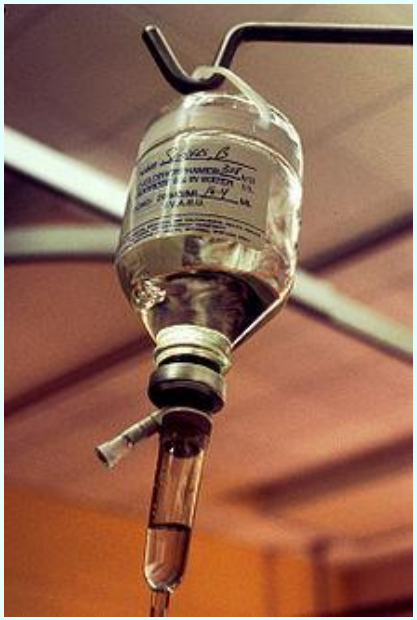
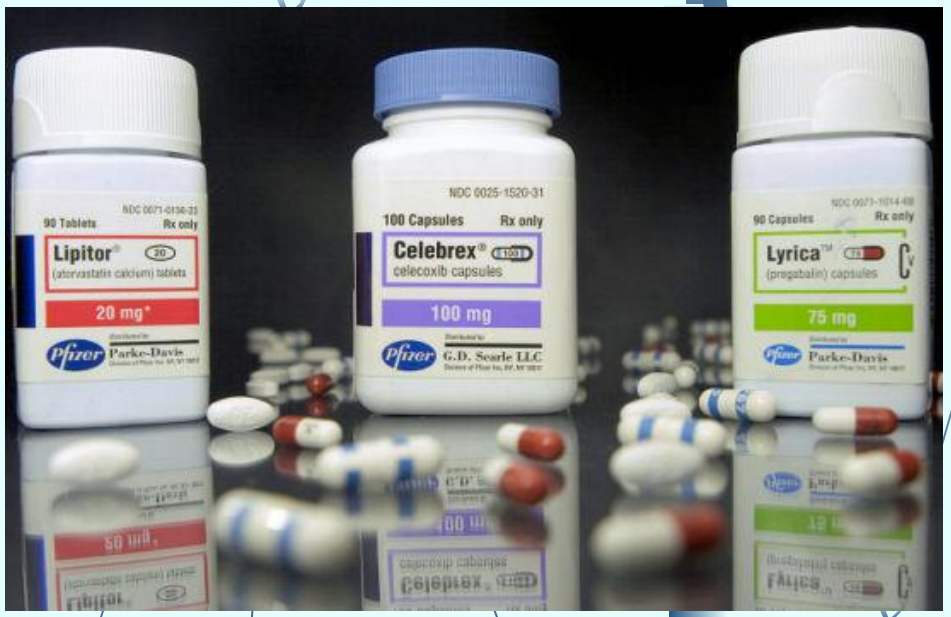
Zaporizhian State Medical University

Pharmacology Department

Lecture № 5

SIDE EFFECTS OF CHEMOTHERAPEUTIC DRUGS, CYTOSTATICS, HORMONAL MEDICATIONS





Adverse Effects of Penicillins

The most important side-effect is Hypersensitivity (1–10%);

The allergic reactions have been divided into 3 types:

- **Immediate Reaction :** the most severe and occurs within 20 min after parenteral administration and appears to be mediated by **IgE**.

It consists of pruritus, paraesthesia (numbness and tingling), wheezing, choking, fever, edema, and generalized urticaria and can lead to hypotension, shock, loss of consciousness, and death.

- **Accelerated Reaction** appears 1–72 hours after administration and consists mainly of urticaria.
- **Late Reaction** appears 72 hours to several weeks after drug administration. It consists mainly of skin rashes.

Non-allergic Reactions to Penicillins

- Transient palpitation, Hypertension.
- Toxicity to the brain may manifest as mental confusion, twitching, auditory and visual disturbances, convulsions and coma, when large doses >20 MU, esp. *Novocaine Benzylpenicillin,* are injected.

Novocaine Benzylpenicillin may produce CNS stimulation with psychiatric symptoms like fear of imminent death, acute depersonalization and hallucinations.

Being insoluble, it can also cause microembolism.

Bleeding has occurred with high doses due to interference with *platelet* function.

Local irritancy and direct toxicity -

pain at IM injection site and thrombophlebitis of injected vein are dose related expression of irritant action.

Benzylpenicillin Potassium (*Penicillin G potassium*) –

15 million units contain 975 mg of ionic $K^{\pm}$

Hyperkalemia may develop especially if the drug is administered to patients with impaired renal function,

receiving ACE inhibitors or potassium sparing diuretics.

Benzylpenicillin Sodium (*Penicillin G sodium*) –

risk of edemas, pulmonary edema, acute heart failure

in patients with congestive heart failure.

* Superinfection- in the form of **Intestinal** or **Urinary Infection**, **Pneumonia** or **Bacteraemia** may develop due to **overgrowth** such resistant organism as

lebsiella

erobacter

seudomonas auroginosa

andida albicans

E.g., ***Candida albicans*** is a normal resident of the vagina and GIT.

An antibiotic may destroy the normal bacterial flora without affecting the fungal organism. As a result, *Candida albicans* can proliferate and cause **CANDIDIASIS**, manifesting as diarrhea, soreness and redness of the mouth (thrush), glossitis, and vaginitis.

* **Nystatin** is used for the prevention of fungal infections and for the treatment of oropharyngeal, vaginal and perineal lesions.
* **Amphotericin B** is administered for **s**erious systemic fungal infections.
*

Adverse effects of Cephalosporins

1. **Allergy** (1–2%). The cephalosporins should be avoided in patients allergic to *penicillin:* 5–15% show cross-sensitivity.
2. **Bleeding** (II and III generations) due to **antivitamin K** effects. Cephalosporins that contain **methylthiotetrazole ring** frequently cause hypoprothrombinemia and bleeding disorders.

Cefamandole, Cefotetazole, Cefmetazole, Cefotetan (II generation), and

III generation drugs influence on hemostatic properties since they possess ***coumarin-like* action**, interfere with hepatic **vitamin K metabolism**, leading to a deficiency of vitamin K-dependent *plasma* ***coagulation factors*** (II, VII, IX, X), inducing ***hypoprothrombinemia***.

Administration of vitamin K 10 mg twice weekly, can prevent this.

3. **A disulfiram-like effect**. Drugs with **methylthiotetrazole ring** can cause ***disulfiram*-like action**: they block **aldehyde dehydrogenase** and cause accumulation of **acetaldehyde** and can cause all the typical and serious consequences of a ***disulfiram-like action***.

Adverse effects of **Tetracyclines**

Tetracycline, **Doxycycline** (***Vibramycin***) should be avoided for pregnant women and for children under 8 y.o. as:

Tetracyclines **chelate Ca^{+}** and are deposited in growing bones and teeth, causing staining, dental hypoplasia and bone deformities.

Tetracyclines interact with polyvalent **Metal Cations (Al, Fe)** and reduce their absorption from the gut.

Superinfection and

Vitamin B complex deficiency may develop as *tetracyclines* are incompletely absorbed after oral administration and interfere with the Colonic Bacteria Flora.

Anti-anabolic effect: high doses decrease protein synthesis in host cells which may result in renal damage.

Disturbances of the bone marrow, Photophobia (abnormal sensitivity of the eyes to light), **Unsteady gait, Intracranial Hypertension.**

Adverse Effects of Aminoglycosides: *Streptomycin, Gentamicin, Amikacin*

- **Ototoxicity** - they can affect both branches of the 8th cranial nerve.

  1). **Cochlear toxicity** includes **hearing loss**, **tinnitus** (ringing in the ears).

  Hearing loss may occur with loop diuretics (***Furosemide***, ***Ethacrynic acid***), anticancer drugs ***Cisplatin*** and the ***Vinca alkaloids***.

  Tinnitus is associated with ***Aspirin*** and ***Quinidine***.

  2) **Vestibular** toxicity, which manifests as **balance gait problem**, **vertigo**, and **nausea** resulting from **vestibular apparatus dysfunction**.

- **Nephrotoxicity** - from mild renal impairment to severe acute tubular necrosis.

  Retention of the aminoglycosides by the proximal tubular cells disrupts Ca^{2+} mediated transport processes and results in kidney damage.

- **Neuromuscular Toxicity: Skeletal Neuromuscular Blockade – inhibition of neuronal acetylcholine release**

(due to inhibition of Ca^{2+} uptake necessary for the release of ACh), and direct blockade of **Nicotinic Receptors** of skeletal muscles.

Adverse Effects of Macrolide Antibiotics: *Erythromycin, Azithromycin, Clarithromycin, Roxithromycin, Spiramycin,*

- **Allergic reactions:** fever, eosinophilia, urticaria, dermatitis and lymphadenopathy.
- GI disturbances, cholestatic hepatitis, jaundice,
- Superinfection with Gr(–) organisms and *Candida*.

* **Hepatic dysfunction** is a contraindication for *erythromycin* therapy. Compared with *erythromycin*, the newer drugs require less frequent administration and cause less nausea, vomiting, and diarrhea.

Erythromycin is an inhibitor of hepatic microsomal CYP-450, interfering with the metabolic degradation of number of drugs.

As a result, *erythromycin* reduces **plasma clearance** with **Increased Plasma Levels** and **Increased Toxicity** of:

Terfenadine, Ketoconazole, Cimetidine, Theophylline, Carbamazepine, Cyclosporine, Digoxin, Warfarine, Disopyramide, Methylprednisolone.

Erythromycin has antiarrhythmic properties similar to those of **Class IA antiarrhythmic drugs**, and causes an **increase** in **Atrial** and **Ventricular refractory periods**.

This is to be a problem in patients with heart disease or in those who are receiving drugs that **delay Ventricular Repolarization**.

High-doses IV have caused **ventricular fibrillation** and **torsade de pointes**.

Each episode of **arrhythmia**, **QT interval prolongation**, and **myocardial dysfunction** occurred 1–1.5 hours after **Erythromycin** infusion and resolved after withdrawal.

In an FDA database analysis, 346 cases of cardiac arrhythmias associated with ***Erythromycin*** were identified.

There was a **Preponderance** of **Women**, as there was among those with life-threatening **Ventricular Arrhythmias** and **deaths** after IV ***Erythromycin*** **lactobionate.**

Pseudomembranous Colitis -

the most serious potentially fatal adverse effect of Clindamycin and Lincomycin

- Caused by overgrowth of *Clostridium difficile* (Superinfection Development) which elaborates necrotizing toxins .

Manifestation:

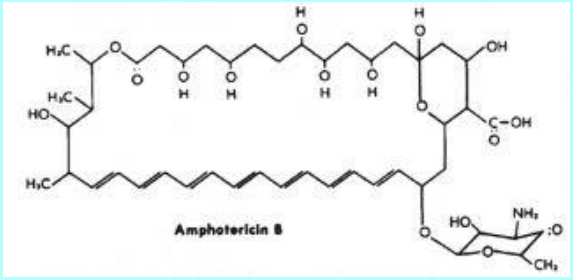
- The patient develops profuse, watery diarrhea, fever, abdominal pain, leukocytosis.
- *Clostridium difficile* infection is confirmed.

Treatment:

- PO Metronidazole or Vancomycin is effective in controlling this serious problem.

Amphotericin B – an antifungal drug, polyene highly toxic antibiotic, produced by *Streptomyces nodosum*.

It is the drug of choice used in the treatment of the **systemic mycoses**.



Adverse effects:

- **Renal Toxicity** - the most serious side effect. Some degree of reduction of renal function occurs in > 80% of patients receiving the drug.
- **Hypokalemia** (25%) may require *KCl* supplementation.
- **Hypomagnesaemia**
- **Anaemia, Thrombocytopenia**
- **Impaired hepatic function**
- **Phlebitis** at the site of injection
- **Profound generalized malaise**
- **Anaphylactic reactions**.

Synthetic Antifungal Agents –

Azoles: *Miconazole, Ketoconazole*

Triazoles: *Fluconazole, Itraconazole*

These drugs produce inhibition of the fungal CYP-450 enzyme,

Lanosine 14α-demethylase which is responsible for converting

Lanosterol to

Ergosterol - the main sterol in the fungal cell membrane.

The depletion of ergosterol alters

the fluidity of the membrane and interferes with

the action of the Membrane-Associated Enzymes.

=> Inhibition of Replication.

Ketoconazole (*Nizoral*) –

is distinguished from *Fluconazole and Itraconazole*

by its greater propensity to **inhibit CYP-450** enzymes.

Inhibition of CYP-450 enzymes:

◊ Interferes with biosynthesis of **adrenal** and **gonadal steroid hormones**,

producing significant endocrine effects such as:

Gynecomastia

Infertility

Menstrual irregularities.

◊ ↓↓**Metabolism** of other drugs,

leading to enhanced toxicity.

Adverse effects of Sulfonamides: *Co-trimoxazole (Biseptol), Ethazol, Sulfasalazine, Norsulfazol, Sulfazine, Sulfadimezine*

All sulfonamides and their derivatives, including thiazides, *Diacarb*, *Furosemide*, *Diazoxide*, and the sulfonylurea hypoglycemic agents(*Butamide, Glibenclamide*), are cross-allergic. The most common adverse effects are:

- **Urinary tract disturbances**: **crystalluria, haematuria**, or even obstruction as sulfonamides may precipitate in urine, especially at acid pH.
- **Nephrotoxicity** develops as a result of crystalluria.

Adequate hydration and **alkalinization** (consumption of alkaline mineral water, 1–2% *sodium bicarbonate* solution) of urine prevent the problem by reducing the concentration of drug and promoting its ionization;

· **Hypersensitivity reactions:** rashes, angioedema;

- **Haemopoietic disturbances**: hemolytic anemia, agranulocytosis, leucopenia, thrombocytopenia;

· CNS: depression, aseptic meningitis, seizures;

· **Stevens-Johnson syndrome**, although relatively uncommon (<1%), is a particularly serious and potentially fatal type of skin and mucous membrane eruption associated with sulfonamide use.

Acute poisoning / overdose with Sulfonamides

Sulfonamides are able to form *methemoglobin* and *sulf-methemoglobine* in the blood, block the medullary haemopoiesis and characterized by high **hepato-** and **nephrotoxicity**.

Manifestation: dizziness, drowsiness, headache, unconsciousness, anorexia, abdominal pain, nausea, vomiting, haemolytic anemia, agranulocytosis, dermatitis, acidosis, sensitivity reactions, jaundice, hepatomegalia.

Treatment: gastric lavage, IV infusion therapy:

5% *Glucose solution, Neohemodes*, *Polyglucin*

Antidotes: *Nicotinic acid* (IV 2–5 ml of 1% solution) or *Nicotinamide*, *Chromosome* (0.1 ml/kg),

Lipoic acid (*0.5% solution 60-80 ml in 500 ml of 5% Glucose solution*).

Folic acid is used to rescue bone marrow.

Treatment of renal failure and transfusion of appropriate blood product (in severe hematologic toxicity) may be required.

Adverse effects of Fluoroquinolones: *Ciprofloxacin, Ofloxacin, Pefloxacin, Lomefloxacin, Levofloxacin, Sparfloxacin*

- **GI toxicity:** Anorexia, nausea, vomiting, and diarrhoea.
- **CNS toxicity**: Fluoroquinolones are **GABA inhibitors**.

CNS **stimulation** may lead to tremor, restlessness, confusion, nervousness, agitation, convulsions and hallucinations.

- They are used with caution in patients with CNS disorders (**epilepsy, severe cerebral atherosclerosis**) or in patients, which are taking *isoniazid, theophylline, warfarine, cyclosporine* or NSAIDs.
- **Tendon and cartilage damage**: Fluoroquinolones can cause arthropathy: **rupture** of shoulder, hand and **Achilles tendons** that require surgical repair.

! **Treatment should be discontinued** if the patient experiences pain, inflammation and rupture of tendon.

Because of cartilage damage they should be avoided in pregnant and nursing mothers and in young children.

- Miscellaneous toxicity: Allergic reactions, leucopoenia, renal damage and acute renal failure.

Isoniazid *(isonicotinic acid hydrazide – **INH**)* -
an analog of Pyridoxine (Vitamin B_6) a potent anti-tubercular drug.

Adverse effects:

· Peripheral neuritis (10-20% of patients)

•Neurological manifestations: paresthesias, numbness, mental disturbances, optic neuritis, convulsions – appear to be due to a relative vitamin B_6 (*Pyridoxine*) deficiency. This has been attributed to a competition of **isoniazid** with ***Pyridoxal phosphate*** for the enzyme **apotryptophanase**.

Vitamin B_6 10 mg/day prevents neurotoxicity even in higher doses, but routine use is not mandatory.

· **Isoniazid neurotoxicity** is treated by Vitamin B_6 100 mg/day.

· Potentially fatal **hepatitis** is the most severe side effect.

· Hypersensitivity reactions include rashes and fever.

Isoniazid can potentiate the adverse effects of *difenin* (nystagmus, ataxia) as *isoniazid* inhibits metabolism of *difenin*.

· **Slow acetylators** are particularly at risk.

Adverse Effects of Cyclophosphamide:

- **Chemotherapy-induced nausea** and **vomiting**,
- **Bone marrow suppression**,
- **Stomachache, diarrhea**
- **Hemorrhagic cystitis-** is a frequent complication, but this is prevented by adequate fluid intake and **Mesna –**

  a sulfhydryl **SH- donor** which binds acrolein.
- Unusual decrease in the amount of urine
- Darkening of the skin /n ails,
- **Alopecia** (hair loss) or thinning of hair, changes in color and texture of the hair,
- **Letahrgy**, slow-healing existing wounds
- Temporary or permanent **sterility**
- Mouth sores, joint pain,
- Easy bruising/bleeding
- Slow-healing existing wounds

· High-dose ***Cyclophosphamide*** (120–200 mg/kg) can cause lethal **cardiotoxicity**, and **severe congestive heart failure** can develop 1–10 days after the first dose.

· Severe CHF is accompanied by ECG findings of:

Diffuse Voltage Loss

Cardiomegaly

Pulmonary Vascular Congestion

Pleural and **Pericardial Effusions**.

Pathological findings: hemorrhagic myocardial necrosis, thickening of the left ventricular wall, and fibrinous pericarditis.

Of **80** patients who received *Cyclophosphamide* 50 mg/ kg/day for 4 days in preparation for **bone marrow grafting 17%** had symptoms consistent with cyclophosphamide cardiotoxicity.

6 patients died from CHF.

Corrected **QT dispersion** was a predictor of **acute heart failure** after high-dose cyclophosphamide chemotherapy (5.6 g/m^2 over 4 days)

Antitumour Antibiotics ***Daunorubicin*** and ***Doxorubicin*** may induce **cardiotoxicity** as a unique adverse effect.

They intercalate between DNA strands and interfere with its template function.

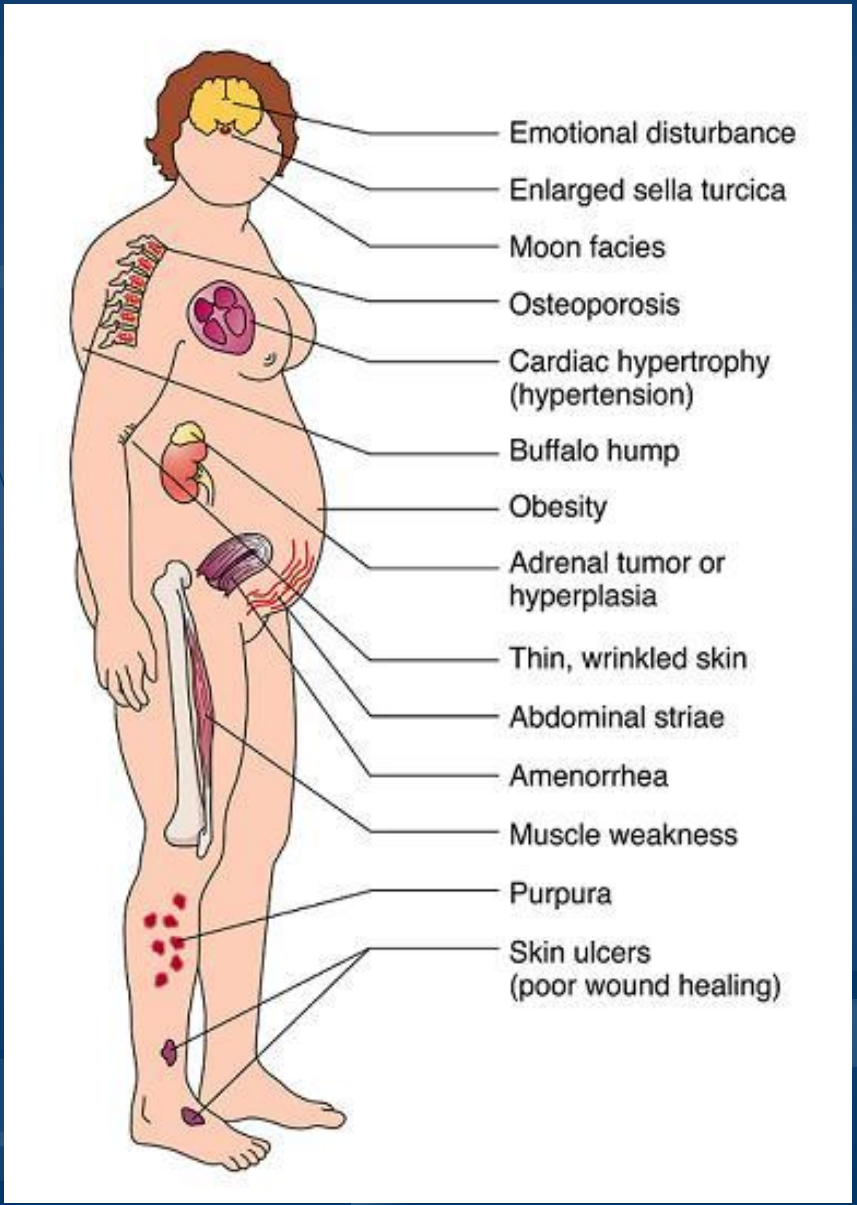
Antitumour antibiotics are active *in all phases of the cell cycle* and their cytotoxic effects are similar to those of the alkylating agents.

This can manifest either acutely with ECG changes, arrhythmias and hypotension or be delayed – CHF that is due to cardiomyopathy and may be fatal.

Adverse effects of Glucocorticoids

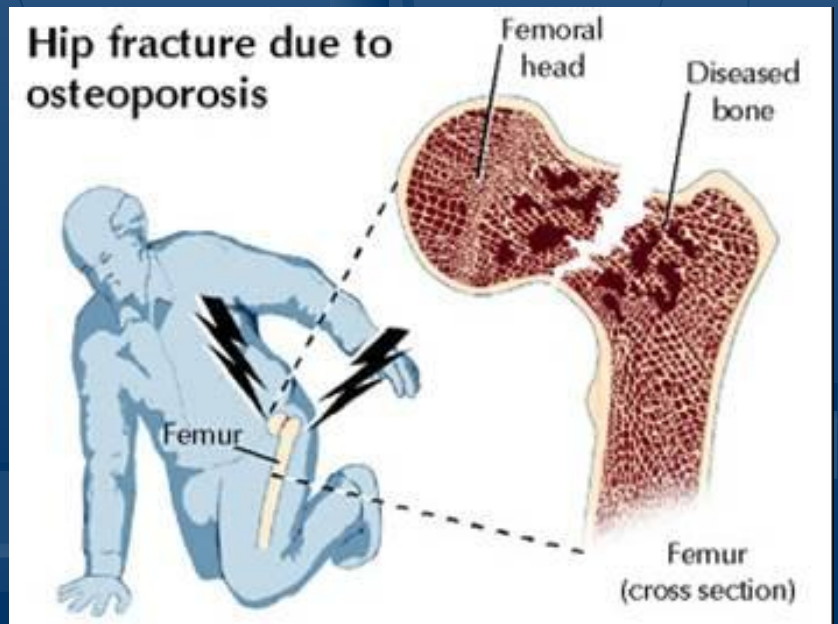
Cushing's syndrome:

- Moon face, with red cheeks
- Thin arms and legs: muscle wasting
- BP, Itracranial Hypertension
- Osteoporosis
- Cataracts
- Thinning of skin
- Increased abdominal fat
- Buffalo hump
- Euphoria
- Depression or emotional lability
- Avascular necrosis of femoral head
- Appetite, Obesity, Hyperglycemia



INHIBITORS of ADRENOCORTICOID BIOSYNTHESIS

- **Mifepristone** (Ru-486), an antiprogestin;
- **Metyrapone**
- **Ketoconazole** (an antifungal agelibidinalnt)
- **Spironolactone**



Adverse Reactions to Estrogens:

1.Those following physiological doses in hormonal replacement therapy (HRT):

- Nausea, vomiting, anorexia - can be minimized by taking the drug with food or at bedtime rather than in the morning.
- Na+ and water retention can cause edema, and fullness and tenderness of the breasts.
- Intermittent vaginal bleeding
- Uncontrolled Hypertension and Migraine may worsen
- Greater cholesterol saturation in the bile predisposes to **gall stones**.
- An increase in the plasma triglycerides
- Prolonged therapy is known to increase the risk of endometrial carcinoma
- Any existing breast carcinoma can undergo exacerbation

Adverse reactions to estrogens:

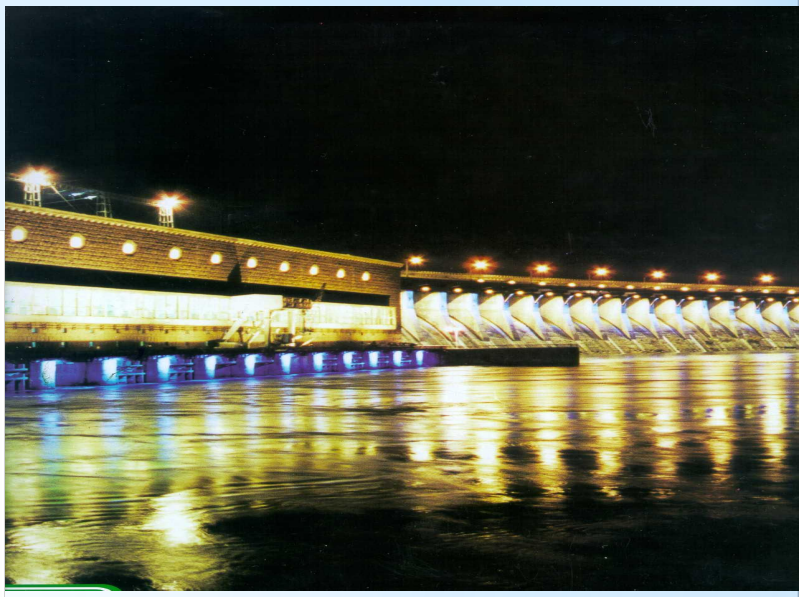
- Administered to prepuberal girls can cause premature development of secondary sex characters such as growth and proliferation of mammary gland tissue and lead to precocious puberty.
- Can Stunt the Linear Growth of the Long Bones by accelerating the closure of the epiphysial plate.

- The administration of *Diethylstilbestrol to* pregnant women caused a variety of genital abnormalities, including
  Vaginal adenosis and
  Vaginal adenocarcinoma
  in the female offsprings of such women.

2. Adverse Effects of Contraceptives.

- Weight gain, depression, irritability, edemas, headache, nausea, and vomiting.
- Cardiovascular diseases, including:
  - Thromboembolism
  - Thrombophlebitis
  - Hypertension
  - Increased incidences of Myocardial Infarction and Cerebral and Coronary Thrombosis.
- Carcinogenicity
- Diabetes Mellitus
- Pyelonephritis
- An increase in LDL and a decrease in HDL.

ЗАПОРІЗЬКИЙ ДЕРЖАВНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ



Thank You for Attention!