usually results in **cure** of the hypertension, but careful preoperative management is required to control blood pressure and heart rate, to correct fluid volume, and to prevent intraoperative hypertensive crises.**Laparoscopic**adrenalectomy should be performed for **small** adrenal pheochromocytomas, while **open resection** reserved for **very large** or **invasive**pheochromocytomas.

A high-sodium diet is combined with fluid intake to prevent severe hypotension after removal of the tumor. Blood pressure, heart rate, and glucose levels should be **monitored immediately** after surgery.

Alpha blockers, beta blockers, calcium channel blockers, and angiotensin receptor blockers all are recommended to **control hypertension prior to surgery**. Start alpha blockade with phenoxybenzamine**10-14 days** preoperatively to allow for **expansion** of blood volume. Initiate a beta blocker only **after** adequate alpha blockade (usually, 2 days). If beta blockade is started prematurely, unopposed alpha stimulation could precipitate a hypertensive crisis. Administer the last doses of oral alpha and beta blockers on the morning of surgery.

Multiple Myeloma Lec:5

- Multiple myeloma (MM) is a malignancy of the plasma cell and is characterized by an abnormal production of a monoclonal protein in the bone marrow. Features of the disease include bone lesions, anemia, and renal insufficiency.
- Multiple myeloma is an incurable disease; however, advancements in the treatment of myeloma have significantly extended survival.

1-Under normal circumstances, maturation to antibody-secreting plasma cells is stimulated by exposure to the antigen; however, in the plasma cell disorders (like multiple Myeloma ,…) the control over this process is lost .

2-In multiple myeloma, plasma cells produce immunoglobulin of a single heavy and light chain, a monoclonal protein commonly referred to as a paraprotein or M protein (M for monoclonal) . In some cases only light chain is produced and this appears in the urine as Bence Jones proteinuria .

Epidemiology and Etiology:

- Multiple myeloma (MM) is the second most common hematologic malignancy. It is estimated that approximately 26,850 new cases of MM would be reported in 2015, accounting for 1% to 2% of all cancers.
- The median age of diagnosis is 60-70 years and the disease occurs more Frequently in men than in women.
- The etiology of multiple myeloma is unknown although a exposure to ionizing radiation and genetic factors have been implicated..

Pathophysiology

- Although a small number of malignant plasma cells are present in the circulation, the majority are present in the bone marrow. The malignant plasma cells produce cytokines, which stimulate osteoclasts and result in net bone absorption. The resulting lytic lesions cause bone pain, fractures and hypercalcaemia. Marrow involvement can result in anaemia or pancytopenia
- The pathophysiology of MM involves complex bone marrow microenvironment, and cytokine interactions. Interleukin-6, tumor necrosis factor, vascular endothelial growth factor, and stromal-derived factor-1 support the establishment and proliferation of myeloma cells.
- The understanding of these interactions has led to novel agents used in the treatment of MM.

Clinical feature

- **Skeletal involvement**: pain, reduced height, pathologic fractures, hypercalcemia .

- **Anemia**: mainly caused by decreased erythropoiesis; produces weakness and fatigue .
- **Renal insufficiency**: mainly caused by "myeloma kidney" from light chains or hypercalcemia .
- **Recurrent infections**: respiratory and urinary tract infections or septicemia caused by gram-positive or gram-negative organisms .
- **Bleeding diathesis**: from thrombocytopenia or coating of platelets with M protein
- **Amyloidosis** (develops in 10%) (Amyloidosis is an extracellular deposition of an insolouble protein called amyloid in various tissues which affect the normal function and structure of the affected tissue)

Poor Prognostic Factors

•• High serum β2-microglobulin and low serum albumin
•• Elevated C-reactive protein
•• Elevated lactate dehydrogenase
•• IgA isotype
•• Low platelet count
•• Chromosome 13 deletions and other cytogenetic abnormalities

Investigations

The diagnosis of myeloma requires two of the following criteria:

1-increased malignant plasma cells in the bone marrow

2-serum and/or urinary paraprotein

3-skeletal lesions.

Bone marrow aspiration, plasma and urinary electrophoresis, and a skeletal survey are thus required.

Treatment

- Multiple myeloma is an incurable disease; however, advancements in the treatment of myeloma have extended survival significantly. Almost all patients will become refractory to initial treatment.
- A "watch and wait" approach is an option for asymptomatic patients who have no lytic lesions in the bone. Once symptoms occur, treatment is required

Nonpharmacologic Therapy

- Autologous stem cell transplantation results in higher response rates and extends overall survival .

Pharmacologic Therapy

There are five main classes of drugs used in the treatment of multiple myeloma:

alkylating agents, anthracyclines, corticosteroids, immunomodulatory agents, and proteasome inhibitors.

Immediate support :

- High fluid intake to treat renal impairment and hypercalcaemia ,
- Analgesia for bone pain ,
- Bisphosphonates for hypercalcaemia and to delay other skeletal related events,
- Allopurinol to prevent urate nephropathy, Plasmapheresis, as necessary, for hyperviscosity.
- Plasmapheresis is an operation to take blood from someone, then to separate the red blood cells from the plasma, and to return the red blood cells suspended in a saline solution to the patient.

Conventional-Dose Chemotherapy

- Patients who present with symptomatic disease will be started on therapy. Two regimens used are : (VAD)vincristine, doxorubicin & dexamethasone (MP) melphalan and prednisone .
- VAD like chemotherapy regimens are used most often in transplant candidates because it avoids the alkylating agent melphalan, thus minimizing damage to the stem cell compartment .

Immunomodulatory Drugs

-Corticosteroids

High-dose dexamethasone (40 mg/day) is an option for patients who cannot tolerate chemotherapy or have few high-risk features. Advantages of this regimen include ease of administration and lack of hematologic adverse effect .

-Thalidomide (Thalomid®)

Thalidomide as monotherapy or combination therapy is beneficial in the treatment of multiple myeloma.. Thalidomide may be given in combination with dexamethasone, resulting in greater response rates than when given alone.

Common side effects of thalidomide therapy include somnolence, constipation, peripheral europathy, deep vein thrombosis.

Prophylactic anticoagulation should be considered to prevent deep vein thrombosis associated with thalidomide therapy. There are substantial teratogenic effects of thalidomide if used during pregnancy .

-Lenalidomide :

Lenalidomide is an immunomodulating agent related to thalidomide that was recently approved for the treatment of patients with multiple myeloma.

Lenalidomide lacks the common side effects of thalidomide, such as constipation and peripheral neuropathy 6-Bisphosphonates:

Bone disease is a common manifestation of multiple myeloma. Bisphosphonates should be initiated in symptomatic patients with bone lesions to slow osteopenia and reduce the fracture risk associated with the disease.

Pamidronate and zolendronic acid have equivalent efficacy in the management of osteolytic lesions, but because of relative ease of administration, zolendronic acid is used most frequently .

Proteasome Inhibitors

- Bortezomib (Velcade) and carfilzomib (Kyprolis) are proteosome inhibitors approved for the treatment of MM. Proteosome inhibitors induce myeloma cell death by modulating nuclear factor kappa-B products, including inflammatory cytokines and adhesion molecules that support myeloma cell growth.
- These drugs also disrupt the myeloma microenvironment by inhibiting the binding of myeloma cells to the bone marrow stromal cells
- Bortezomib is a member of a new class of agents known as proteosome inhibitors . It induce myeloma cell death . It Approved for the treatment of relapsed disease

(Drugs Used in Multiple Myeloma)

Drug	Adverse Effects	Comments
Bortezomib (Velcade)	Constipation, decreased appetite, asthenia, fatigue, fever, thrombocytopenia, dose-related, reversible peripheral neuropathy	Dose: 1.3 mg/m^2 IV bolus twice weekly for two weeks; week 3 off; repeat
Dexamethasone	Hyperglycemia, edema, adrenal cortical insufficiency	Dose given orally once daily
Doxorubicin (Adriamycin)	Myelosuppression, alopecia, cumulative dose-limiting toxicity, myocardium damage	Given in combination with vincristine and dexamethasone (VAD)
Lenalidomide (Revlimid)	Possible birth defects (since analogue of thalidomide), neutropenia, thrombocytopenia, deep vein thrombosis, pulmonary embolism, pruritis, fatigue	Dose is 10 mg orally taken with water once daily Women of childbearing age must use two forms of contraception Pregnancy test must be taken before and during use
Melphalan (Alkeran)	Myelosuppression, secondary malignancies, pulmonary fibrosis, sterility, alopecia	Dose of 0.15 mg/kg for 7 days given orally once daily, repeated every 4–6 weeks IV formulation used for stem cell transplantation
Thalidomide (Thalomid)	Severe birth defects, peripheral neuropathy, deep vein thrombosis, somnolence, constipation	Start at 50 mg by mouth daily and titrate to a maximum of 800 mg; doses are taken nightly Women of childbearing age must use two forms of contraception Pregnancy test must be taken before and during use
Vincristine (Oncovin)	Dose limiting toxicity: peripheral neuropathies, paresthesias, constipation, alopecia	Given in combination with doxorubicin and dexamethasone (VAD)

Colorectal Cancer Lec:6

Colorectal cancer is caused by the abnormal growth of epithelial cells which form the lining of the colon or rectum. These small growths (known as **polyps**) are often benign, although some have the potential to develop and become cancerous

Epidemiology

- Colorectal cancer is the third leading cause of cancer deaths in the U.S. adult population.
- Approximately 70% of these cancers will arise in the colon, whereas 30% will occur in the rectum.

Risk Factors

General

- **Age** is the primary risk factor --Age appears to be the biggest risk factor for the development of colorectal cancer with 70% of cases diagnosed in adults older than 65 years of age.

Dietary

- High-fat, low-fiber diets increase risk.
- The risk of colorectal cancer appears to be inversely related to calcium and folate intake.
- Higher intake of calcium and vitamin D has been associated with a reduced risk of colorectal cancer in epidemiologic studies and polyp recurrence in polyp-prevention trials.
- Regular (at least two doses per week) nonsteroidal anti-inflammatory drug (NSAID) and aspirin use is associated with a reduced risk of colorectal cancer.

Lifestyle

- Alcohol, Smoking
- Obesity or physical inactivity

Comorbid Conditions

- Inflammatory bowel disease (ulcerative colitis and Crohn's disease)

Hereditary or Genetic

- Familial adenomatous polyposis (FAP)
- Hereditary nonpolyposis colorectal cancer (HNPCC)
- Family history

Symptoms and diagnosis

- Early diagnosis of colorectal cancer has thepotential to improve survival rates; howeverearly symptoms (such as abdominal pain)may be confused with other diseases, meaning many patients have advanced disease when diagnosed.

Symptoms: Changes in bowel habits, anorexia, nausea and vomiting,weakness (if anemia is severe).
Signs: Blood in stool, weight loss, abdominal pain.

Almost 85% ofpatients referred to hospital have one or more of the following high-risk symptoms:

- Rectal bleeding
- A mass in the abdomen or rectum
- Change in bowel habit
- Perianal symptoms, such as abscesses or lesions

As the cancer becomes more advanced,other symptoms can develop. For example,excessive bleeding from the colon cancause anaemia, which leaves the patientfeeling breathless and tired.
If the cancerbegins to obstruct the colon, furthersymptoms include bloating, constipation and vomiting.

Methods of diagnosis vary from country to country but typically if a patient presents high-risk symptoms to their doctor they will be given a physical examination. If this raises any concerns, a number of additional tests may be performed:
• Colonoscopy – the entire length of thecolon is viewed using a colonoscope.
• Sigmoidoscopy – a small tube(sigmoidoscope) is used to view thelower colon.
• Double contrast barium enema – x-raysof the colon and rectum. Barium lines the colon allowing an outline to be viewed in an x-ray.

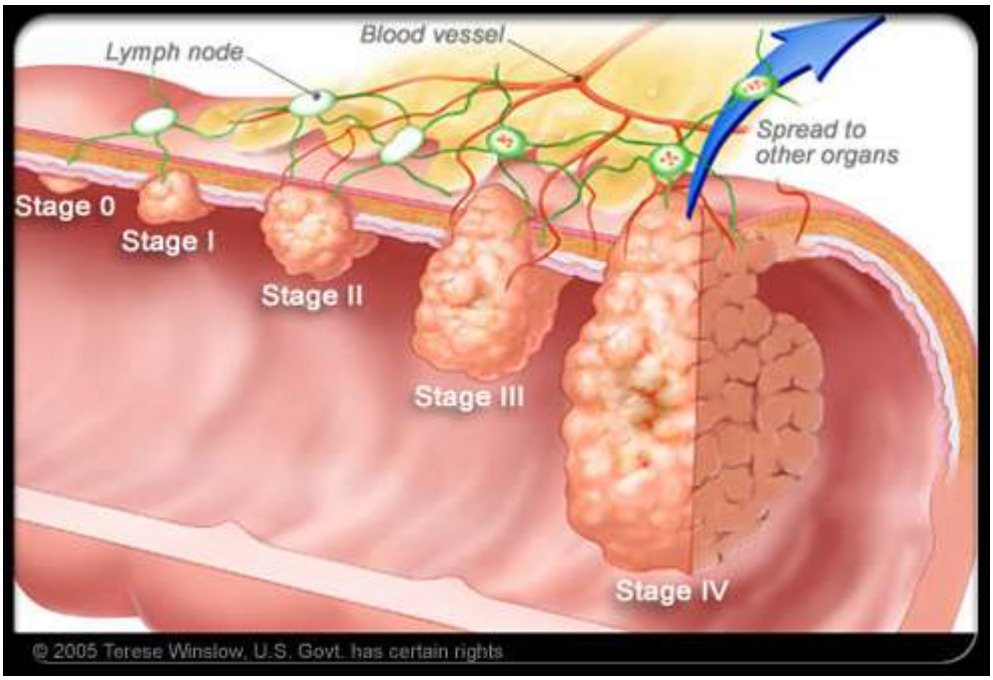
- A biopsy, where sample tissue is removedduring a colonoscopy or sigmoidoscopy,is required to confirm the diagnosis ofcolorectal cancer and determine how advanced the disease is.
- Fecal Occult Blood Testing (FOBT)

Staging and prognosis

- When colorectal cancer is diagnosed in the early stages, it is curable with surgical intervention and >90% of patients survive 5 years.
- The Tumor Node Metastasis (TNM) staging system is most commonly used for colon cancer.

  Stage I indicates penetration into (but not through) the bowel wall.
  Stage II generally indicates penetration through the bowel wall;
  stage III indicates lymph node involvement; and
  stage IV indicates metastatic disease.

- Optimal node sampling at the time of surgery is critical to staging and should include the evaluation of 12 to 17 lymph nodes.
- Patients with early-stage colorectal cancer often are asymptomatic; therefore, intensive screening programs as just described are advocated to reduce the mortality of this disease.
- Of patients with metastatic and recurrent colorectal cancer, 60% to 90% have elevated CEA (CarcinoEmberyonic Antigen) or CA-19–9 levels.
- Levels are elevated in relation to the stage and extent of disease, the degree of tumor differentiation, and the site of metastases.



prognosis

- The overall 5-year survival rate for colorectal cancer patients is 65%, although this differs greatly depending on how advanced the cancer is.

- **CEA** levels every 3 months for the first 3 years, then every 6 months for the next 2 years, and then annually.[43]
- **Colonoscopy** is repeated annually for several years and then every 3 to 5 years.
- More than 50% of patients who have recurrent disease also have elevated CEA levels.

Treatment

- The stage of colorectal cancer upon diagnosis is the most important prognostic factor for survival and disease recurrence.
- Stages I, II, and III disease are considered potentially curable and are aggressively treated in an attempt to cure these patients.
- Patients who develop stage IV disease are treated to reduce symptoms, avoid disease-related complications, and prolong survival.

Non pharmacologic Therapy

Operable Disease (Stages I–III)

- **Surgery** Individuals with ***stage I to III*** colorectal cancer should undergo a complete surgical resection of the tumor mass with removal of regional lymph nodes as a curative approach for their disease
- **Radiation Therapy -*Adjuvant radiation plus chemotherapy*** is considered standard treatment for patients with ***stage II or III*** rectal cancer after the surgical procedure is complete.

Metastatic Disease (Stage IV)

- **Surgery-**Select patients who have from one to ***three small nodules isolated to the liver, lungs***, or ***abdomen*** may have a prolongation of survival, although cure is rare.
- **Radiation** -Symptom reduction is the primary goal of radiation for patients with advanced or metastatic colorectal cancer.

Pharmacologic Therapy

- Tumor recurrence is a significant problem associated with **stage III** colon and rectal cancers, with up to 60% of all surgically treated patients.
- Causes of these relapses may include peritoneal seeding caused by exfoliation of tumor cells in the colonic lumen and spillage during surgery.

Chemotherapy

- Currently, agents used in combination chemotherapy for the adjuvant treatment of colorectal cancer, improves disease-free survival (DFS).
- 5-Flurouracil-based chemotherapy is the standard regimen used in adjuvant treatment of colon cancer
- Triple-drug therapy (5-FU, leucovorin, and oxaliplatin) (FOLFOX)–based chemotherapy is the standard regimen used in adjuvant colon cancer. It is usually given for 6 months).
- (FOLFIRI) based chemotherapy is of (5-FU, leucovorin, and irinotecan).

Biological therapies

- Adjuvant chemotherapy is standard therapy for patients with stage III colon cancer

- Ongoing trials are evaluating the role of the monoclonal antibodies **Bevacizumab (**targeting VEGF) and **Cetuximab** (targeting EGFR) epidermal growth factor receptor (EGFR) inhibitor in combination with **FOLFOX** in the adjuvant setting.

Some patients with advanced colorectal cancer who are not initially able to undergo surgery due to invasive tumours can be treated with chemotherapy before being considered for surgery (called neo adjuvant treatment).

TABLE 88–3. Common Regimens Used in Colon Cancer

Acronym	Regimen
5-Fluorouracil	5-Fluorouracil given alone as a bolus or continuous infusion
LV/5-fluorouracil	Leucovorin + 5-fluorouracil given as a bolus or continuous infusion
IFL	Irinotecan + 5-fluorouracil + leucovorin given as IV boluses
IFL + bevacizumab	IFL as above plus bevacizumab
FOLFIRI	Folinic acid (leucovorin) + 5-fluorouracil + Irinotecan given as combined IV boluses and continuous infusions
FOLFOX	Folinic acid (leucovorin) + 5-fluorouracil + oxaliplatin given as combined IV boluses and continuous infusions
CAPOX	Capecitabine + Oxaliplatin given as oral therapy and IV boluses
CAPIRI	Capecitabine + Irinotecan given as oral therapy and IV boluses

Note: Many variations exist, and current literature should be checked prior to administering any chemotherapy regimen.

Table 91–5

Treatment Regimens for Adjuvant Colon Cancer

Stage II[a]	Stage III
High Risk • Capecitabine or 5-FU plus leucovorin • FOLFOX	Good Performance Status • FOLFOX • Capecitabine or 5-FU plus leucovorin
Low Risk[b] • Observation or clinical trial • Capecitabine or 5-FU plus leucovorin	Poor Performance Status • Capecitabine

5-FU, 5-fluorouracil.

Chemotherapy for Metastatic Disease stage IV

- Metastasis to the liver via hematogenous spread (through the portal circulation) is the most common site of disease spread beyond the regional lymph nodes and occurs in 50% of patients with invasive disease.
- Traditional chemotherapy and targeted biological therapies are the mainstay of treatment for metastatic colon or rectal cancer and have improved the median survival time of these patients to more than 20 months
- (The most important factor in patient survival is not the initial regimen but whether or not patients receive all three active chemotherapy drugs (5-FU, irinotecan, and oxaliplatin) at some point in their treatment course.)

- Before using these agents, testing for KRAS mutation status should occur. Extensive literature exists documenting evidence demonstrating failure of EGFR inhibitors in patients whose tumors have a mutation in codon 12 or codon 13 of the KRAS gene.

Breast Cancer **Lec:7**

Breast cancer begins in breast tissue in lobules (gland for milk production), and the ducts that connect the lobules to the nipple.

Types of breast tumor

The most common type of benign breast tumour is called a fibroadenoma. This may need to be surgically removed to confirm the diagnosis. No other treatment is necessary.

Malignant tumor (which can metastasis if untreated)

Etiology and Risk factor

The causes of breast cancer are unknown.

risk factors canincrease a woman′s chances of getting breast cancer:-

1-Age: It's rare in women under 35. (80%) of cases occur in women aged 50 or over.
2- lack of childbearing or breastfeeding
3-Hormonal factors: Exposure to the hormonesoestrogen and progesterone for long, uninterrupted periods can affect your breast cancer risk
4- Genetic factors (family history)
5- Lifestyle factors alchol, smoke, obesity

Symptoms:-

•A lump in the breast
• A change in the size or shape of the breast
• dimpling of the skin or thickening in the breast tissue
• A nipple that’s turned in (inverted)
• Rash (like eczema) on the nipple
• Discharge from the nipple
• Swelling or a lump in the armpit.

Diagnosis:-

- ✓ **A mammogram:**
  Mammograms are usually only done in women over 40.
  Ultrasound:
  ultrasound is more useful than a mammogram in women under 40.
- ✓ **Fine needle aspiration (FNA):**
- ✓ **Biopsy:**
- ✓ **CT (computerised tomography) scan:**
- ✓ **Blood tests:**

Occasionally, a blood test may be used to check whether the breast cancer cells are producing certain chemicals (tumour markers). But this isn't usually done.

Stages of breast cancer

- ✓ **Stage I**
  tumor is less than 1 cm across, and has not spread into the surrounding areas.
- ✓ **Stage II**
  anywhere from 1-2 cm across, and has spread into the surrounding areas including the lymph nodes

Stage III (inflammatory breast cancer)

Its more than 2 cm across and has spread to the lymph nodes.

A type of cancer most associated with this is called inflammatory breast cancer, because the breast is inflamed because the cancer is blocking the lymph nodes.

- ✓ **Stage IV**
  The cancer has spread to other parts of the body such as the bones, liver or lungs. This is called secondary or metastatic breast cancer.

Types of breast cancer

✓ DCIS - ductal carcinoma in situ (non invasive)

it means that cells inside some of the ducts of your breast have started to turn into cancer cells. There is very little chance that any of the cells have spread to the lymph nodes or elsewhere in the body.

✓ Invasive ductal breast cancer

It is also called ductal carcinoma. A ductal carcinoma of the breast is a cancer that started in the cells that line the ducts of the breasts and has begun to spread into the surrounding breast tissue.

✓ Invasive lobular breast cancer

This means that the cancer started in the cells that line the lobules of the breast and has spread into the surrounding breast tissue. It is most common in women between 45 and 55 years old.

If you have invasive lobular breast cancer diagnosed in one breast, there is a slightly higher risk of getting it in the other breast in the future.

✓ Inflammatory breast cancer

This is a rare type of breast cancer. It is called inflammatory because the breast tissue becomes inflamed. The cancer cells block the smallest lymph channels in the breast.

Symptoms of inflammatory breast cancer

Because the lymph channels are blocked, the breast may become

- Swollen
- Red
- Firm or hard
- Hot to the touch

The breast can also be painful in inflammatory breast cancer, but this is not always the case.

Treatment

The first type of treatment for breast cancer is usually surgery. The type of surgery depends on the type of breast cancer you have. Surgery is usually followed by chemotherapy or radiotherapy or, in some cases, hormone or biological treatments.

The main treatments for breast cancer are:

- surgery
- radiotherapy
- chemotherapy
- hormone therapy

The type of treatment or the combination of treatments will depend on how the cancer was diagnosed and the stage it is at.

1-surgery

✓ **Removing the breast cancer (lumpectomy**): Lumpectomy is typically reserved for smaller tumors that are easily separated from the surrounding tissue.
✓ **Removing the entire breast (mastectomy):**Mastectomy is surgery to remove all of your breast tissue.
✓ **Removing one lymph node (sentinel node biopsy):**

✓ **Removing several lymph nodes (axillary lymph node dissection):**

Removal of additional affected lymph nodes does not improve survival in cases of early breast cancer following a lumpectomy,

2- Radiation therapy

External beam radiation is commonly used after lumpectomy for early-stage breast cancer. Doctors may also recommend radiation therapy after mastectomy for larger breast cancers.

Side effects: fatigue and sunburn-like rash.

3- Chemotherapy

Either adjuvant (after surgery or radiation) or neoadjuvant (before surgery) systemic chemotherapy.

Side effects: include hair loss, nausea, vomiting, fatigue and a small increased risk of developing infection.

4- Hormone therapy

is often used to treat breast cancers that are sensitive to hormones.

Hormone therapy can be used after surgery or other treatments to decrease relapse.

If the cancer has already spread, hormone therapy may shrink and control it.

Treatments that can be used in hormone therapy include:

- Tamoxifen is the most commonly used selective estrogen receptor modulator (SERM). SERMs act by blocking estrogen from attaching to the estrogen receptor on the cancer cells, slowing the growth of tumors and killing tumor cells. Tamoxifen can be used in both pre- and postmenopausal women .Possible **side effects** include fatigue, hot flashes, night sweats and vaginal dryness. **More significant risks** include cataracts, blood clots, stroke and uterine cancer.
- **Medications that stop the body from making estrogen after menopause.**

One group of drugs called aromatase inhibitors blocks the action of an enzyme that converts androgens in the body into estrogen. These drugs are effective only in postmenopausal women.

Aromatase inhibitors include anastrozole (Arimidex), letrozole (Femara) and exemestane (Aromasin). **Side effects** of aromatase inhibitors include joint and muscle pain, as well as an increased risk of bone thinning (osteoporosis).

Another drug, fulvestrant (Faslodex), directly blocks estrogen (anti estrogen). Fulvestrant is generally used in postmenopausal women for whom other hormone-blocking therapy is not effective or who can't take tamoxifen .Fulvestrant is given by injection once a month.

- **Surgery or medications to stop hormone production in the ovaries**.

  In premenopausal women, prophylactic oophorectomy and may be called surgical menopause.

Prevention

Women may reduce their risk of breast cancer by maintaining a healthy weight, drinking less alcohol, being physically active and breastfeeding their children.

The benefits with moderate exercise such as brisk walking are seen at all age groups including postmenopausal women.

Tamoxifen and raloxifene are able to reduce the risk of breast cancer but increase the risk of thromboembolism.

Pituitary gland disorders

The pituitary gland is referred to as the "**master gland"**because it regulates many other glands & body systems. The pituitary is very small nearly the size of **a pea**, weighing between 0.4 and 1 g in adults. It is located at the base of the brain in proximity to the nasal cavity divided into two distinct regions, the **anterior lobe**, or adenohypophysis, and **the posterior lobe**, or the neurohypophysis.

The posterior pituitary is **innervated** by nervous stimulation from the **hypothalamus**, resulting in the release of specific hormones to exert **direct tissue effects**. The posterior lobe secretes two major hormones: **oxytocin &vasopressin [**alsonamed **arginine vasopressin (AVP), antidiuretic hormone(ADH)**&**argipressin**]. Oxytocin causes **contraction** of the smooth muscles in the breast during **lactation**&plays a role in **uterine** contraction during **parturition.** Vasopressin is essential for proper **fluid balance** and acts on the **renal collecting ducts** to conserve water.

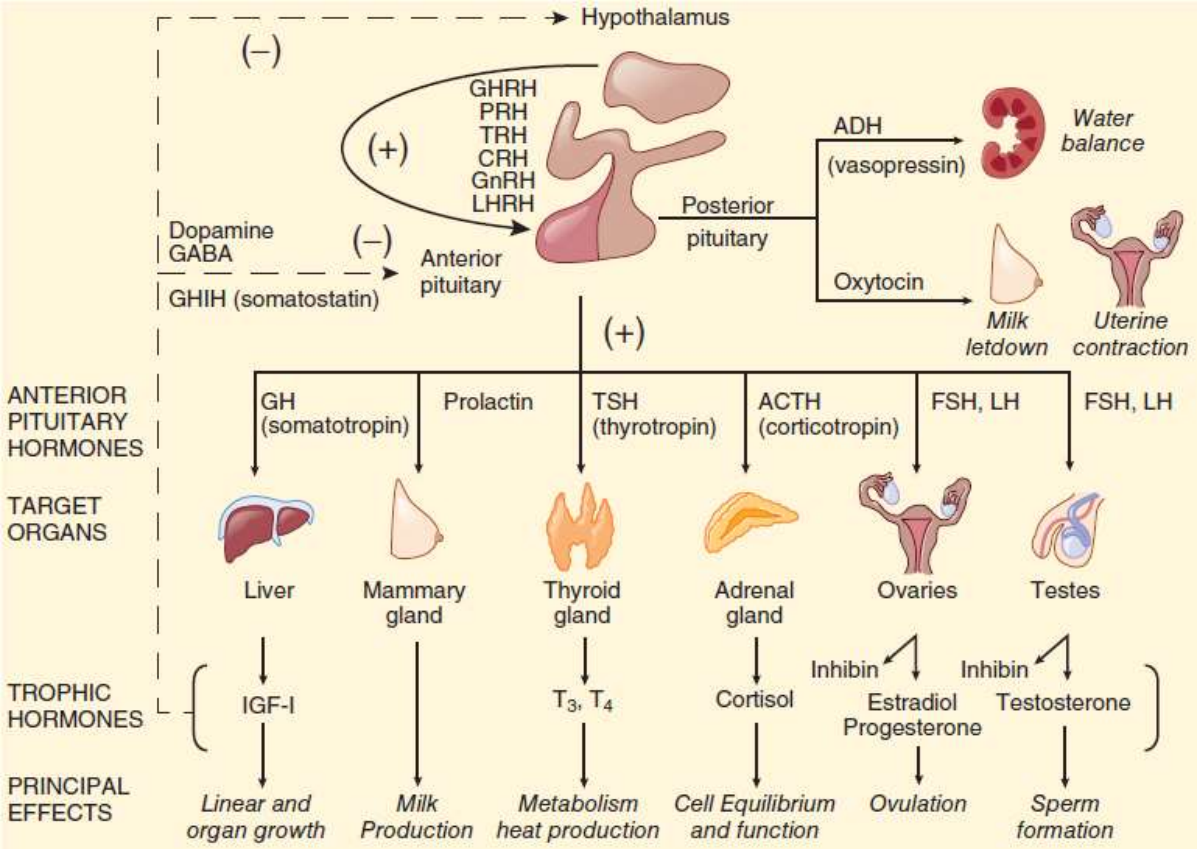
The anterior pituitary lobe is under the control of several **releasing** and **inhibiting** hormones secreted from the **hypothalamus** via **a portal vein system**. The anterior pituitary lobe secretes**six major polypeptide hormones:**

1- Growth hormone (GH) or somatotropin,
2- Adrenocorticotropic hormone (ACTH) or corticotropin,
3- Thyroid-stimulating hormone (TSH) or thyrotropin,
4- Prolactin,
5- Follicle-stimulating hormone (FSH), and
6- Luteinizing hormone (LH).

Hormonal feedback regulatory system

The **hypothalamus** is responsible for the synthesis and release of hormones that **regulate** the pituitary gland. Stimulation or inhibition of the pituitary hormones ends up with specific responses in peripheral target glands. In response, these glands secrete hormones that exert a **negative feedback** on other hormones in the hypothalamic–pituitary axis (Fig-1). This negative feedback serves to maintain body system homeostasis. In general, **high** circulating hormone levels **inhibit** the release of hypothalamic and anterior pituitary hormones.

Damage and **destruction** of the pituitary gland may result in **secondary**hypothyroidism, **secondary** hypogonadism, **secondary**adrenal insufficiency, growth hormone **(GH) deficiency**, or **hypoprolactinemia**, either separately or more than one condition occurring simultaneously due to insufficiency of one or more than one of anterior pituitaryhormones, **but** sometimes there is insufficiency of **all** pituitary hormones (i.e., **panhypopituitarism**).A tumor (**adenoma)** located in the pituitary gland may result in **excess** secretionof a hormone or may physically compress the gland and suppress adequate release of one or more hormones.



Growth hormone (somatotrophin)

Upon stimulation by **GHRH**, somatotropes release GH into the circulation, thereby stimulating the **liver** and other peripheral **target tissues** to produce insulin-like growth factors (IGFs). These IGFs, also known as **somatomedins**, are of two types:**IGF-I** and **IGF-II**.

IGF-I is the hormone generally responsible for growth of **bone** and **other tissues**. **High** levels of IGF-I **inhibit GH** secretion through another hypothalamic hormon**somatostatin**, which inhibit GHRH secretion at the hypothalamus.

Secretion of GH is lowest during infancy, increases during childhood, peaks during adolescence, and then declines gradually during the middle years.

Growth hormone excess

Acromegaly is a rare pathologic condition characterized by excessive production of GH **after** closure of epiphyses of long bones.**Gigantism** which is even **rarer** than acromegaly, is the excess secretion of GH **prior to** epiphyseal closure **in children**.

Patients diagnosed with acromegaly are reported to have a twofold to threefold increase in mortality, usually related to ***cardiovascular, respiratory, or neoplastic diseases***. The most common cause of excess GH secretion in acromegaly is a **GH-secreting pituitary adenoma**, accounting for approximately 98% of all cases.

Clinical Presentation of Acromegaly:

General:

The patient will experience slow development of **soft-tissue overgrowth** affecting many body systems. Signs and symptoms may gradually progress **over 7 to 10 years**.

Symptoms:

Symptoms related to local effects of the GH secreting tumor, such as **headache** and **visual disturbances**. Other symptoms related to elevated GH and IGF-Iinclude **excessive sweating**,**joint pain**, and paresthesias.

Signs:

The patient may exhibit **coarsening** of **facial features**, **increased hand volume**, **increased ring size**, **increased**shoe size, an **enlarged** tongue, **enlarged** nose & forehead, Abnormal enlargement of various organs (**organomegaly)** such as liver, spleen, and heart.

Laboratory tests:

In **normal subjects**, serum GH&IGF-I are **depressed** to **undetectable** levels following an oral glucose tolerance test (OGTT), while these patients show failure of this response due to **autonomous secretion**. Hyperglycemia may be present in 50% of patients.

Additional clinical consequences:

1- Cardiovascular diseases as hypertension, coronary heart disease CHD,cardiomyopathy, and left ventricular hypertrophyLVH.

2- Osteoarthritis and joint damage develops in up to **90%** of patients.

3- Type 2 diabetes develops in approximately 25% of patients.

4- Patients with acromegaly may have an increased risk for development of esophageal, colon, and stomach cancer.

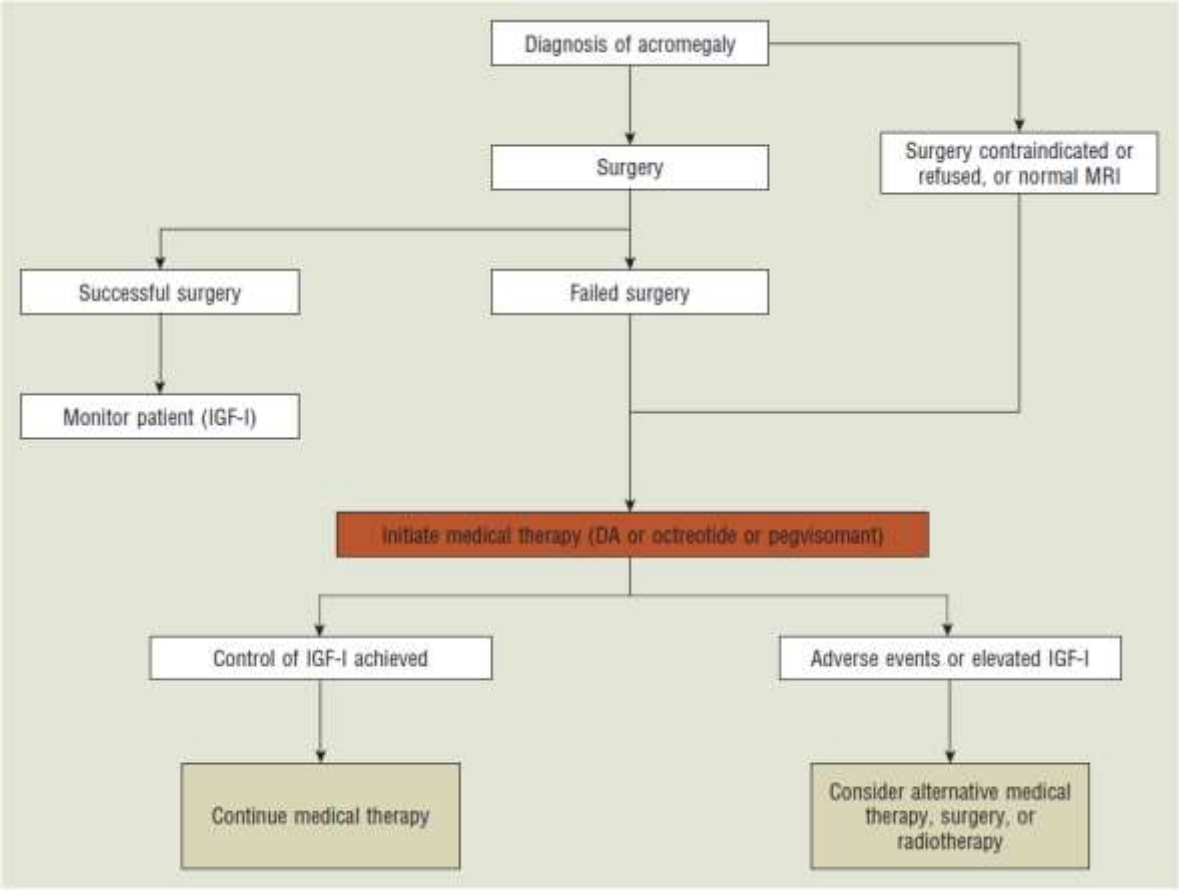
Treament:

1- The primary goals are to reduce GH and IGF-Ilevels, improve the clinical signs and symptoms, and decrease mortality.

2- Most patients with acromegaly are successfully treated with**transsphenoidal surgical resection** of the GH-secreting **adenoma**.

3- For patients who are poor surgical candidates, those who have not responded to surgical intervention, or others who refuse surgical treatment, **radiation therapy** may be considered. Radiation, however, may take several years to relieve the symptoms of acromegaly.

4- Drug therapy is considered when1) surgery and irradiation are contraindicated, 2) when rapid control of symptoms is indicated, or 3) when other treatments have failed to normalize GH and IGF-I concentrations.



1- Dopamine agonists:

- In **normal** healthy adults, dopamine agonists**increase**GH production. However, for patients with acromegaly, there is a **paradoxical decrease in GH production.** Most clinical experience with dopamine agonists in acromegaly is with **bromocriptine.**

- For treatment of acromegaly, bromocriptine is initiated at a dose of 1.25 mg at **bedtime** and is increased by 1.25 mg increments every 4 days as needed.Clinical studies have shown that dosages >20 or 30 mg daily do not offeradditional benefits in the suppression of GH.

- When used for treatment of acromegaly, the duration of action of bromocriptine is **shorter** than that for treatment of hyperprolactinemia. Therefore, the total daily dose of bromocriptine should be divided into **three or four doses**.

2- Somatostatin analogues:

Octreotide is a long-acting somatostatin analog that is approximately **40 times more potent**than is endogenous somatostatin. It is started at a dose of 50 mcg every 8 hours, then increasing the dose to 100 mcg every 8 hours after 1 week, to improve the patient's tolerance of adverse gastrointestinal effects. The dose can be increased by increments of 50 mcg every 1 to 2 weeks based on mean serum GH and IGF-I concentrations.

3- Growth hormone receptor antagonist:

Pegvisomant binds to GHreceptors in the liver and inhibits IGF-I. It does not inhibit GH production; rather, it **blocks the physiologic effects of GH on target tissues**. Therefore, **GH** concentrations **remain elevated** during therapy, and response to treatment is evidenced by a reduction in IGF-I concentrations.

GH Deficiency

Short stature is a condition defined by **subnormal rate of growth** following otherwise **normal** birth weight. Normal growth is defined as more than 5 cm per year in mid-childhood. A **true lack of GH** is among the **least common** causes and is known as growth hormone deficient (GHD) short stature. It is important to exclude hypothyroidism & other cause of short stature.

Several medications such as somatostatin analogs,gonadotrophin releasing hormon(**GnRH) agonists**, glucocorticoids & cimetidine may induce GH insufficiency.

Clinical Presentation of Short Stature:

General:

Suboptimum rate of growth with **normal body proportions**.

Signs:

Children with GH deficient short stature may also present with central obesity, prominence of the forehead, immaturity of the face& delayed skeletal maturation.

Laboratory tests:

Normal subjects show elevated GH levels following **stimulation tests**, but the patients will exhibit none or very small increase following this test. Reduced IGF-Ilevels may be present. Because GH deficiency may be **accompanied** by loss of other pituitary hormones, hypoglycemia and hypothyroidism may be noted.

Treatment:

1- **Recombinant GH (somatropin)** is currently considered the **mainstay** of therapy for treatment of GHD short stature by**IM**or **SC** injection.GH replacement therapy should be **initiated** as **early** as possible after diagnosis of GH insufficiency and **continued until a desirable height**is reached or growth velocity has decreased to <2.5 cm per year after the pubertal growth spurt.

2- **Recombinant IGF-I**has been recently approved by the FDA for the treatment of children with short stature due to **severe primary IGF-I deficiency** or **GH gene deletion** with neutralizing antibodies to GH.

3- **GH releasing hormone**: a synthetic GHRH product known as **sermorelin** currently is FDA approved for the treatment of idiopathic GH deficiency in children.Sermorelin is administered daily by subcutaneous injection. No serious adverse events have been identified.

Hyperprolactinemia

Persistent elevation of serum **prolactin** usually affects women of **reproductive age.** Prolactin concentrations >20 mcg/L observed on multiple occasions are generally considered indicative of this condition. Hyperprolactinemia most commonly affects women and is **very rare** in men.

Clinical Presentation of Hyperprolactinemia:

Signs and symptoms

Symptoms related to **local effects** of the prolactin secreting **tumor**, such as headache and visual disturbances that result from tumor compression of the optic chiasm.

Female patients experience oligomenorrhea, **amenorrhea**, **galactorrhea**, **infertility**,decreased libido, hirsutism, and acne.

Male patients experience decreased libido, erectile dysfunction, **infertility**,**galactorrhea**, and **gynecomastia.**

Laboratory tests:

Prolactin serum concentrations at rest will be >20 mcg/L on multiple occasions.

Additional clinical sequelae:

Prolonged suppression of estrogen in premenopausal women with hyperprolactinemia leads to **decreases in bone mineral density** and significant risk for development of **osteoporosis**.

Treatment:

The **goal of therapy** is to normalize prolactin serum concentrations and re-establish gonadotropin secretion to restore fertility and reduce the risk of osteoporosis.The treatment of hyperprolactinemia depends on the **underlying cause**.

In **drug-induced hyperprolactinemia**, discontinuation of offending medication & initiation of an alternative usually normalizes serum prolactin concentrations.

If a therapeutic alternative does not exist, therapy with **dopamine agonists** is warranted& **sex-steroid replacement** also should be considered.

Transsphenoidal surgery for removal of **prolactinomas** is reserved for patients 1) who are **refractory to or cannot**tolerate dopamine agonists and 2) for **very large tumors** that cause severe compression of adjacent tissues.

Radiation therapy may require several years for effective tumor shrinkage and reduction in serum prolactin concentrations and usually is used only in conjunction with surgery.

Dopamine agonists:

Very effective in **normalizingprolactin** serum concentrations 3 to 6 months of therapy.

1-Bromocriptine inhibits the release of prolactin via its hypothalamic receptors. It normalizes prolactin serum levels, restores gonadotropin production, and **shrinks** pituitary **tumor size**.

It is initiated at a dose of 1.25 to 2.5 mg once daily at bedtime to minimize adverse effects. The dose can be gradually increased by 1.25-mg increments every week. Usual therapeutic doses range from 2.5 to 15 mg/day.

The most common adverse effects include CNS symptoms such as headache, lightheadedness, &dizziness. GI effects such as nausea, abdominal pain, and diarrhea also are common.

Most clinicians **discontinue therapy** as soon as pregnancy is detected because the effects of bromocriptine on **gonadal function** and fertility of the offspring remain unknown.

2- **Cabergoline** is a **long-acting** dopamine agonist with **high** selectivity for dopamine D2-receptorswith the advantage of **less frequent dosing**.It has replaced bromocriptine as the agent of choice.Cabergoline has proved effective in female & male patients who are intolerant of or resistant to bromocriptine.

The initial dose of **cabergoline** is 0.5 mg once weekly. This dose may be increased by 0.5-mg increments at 4-week intervals based on serum prolactin concentrations. The usual dose is 1 to 2 mg weekly; however, doses as high as 4.5 mg weekly have been used.

- The most common adverse effects are nausea, vomiting, headache, and dizziness. Several case reports of women who received cabergoline therapy pregnancy have **not documented** an increased risk of spontaneous abortion or congenital abnormalities. However, prospective data in large numbers of pregnancies are lacking.

Panhypopituitarism

-A condition of **complete (panhypopituitarism) or partial loss of anterior & posterior pituitary hormones** resulting in a complex disorder characterized by multiple pituitary hormonedeficiencies.

Patients with panhypopituitarism may have:

ACTH deficiency,gonadotropin deficiency,GH deficiency,hypothyroidism, and**hypo- or hyperprolactinemia**

- Pharmacologic treatment of panhypopituitarism is essential and consists of **replacemen**t of specific pituitary hormones after careful assessment of individual deficiencies. Replacement most often consists of **glucocorticoids, thyroid hormone preparations, and sex steroids.** Administration of **recombinant GH** also may be necessary. Patients with panhypopituitarism will need lifelong replacement therapy and constant monitoring of multiple homeostatic functions.

Therapeutics II/

Thyroid disorders

The thyroid gland consists of two lobes and is situated in the lower neck. The gland synthesizes, stores and releases twoactive hormones: Tetra-iodothyronine(Thyroxine, T4) and tri-iodothyronine (T3). Regulation ofhormone synthesis is by thyrotrophin[thyroid stimulating hormone**(TSH)**] from the **anterior** lobe of the pituitary gland. In turn,TSH is regulated by the **hypothalamic** thyrotrophin-releasing hormone **(TRH).**Circulating levels of thyroid hormones exert **negative feedback** phenomena on both the pituitary TSH and hypothalamic TRH.

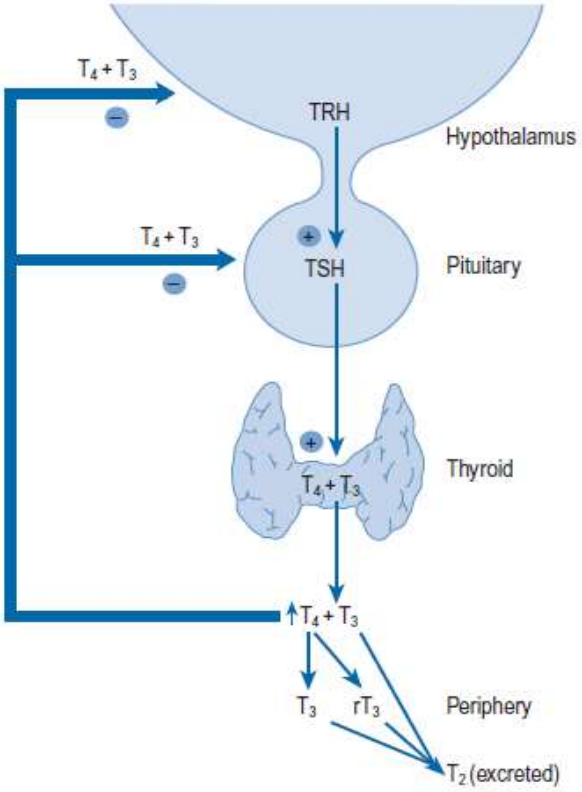


Figure (1): Hypothalamic-anterior pituitary-thyroid axis

Hypothyroidism

Hypothyroidism is the **clinical** status resulting from **decreased** production of thyroid hormones or very rarely from tissueresistance.***Subclinical*** *hypothyroidism* is defined by an **elevated TSH** with **normal** thyroid hormone levels.

The vast **majority** of patients have **primary** hypothyroidism which is due to failure of thyroid gland itself to produce sufficient hormonesdue to:

1-Most commonly ***chronic autoimmune thyroiditis*****(Hashimoto's disease)**.

2-Iatrogenic hypothyroidism because of:

a) exposure to **destructive** amounts of thyroid gland radiation,

b) after total thyroidectomy,

c) **excessive** thionamide (thioamide) doses already used to treat hyperthyroidism,

d) amiodarone & lithium may induce hypothyroidism in up to 10% of patients.

3-Other causes of primary hypothyroidism include iodine deficiency &thyroid hypoplasia.

Secondary disease (reduced TSH levels)is due to **hypopituitarism** which may be due to destruction of thyrotrophs (TSH secreting cells) by pituitary **tumors**, **pituitary surgery** orpituitary **radiation**, while **tertiary** disease due to failureof the hypothalamus to secrete the necessary TRH.

Peripheral hypothyroidism is due to tissueinsensitivity or resistance to the action of often **higher** levels of thyroid hormones.

Clinical presentation

Symptoms of hypothyroidism include dry skin, cold intolerance, weight gain (despite anorexia or normal eating pattern), constipation, lethargy &loss of energy. In children, thyroid hormone deficiency may manifest as growth or intellectual retardation. Physical signs include coarse skin and hair, brittle nails, bradycardia, and slowed or hoarse speech.

Most patients with secondary hypothyroidism have other clinical signs of generalized pituitary insufficiency, such as abnormal menses & decreased libido (from low LH & FSH), or additional evidence of pressuring effect of pituitary tumor, such as visual field defects.

Myxedema coma is a rare consequence of decompensated hypothyroidism manifestedby **hypothermia**, **advanced** stages of hypothyroid symptoms, and

alteredsensorium ranging from **delirium to coma**. Mortality rates of 60% to 70% necessitateimmediate and aggressive therapy of myxedema coma.

Diagnosis

A rise in TSH level is the first evidence of **primary** hypothyroidism (due to reduced negative feedback). Many patients have a **free** T4 level within the normal range (**compensated** hypothyroidism). As the disease progresses, the **free** T4 drops below normal, while T3 concentration is often maintained in the normal range despite low T4. Antithyroid peroxidase antibodies and antithyroglobulin antibodies areusually elevated in case of autoimmune etiology.

Secondary hypothyroidism should be suspected in patients having decreased T4&/or T3 levels with inappropriately normal or low TSH levels.

Treatment

Goals of Treatment: Restore thyroid hormone concentrations in tissues, providesymptomatic relief, prevent neurologic deficits in newborns and children, and reversethe biochemical abnormalities of hypothyroidism.

Levothyroxine (L-thyroxine, T4) is the drug of choice for thyroid hormone replacement because it is chemically stable, relatively inexpensive,& free of antigenicity. Once a particular productis selected, **therapeutic interchange is discouraged**. Because T3 (and not T4) is the biologically active form, levothyroxine administration results in a pool of thyroid hormone that is readily and consistently converted to T3.

In patients with **long-standing** disease and older individuals **without** known cardiacdisease start therapy with levothyroxine 50 mcg daily and increase after **one** month.The recommended initial dose for older patients with known cardiac disease is25 mcg/day titrated upward in increments of 25 mcg at **monthly** intervals to preventstress on the cardiovascular system.

Levothyroxine is the drug of choice for pregnant women, and the goal is to decreaseTSH to the normal reference range for pregnancy.

Treatment of myxedema coma

Immediate and aggressive therapy with **IV bolus** levothyroxine, 300 to 500 mcg.Initial treatment with IV **liothyronine (synthetic T3)**or a combination ofboth hormones is advocated because of impaired conversion of T4 to T3.

Glucocorticoid therapy with IV **hydrocortisone** 100 mg every 8 hours is recommended untilcoexisting adrenal suppression is excluded.

Maintenance levothyroxine doses are typically 75 to 100 mcg IV until the patientstabilizes and oral therapy can be safely re-established.

Supportive therapy is very important to maintain adequate ventilation, euglycemia, adequate BP, andbody temperature.

Hyperthyroidism

Thyrotoxicosis results when tissues are exposed to excessive levels of T4, T3, or both. The causes include:

TSH-secreting **pituitary tumors** release biologically active hormone that is unresponsiveto normal feedback control (secondary cause). These tumors may additionally**secrete** prolactin or growthhormone; therefore, patients may present with **amenorrhea**, **galactorrhea**, or signs of **acromegaly**.

In **Graves disease**, hyperthyroidism results from autoimmune disorder due to the action of thyroid-stimulatingantibodies (TSAb). These immunoglobulins bind to TSH receptor and activate the thyroid gland in the same manner as TSH.

An autonomous thyroid nodule (toxic adenoma) is a thyroid mass whose function is independent of pituitary control. Hyperthyroidism usually occurs with larger nodules(>3 cm in diameter).In multinodular goiter, follicles with autonomous function coexist with normal follicles. Thyrotoxicosis occurs when autonomous follicles generate more thyroid hormone than is required.

Painful subacute (granulomatous or de Quervain) thyroiditis often develops after a viral syndrome, but rarely has a specific virus been identified

Painless (silent, lymphocytic, or postpartum) thyroiditis is a common cause of thyrotoxicosis;its etiology is not fully understood; autoimmunity may underlie most cases.

Thyrotoxicosis factitia is produced by ingestion of exogenous thyroid hormone. This may occur when thyroid hormone is used for inappropriate indications, excessive doses, or ingested accidently.Amiodarone may induce thyrotoxicosis, but at much lower rate than its ability to induce hypothyroidism.

Clinical presentation

Symptoms of thyrotoxicosis include nervousness, palpitations, fatigue, heat intolerance, weight loss concurrent with increased appetite, increased frequency of bowel movements, and scanty mensesin women.Physical signs include warm, smooth, moist skin and unusually fine hair; separationof the ends of the fingernails from the nail beds (onycholysis), tachycardia at rest, and fine tremor of the protruded tongue and outstretched hands.

Graves disease is manifested by hyperthyroidism, diffuse thyroid enlargement, extrathyroidal findings of exophthalmos, and pretibial myxedema

Thyroid storm is a **life-threatening** medical emergency characterized by **decompensated** thyrotoxicosis, high fever (often >39.4°C [103°F]), diarrhea, vomiting, dehydration, tachycardia, tachypnea, delirium and coma.

Precipitating factors include infection, trauma, surgery, radioactive iodine (RAI) treatment, and withdrawalfrom antithyroid drugs.

Diagnosis

Elevated 24-hour radioactive iodine uptake (RAIU) indicates **true** hyperthyroidism(the patient's thyroid gland is overproducing T4, T3, or both).A low RAIU indicates that excess thyroid hormone is not a consequence of thyroidgland hyperfunction but is likely caused by thyroiditis or hormone ingestion.

TSH-induced hyperthyroidism is diagnosed by elevated free thyroid hormone levels, and elevated serum TSH concentrations.TSH-secreting **pituitary adenomas** are diagnosed by demonstrating **lack** of TSHresponse to TRH stimulation.

Treatment

Goals of Treatment: Eliminate excess thyroid hormone; minimize symptoms and long-term consequences & reduce or eliminate the potential for side effects.

Nonpharmacologic Therapy

Surgical removal of the thyroid gland should be considered in patients with a largegland (>80 g), severe ophthalmopathy (exophthalmos), or lack of remission on antithyroid drugs.

If thyroidectomy is planned, **propylthiouracil** (PTU) or **methimazole** is usuallygiven until the patient is **biochemically euthyroid** (usually 6–8 weeks), followed byaddition of **iodides** (500 mg/day) for **7–14 days** before surgery to decrease vascularityof the gland. **Propranolol** has been used for several weeks preoperatively and 7 to 10 days aftersurgery to maintain pulse rate less than 90 beats/min.

Pharmacotherapy

1-Thioureas (Thionamides or thioamides)

PTU and **methimazole** block thyroid hormone synthesis by **inhibiting** the **peroxidase**enzyme system of the thyroid, so inhibiting incorporation of iodide into iodotyrosines.

Improvement in **symptoms** and **laboratory** abnormalities should occur within 4 to 8weeks, at which time a tapering regimen to maintenance doses can be started. Make dosage change **monthly** because the endogenously produced T4 will reach a **new steady-state** concentration in this interval.

Usual initial doses include methimazole 30 to 60 mg daily given in three divided doses. Evidence existsthat both drugs can be given as a single daily dose. Typical daily maintenance doses are methimazole 5 to 30 mg. Continue therapy for 12 to 24 months toinduce long-term remission.

Major adverse effects include **agranulocytosis** (with fever, oropharyngeal infection, and granulocyte count <250/mm3), **aplastic anemia**, and **hypopro thrombinemia**. If it occurs,agranulocytosis usually develops in the first 3 months of therapy; routine monitoring isnot recommended because of its **sudden** onset.

2- Iodides

Iodide **acutely blocks** thyroid hormone release, inhibits thyroid hormone biosynthesis by **interfering** with intra thyroidal **iodide use**, and **decreases size** and **vascularity**of the gland.

Symptom improvement occurs within **2 - 7 days** of initiating therapy, and serum T4and T3 concentrations may be reduced for a few weeks.Iodides are often used as **adjunctive** therapy to prepare a patient with Graves diseasefor surgery, and to acutely inhibit thyroid hormone release and quickly attain the euthyroidstate in severely thyrotoxic patients.

Potassium iodide is available as a saturated solution (**SSKI,** 38 mg iodide per drop)or as **Lugol solution,** containing 6.3 mg of iodide per drop. When used to prepare a patient for surgery, it should be administered 7 to 14 dayspreoperatively.

3-<u>Adrenergic blockers</u>

β-Blockers are used to **ameliorate** thyrotoxic **symptoms** such as palpitations, anxiety,tremor, and heat intolerance. β- blockers are usually used as **adjunctive** therapy with antithyroid drugs, RAI, oriodides when treating Graves' disease or toxic nodules; in preparation for surgery; orin thyroid storm

Initial dose of propranolol of 20 to 40 mg orally four times daily is effective for most patients (heart rate <90beats/min). Younger or more severely toxic patients may require 240 to 480 mg/day.

Centrally acting sympatholytics (eg, **clonidine**) and calcium channel antagonists (eg,**diltiazem**) may be useful for symptom control when **contraindications** to β-blockadeexist.

4- **<u>Radioactive iodine</u>**

Sodium iodide–131 is an **oral liquid** that concentrates in the thyroid and initially disrupts hormone synthesis by incorporating into thyroid hormones and thyroglobulin. Over a period of weeks, follicles that have taken up RAI and surrounding folliclesdevelop evidence of **cellular necrosis** and **fibrosis** of **interstitial tissue**.

RAI is the **agent of choice** for Graves disease, toxic autonomous nodules, and toxicmultinodular goiters. **Pregnancy is an absolute contraindication** to use of RAI.

Antithyroid drugs **are not** routinely used after RAI because their use is associated with a higher incidence of **post-treatment recurrence** or **persistent hyperthyroidism.**

A single dose of 4000to 8000 rad results in a euthyroid state in 60% of patients at **6 months** or sooner. Asecond dose of RAI should be given **6 months** after the first RAI treatment if thepatient remains hyperthyroid.

Parathyroid gland

Physiology

Most individuals possess **four** parathyroid glands situated posteriorto the upper and lower lobes of the thyroid. These glandssecrete parathyroid hormone (PTH). The unbound ionised plasma **calcium levels** regulate the secretion of PTH, increased calcium concentration suppressing PTH secretionand low levels stimulating it.PTH acts on the renal tubular transport of calcium and phosphate and also stimulates the renal synthesis of 1,25-dihydroxycolecalciferol (active vitamin D).PTH and active vitamin D act to maintain plasma calcium levels within the normal range. PTH increases distal tubular reabsorption of calcium and decreases proximal and distal tubular reabsorption of phosphate. PTH stimulates osteoclast-mediated bone resorption but, in addition, has an anabolic effect on bone, with an increase in osteoblast numberandfunction.

Hypoparathyroidism/hypocalcaemia

Hypoparathyroidism is the clinical state which may arise either from failure of the parathyroid glands to secrete PTHor from failure of its action at the tissue level.

Aetiology

Hypoparathyroidism most commonly occurs as a result of**surgery** for **thyroid disease** or after neck exploration and **resection**of adenoma causinghyperparathyroidism. Othercauses include **autoimmune** parathyroid destruction.

Clinical manifestations

Most of the clinical features of hypoparathyroidism are due to**hypocalcaemia**. The decrease in **ionised** plasma calcium levelsleads to increased **neuromuscular excitability**. The major signsand symptoms are shown in the box 1.

Numbness and tingling in the extremities and around the mouth
Muscle spasm (tetany)
Epilepsy
Irritability
Cataracts (prolonged hypocalcaemia)
Chvostek's sign (facial spasm on tapping the 7th cranial nerve)
Trousseau's sign (spasm of hand when blood pressure cuff inflated above systolic pressure)

Treatment

Severe, acute hypocalcaemia **with tetany** should be treatedwith intravenous calcium gluconate. **Initially**, **10 mL** of 10%calcium gluconate is given by **slow** intravenous injection, preferably with ECG monitoring. If **further** parenteraltherapy is required, **20 mL** of 10% injection should beadded to each **500 mL** of **intravenous fluid** and given **over 6hr**. The plasma magnesium level should always be measured inpatients with hypocalcaemia, and if low, magnesium therapyinstituted.

For **chronic** treatment, PTH therapy is **not** currently a practical option as the hormone has to be administered parenterally,and the current high cost is prohibitive. Maintenancetreatment for hypoparathyroidism is easily achieved with a**vitamin D** preparation to increase intestinal calcium absorption,often in conjunction **with calcium** supplementation.

Hyperparathyroidism

Hyperparathyroidism occurs when there is increasedproduction of PTH by the parathyroid gland. **Primary**hyperparathyroidism causes **hypercalcaemia**. **Secondary** hyperparathyroidism reflects a physiological response to **hypocalcaemia**or **hyperphosphataemia**.

Primary hyperparathyroidism is due to the development of either single parathyroid adenomas or rarely (<5%) hyperplasiaof all four glands.

There are several conditions associated with secondary hyperparathyroidism, including **chronic renal failure** and**vitamin D deficiency**.

Clinical manifestations

The clinical features of hyperparathyroidism are shown in box 2. Theseare related to the effects of **hypercalcaemia (if primary disease)**itself, or the effects of **mobilisation** of calciumfrom the skeleton and **excretion** in the urine.

Anorexia, weight loss
Polydipsia, polyuria
Mental changes: poor concentration and memory
Fatigue
Nausea, dyspepsia and vomiting
Constipation
Hypertension
Renal stones
Conjunctival and corneal 'calcium' deposits
Bone pain and deformity
Pathological fractures

Treatment

Surgical **removal** of the adenoma or removal of all hyperplastic tissue is the **only curative** treatment for **primary** hyperparathyroidism. The main indications for surgical treatment are persistenthypercalcaemia > 2.85 mmol/L, symptomatic hypercalcaemia, and progression of osteoporosis. Postoperatively, **temporary hypocalcaemia**is common.

In patients with bone disease,treatment with alfacalcidol (vitamin D analog) and calcium supplements shouldbe started on the day before the operation. Approximately10% of surgically treated patients develop permanenthyperparathyroidism.