

Cancer Chemotherapy

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Normal cells...

- Differentiate, grow, mature, divide
 - Regulated, balanced; cell birth=cell death
 - Regulation: intracell signaling
 - Neoplasia: abnormal growth
 - invasion of cells
 - Metastatic function

Neoplasms

- = Tumors = groups of neoplastic cells
- Two major types: benign, malignant
- Benign – “noncancerous”
 - Local; cells slow growing, well-defined borders
 - Push adjacent tissue away
 - Doesn’t spread beyond original site
 - Often has capsule of fibrous connective tissue-
 - treatment surgical removal

- Malignant – grow more rapidly; often called “cancer”
 - Fast growth; seldom have capsule
 - Irregular shape; disrupted architecture
 - Invade surrounding cells
 - break to form second tumor Metastasis”

Stimulus (initiator) causes genetic mutation
(oncogenes and tumor suppressor genes)

Normal cells

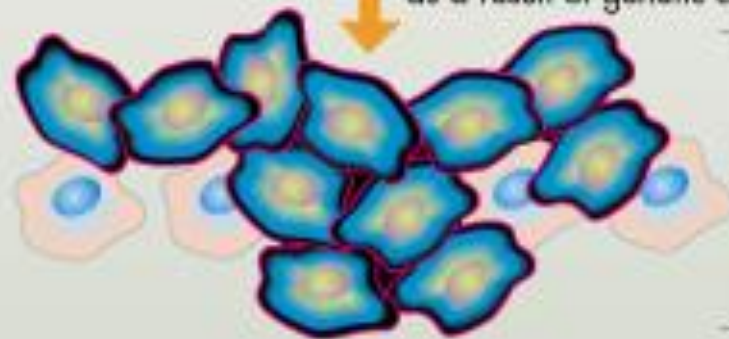


Transformed cell



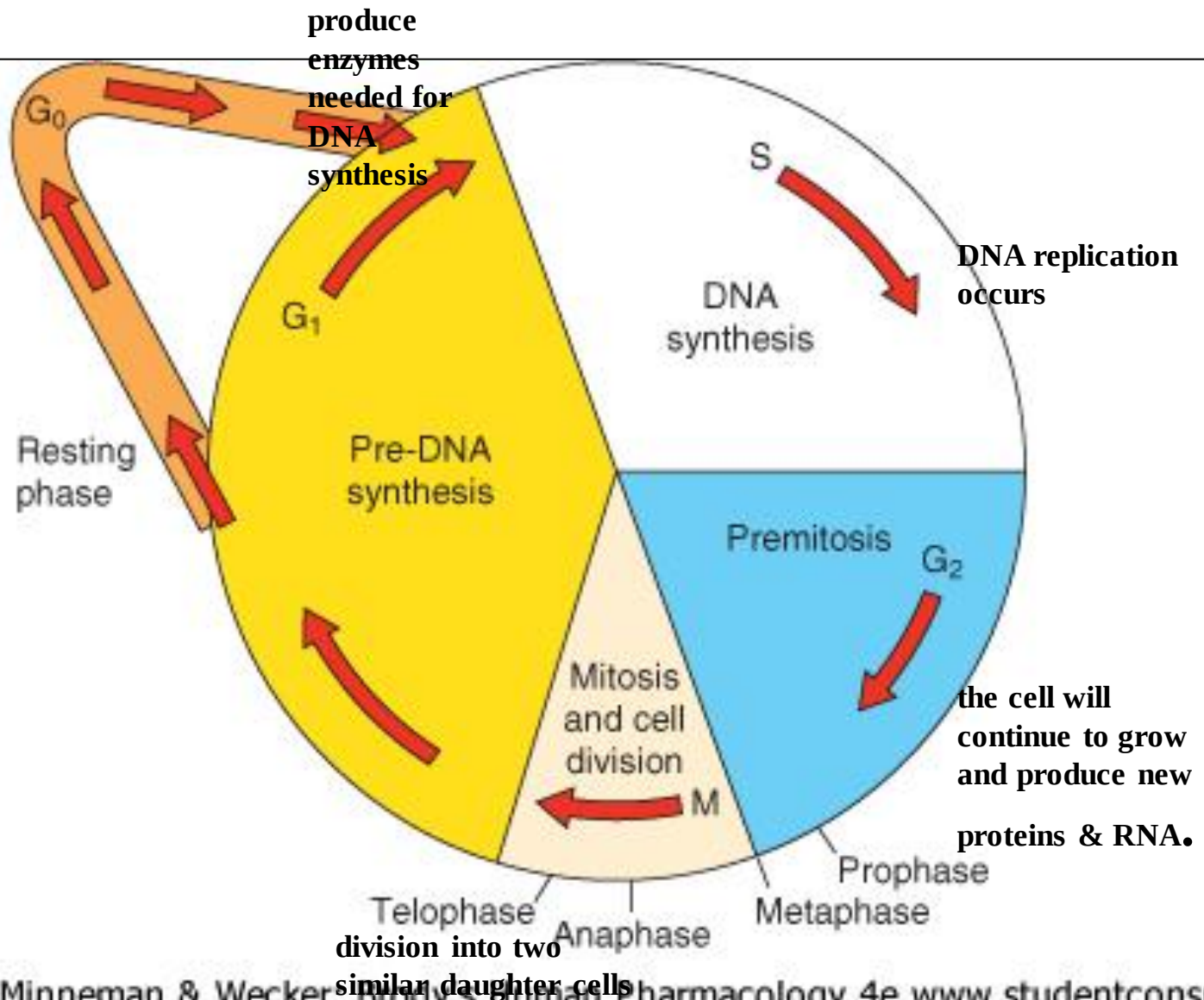
- Altered genes for:
- Growth factors
 - Growth factor receptors
 - Signal communication (transduction)
 - Transcription regulation

Transformed cell proliferates
with abnormal and auto-
nomous regulation of growth
as a result of genetic changes



Tumor

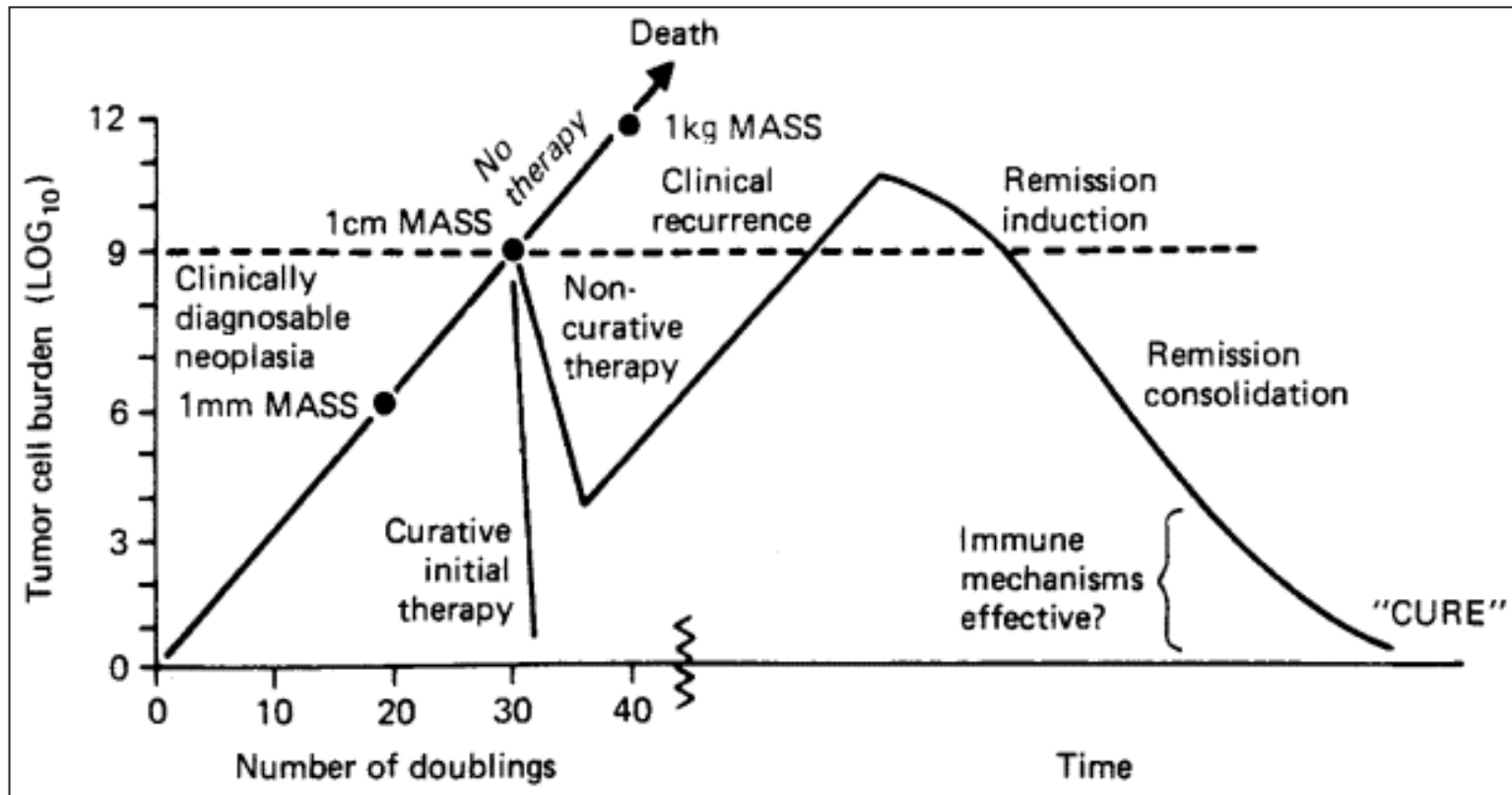
quit dividing.
a temporary
resting period



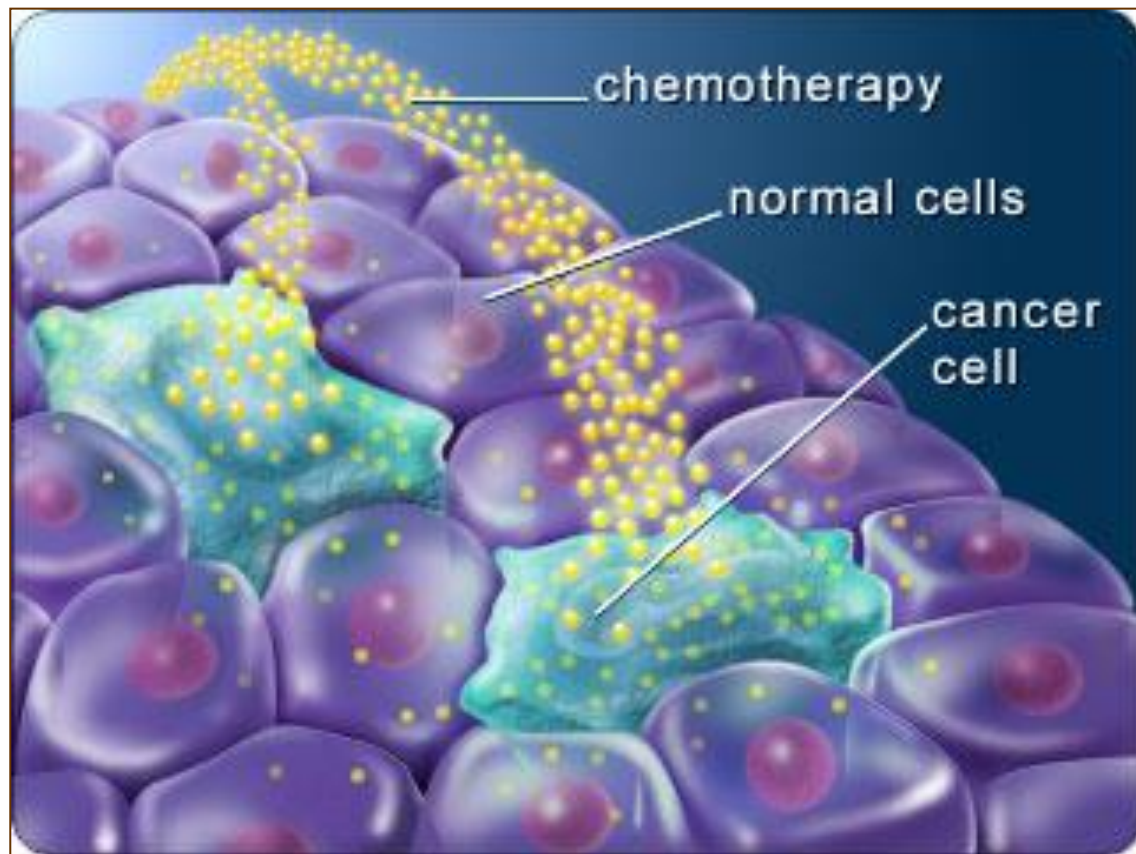
Modalities of treatment:

- 1-local therapy:
 - -surgery.
 - -radiation therapy.
- 2-systemic treatment:
 - chemotherapy.
 - Hormonal therapy.
 - Monoclonal antibodies.
 - Radioactive material.
- 3-supportive care.
- 4-non-conventional therapy.

Kinetics of cancer treatment



Chemotherapy



Chemotherapy – *classes of drugs*

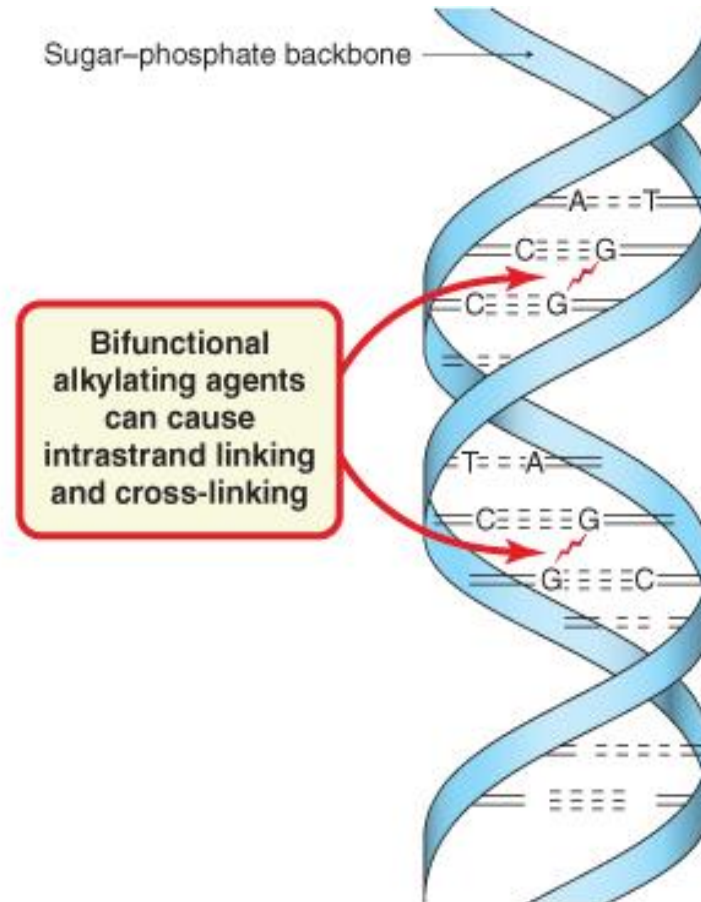
- alkylating agents
- antimetabolites
- antibiotics
- plant alkaloids
 - *Vinca* alkaloids
 - taxanes
- topoisomerase inhibitors
- miscellaneous

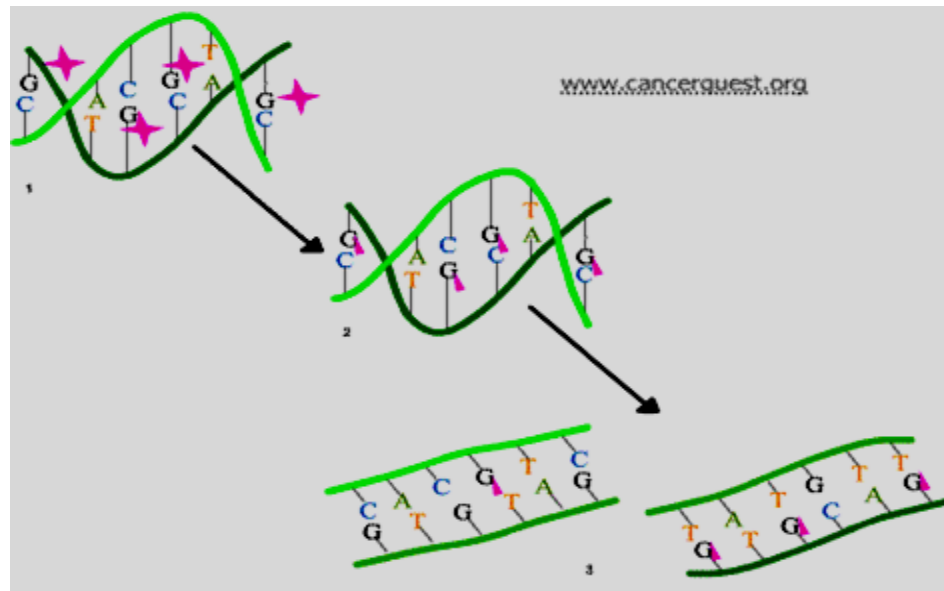
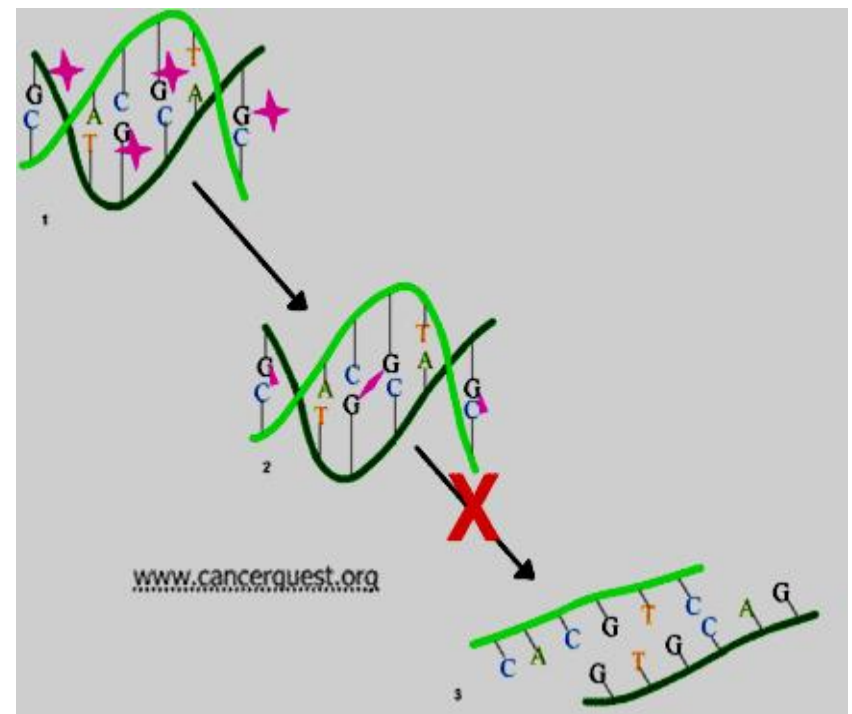
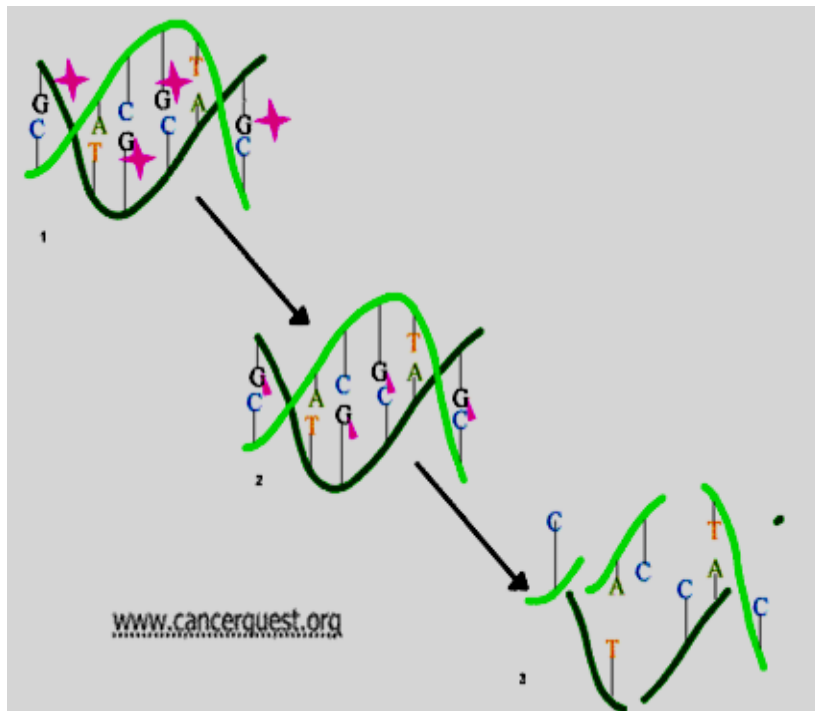


Alkylating Agents(CCNS)

Subgroups of Alkylating Agents

- 1) Nitrogen mustards
- 2) Nitrosoureas
- 3) Alkyl sulfonates
- 4) 4-Platinum Coordination Compounds cisplatin





Chemotherapy

alkylating agents

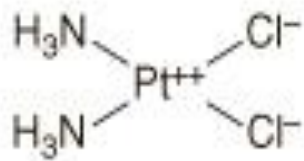
- chemical interaction with DNA by forming covalent bonds with nucleic acid react to COO OH NH₂ SH group of biomacromolecules



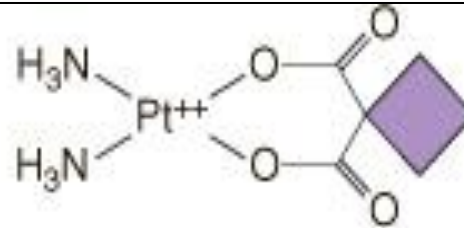
- ✓ misreading of DNA code
 - ✓ cross-linking of DNA
 - ✓ single-strand breaks
 - ✓ double-strand breaks
- alkylation of RNA and proteins

Cisplatin

- Cl^- dissociates $\rightarrow$ reactive complex that reacts w/ H_2O and interacts w/ DNA $\rightarrow$ intrastrand cross-link $\rightarrow$ denaturation DNA
- Enters in cell by copper transporter system



Cisplatin



Carboplatin

All alkylating agents are cell cycle nonspecific

II-Antimetabolites

- Antimetabolite- chemical with a similar structure to a metabolite required for normal biochemical reactions, yet different enough to interfere with the normal functions of cells, including cell division.
- thus- interfere with DNA production and therefore cell division and the growth of tumors (mainly in S-phase specific).
- They are classified into:
 - 1- Folic acid analogues
 - 2- Purine analogues
 - 3- Pyrimidine analogues
- Purin and pyrimidine antagonists are phosphorelated inside the body into nucleotid form in order to be cytotoxic

1-Folic acid analogues

Methotrexate: taken up into the cells by the same transport system for folate

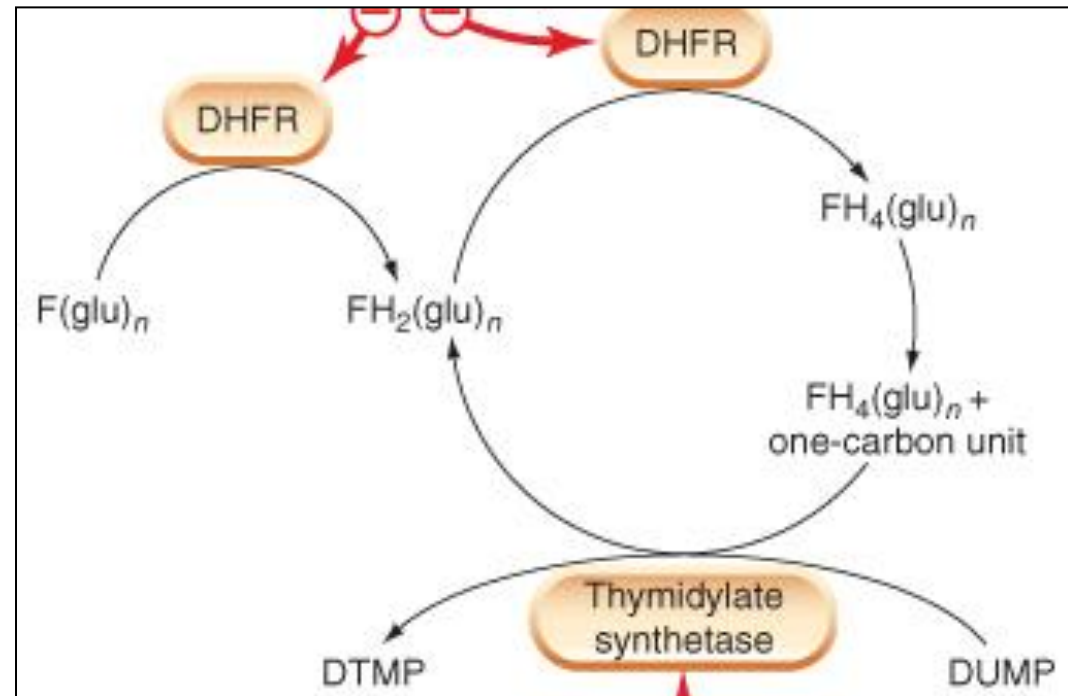
-A folic acid analogue, converted in liver to polyglutamate which prevents the formation of tetrahydrofolate, essential for purine and pyrimidine synthesis, by inhibiting dihydrofolate reductase.



inhibition of production of DNA, RNA and proteins (as tetrahydrofolate is also involved in the synthesis of amino acids as serine and methionine).

- Inhibits S phase of cell cycle

- Folate $\rightarrow$ FH4
cat'd by dihydrofolate reductase in 2 steps:
 - Folate $\rightarrow$ FH2
 - FH2 $\rightarrow$ FH4
- FH4 serves as methyl grp donor to deoxyuridine to form thymidylate (dUMP $\rightarrow$ dTMP), also regenerating FH2
- depl'n dTMP $\rightarrow$ “thymine-less death”



2-Purine analogues

Mercaptopurine (6 – mercaptopurine) :

-It acts as a purine analogue and once enters the cell,
Phosphorylated to 6-MP-ribosephosphate
incorporated into RNA & DNA
non functioning RNA & DNA
finally inducing cell cycle arrest and apoptosis.

also inhibits purine ring biosynthesis

Azathioprine:

nonenzymatically cleaved to 6 - M P

3-Pyrimidine analogues

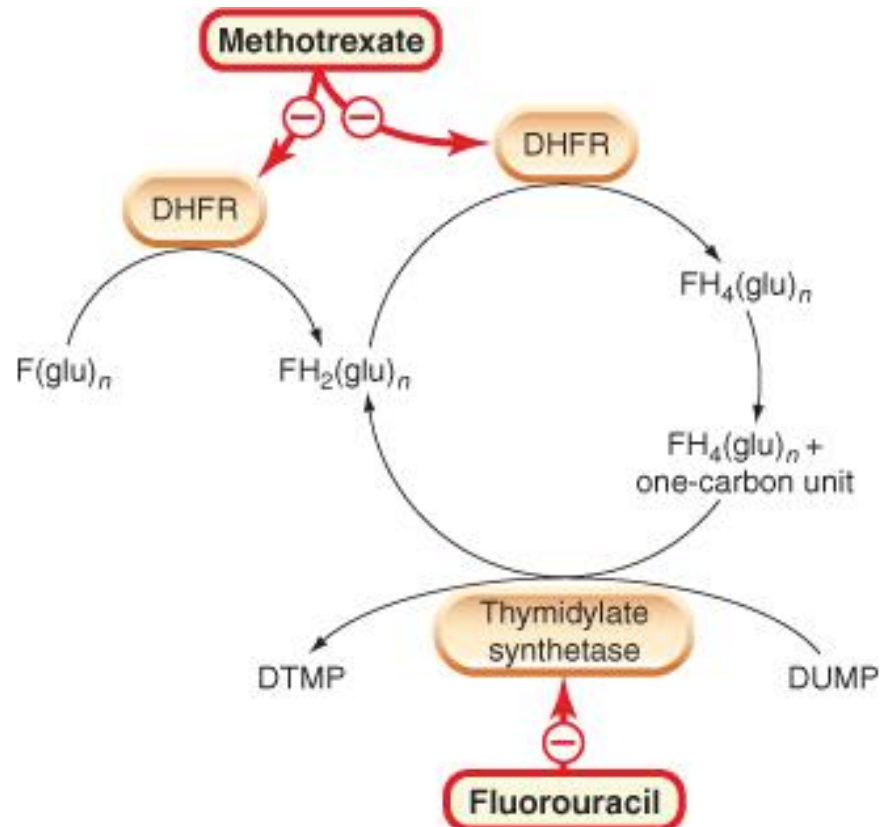
5-flurouracil (5-FU)

- a uracil analogue,
phosphorylated inside the cell into 5-FU deoxynucleotide
compete with deoxyuridine monophosphate DUMP for
thymidylate synthase
inhibition of deoxythymidine monophosphate DTMP synthesis
inhibition of DNA synthesis (Not RNA or protien)
- Also it is incorporated into DNA to make non functioning DNA .
 - inducing cell cycle arrest and apoptosis by inhibiting the cell's ability to synthesize DNA.
 - It is an S-phase specific drug

Cytarabine

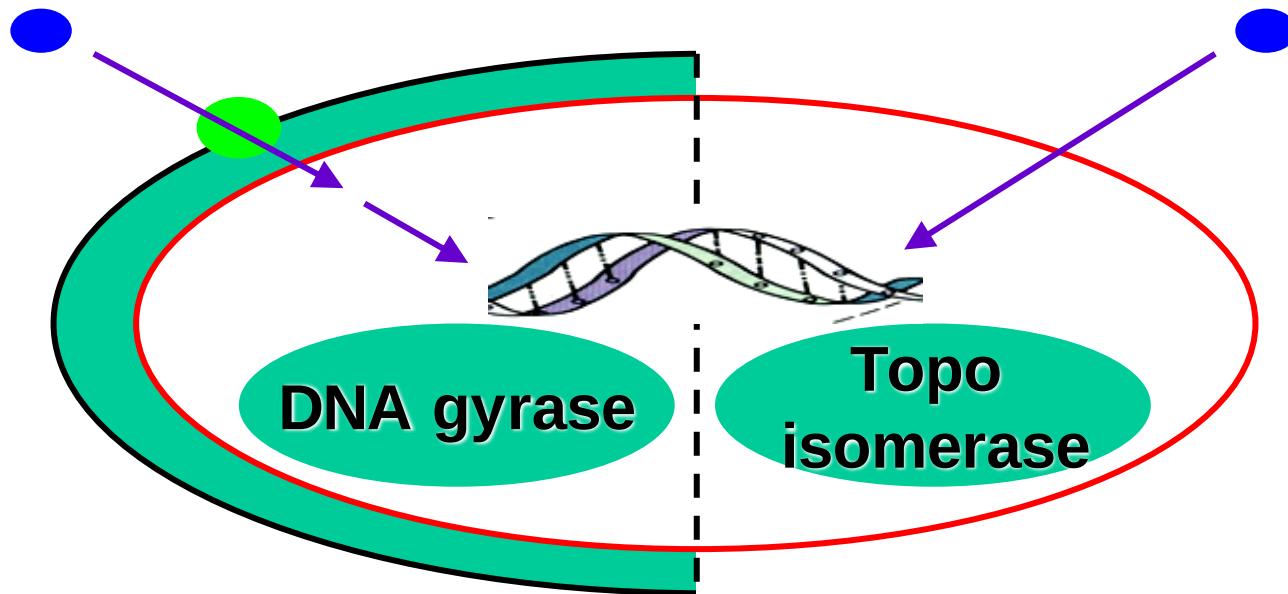
It is analogue to 2-deoxycytidine and in the body it is converted into cytosine triphosphate and inhibit DNA polymerase thus inhibiting DNA synthesis.

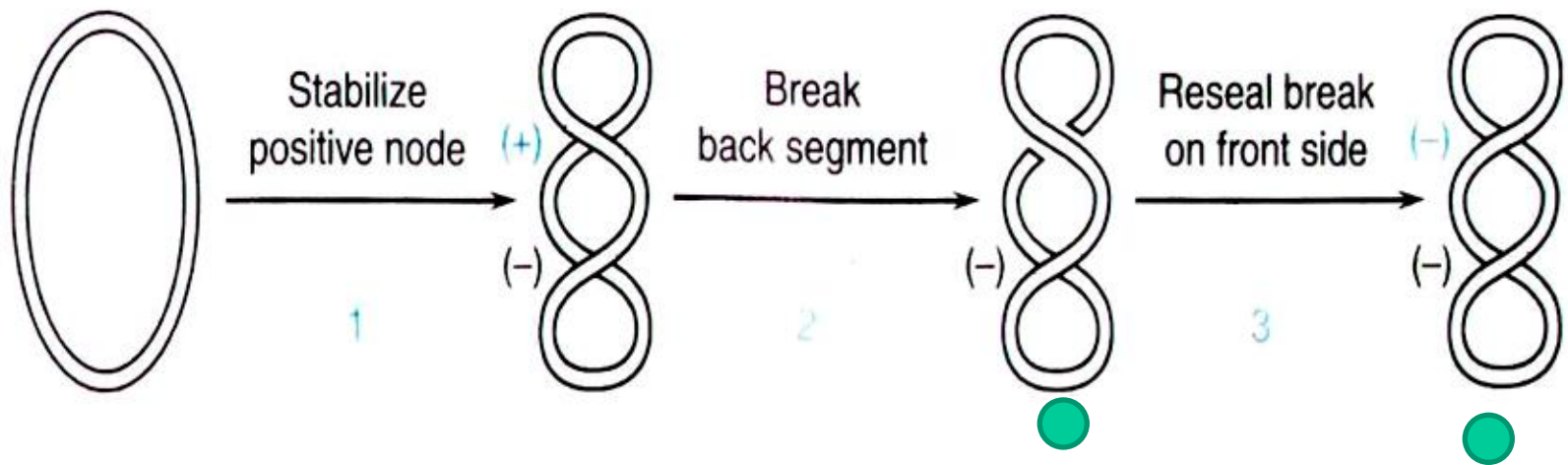
5-fluorouracil (5-FU)



Cytotoxic Antibiotics

- Substances of microbial origin that prevent mammalian cell division
- Anthracyclines
 - Doxorubicin Epirubicin, mitozantrone
 - Intercalates in DNA
 - Inhibits repl'n via action at topoisomerase II
 - Topoisomerase II catalyzes nick in DNA strands
 - Intercalated strand/topoisomerase complex stabilized → permanently cleaved helix
 - thus damage DNA





Topoisomerase

antibiotics

▶ anthracyclines

- intercalation between DNA base pairs
- inhibition of DNA topoisomerases I and II
- free radical formation

▶ bleomycin

- intercalation of DNA sequences, resulting in spontaneous oxidation and formation of free oxygen radicals that cause strand breakage

Chemotherapy

– *mechanism of action*

▶ mitomycin C

- alkylation and cross-linking of DNA
- lipid peroxydation

▶ actinomycin D

- DNA intercalation
- single strand breaks formation
- free radical formation

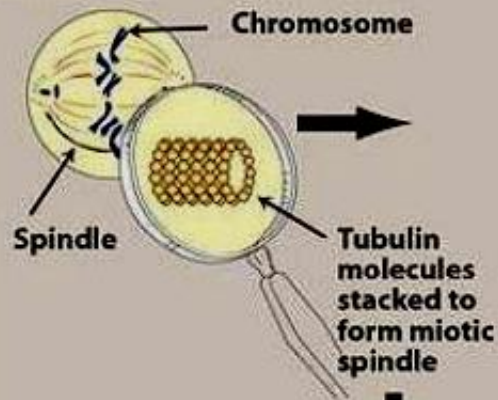
Plant Alkaloids

- Work at mitosis
- Effect tubulin, therefore microtubule activity
 - → Prevention spindle form'n OR
 - Stabilize (“freeze”) polymerized microtubules
- → Arrest of mitosis
- Other effects due to tubulin defects
 - Phagocytosis/chemotaxis
 - Axonal transport in neurons
 - Vinca alkaloid- vincristin, vinblastin
 - Taxanes- paclitaxel

Mechanism of action

A Normal mitosis

Metaphase

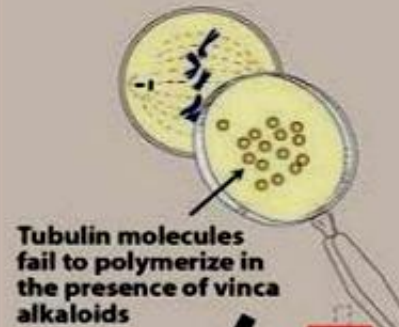


Anaphase

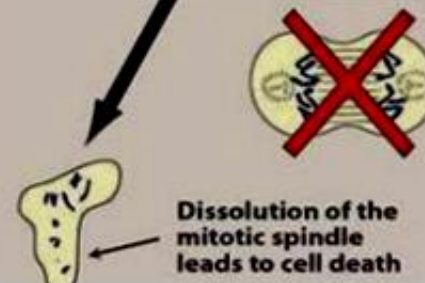


B Mitosis blocked by vinca alkaloids

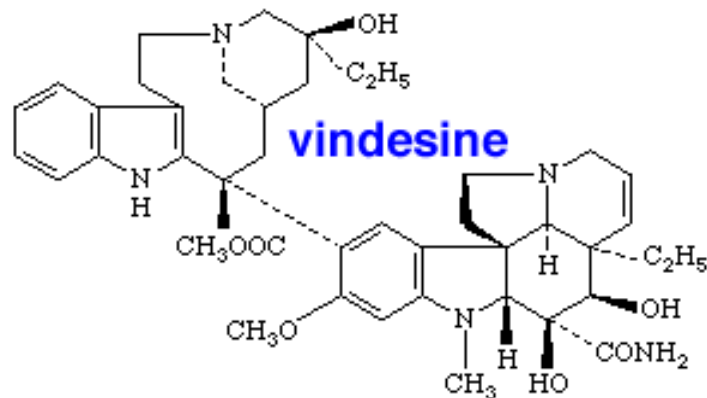
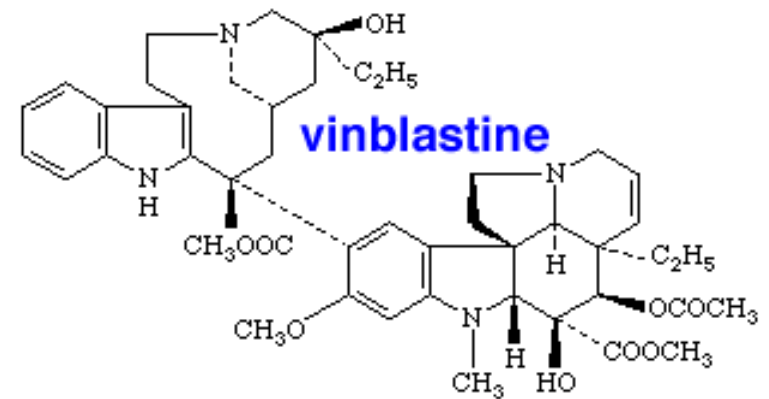
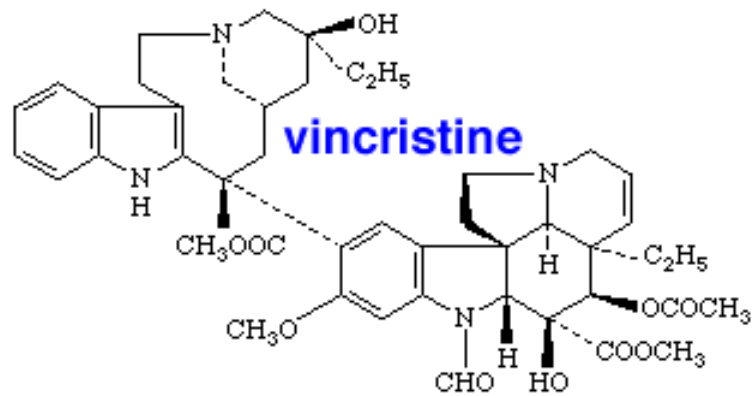
Metaphase



Anaphase



Vinca Alkaloids



L asperginase Lasp-ase

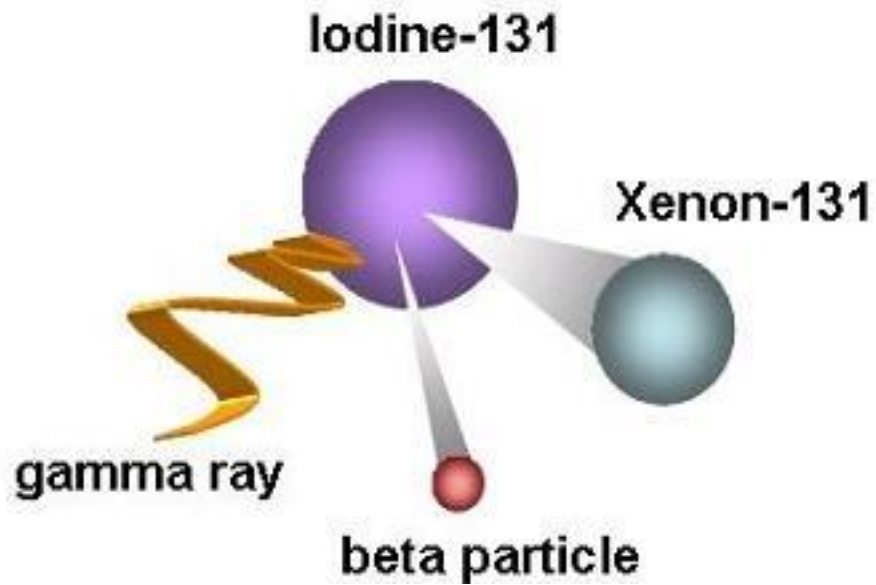
- A bit tumor specific
- Few tumor cells are deficient in aspergine synthase enzyme
- So have to fulfil requirement of aspergine from surroundings
- Lasp-ase degrades aspergine to aspartic acid
- Depriving tumor cells of essential metabolites
- Causing cell death effective against lymphoblastic leukemia

Radionuclides:

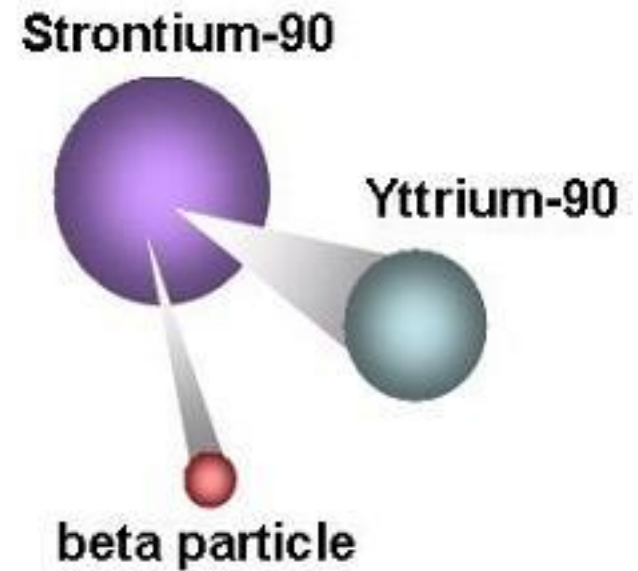
- For decades have been used systemically to treat malignant disorders.
- They are administered by specialists in nuclear medicine or radiation oncologist.
- Radioactive iodine: in the form of ^{131}I is effective therapy for well differentiated thyroid ca
- Strontium-89. Is used for the treatment of body metastasis. It is an alkaline earth element in the same family as calcium

Radioactive nucleotides

thyroid



bone



^{198}Au

cavities

- Side effects greatest in other rapidly-dividing cells
 - Bone marrow toxicity
 - Impaired wound healing
 - Hair follicle damage
 - Gi epith damage
 - Growth in children
 - Gametes
 - Fetus
- May themselves be carcinogenic
- Nausea and vomiting
- hyperurecemia

Cancer chemotherapy

- Drugs do not destroy tumor tissue
- Reduces its proliferation by altering biological response of body to tumor tissue
- Minimum effect on nontumor cells

Endocrine therapy

- Option for tissues whose growth is under hormonal control, especially breast, prostate, and endometrial cancers
- ? Lymphatic tissue
- These cancers may regress if concerned hormone is eliminated or antagonized.

least toxic

Useful as adjuvant therapy/treatment of disseminated disease

Endocrine therapy:

- Many hormonal affecting tumor growth are
- corticosteroids:
- Androgens
- Estrogen:

glucocorticoids

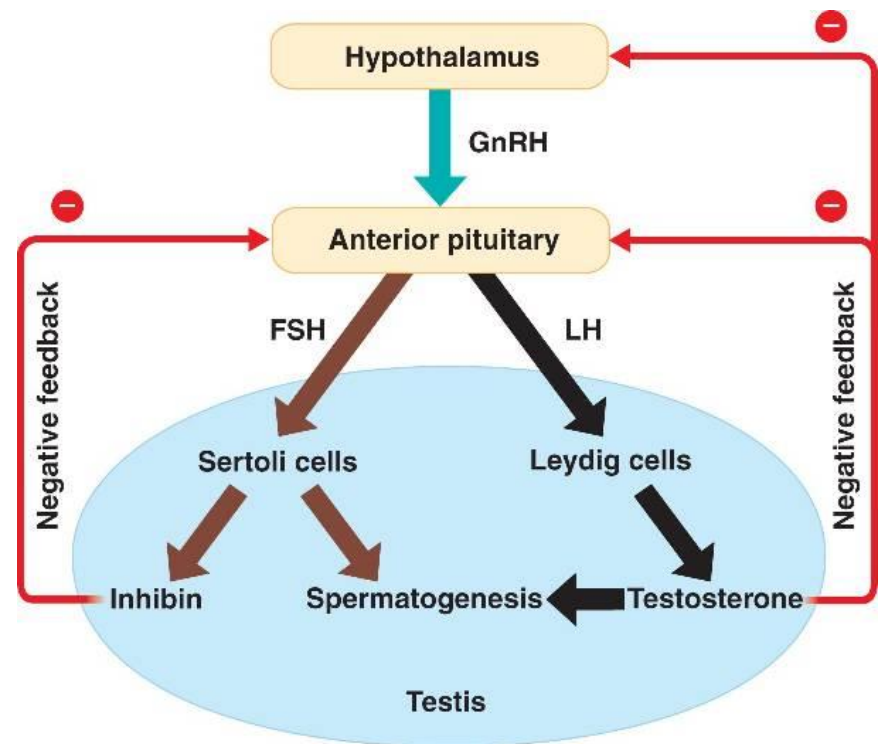
- Useful as supportive care of
- malignancies in which lymph tissue as lymphocytic leukemia, lymphoma as Corticosteroids are lymphocytotoxic
- bind to glucocorticoid-specific receptors in lymphoid cells and initiate programmed cell death
- commonly used agent-
prednisone, methylprednisone, dexamethasone.

glucocorticoids

- Additional uses in malignancy associated-
- Hypercalcemia
- Radiation induced mediastinal oedema/
raised intracranial tension
- Mood elevating/antiemetic effect
- As used in high dose –dose related
toxicities are observed

Androgen dependent malignancy

- Prostate malignancy is androgen dependent
- Estrogen –
- Estrogen can suppress androgen production by inhibiting hypothalamus and pituitary
- Physiological antagonist on prostate
- Not proffered due to ADR



GnRH agonist

- Only pulsatile exposure to GnRH induces FSH/LH secretion while continuous exposure can desensitize pituitary ➡ loss of pituitary Gn release
- Synthetic analogues are 15-150 times potent to natural GnRH and have longer duration
- Goserelin- once monthly injection
- Triptorelin, luperolide

Antiandrogens:

- Flutamide :

Nonsteroidal AR antagonist on accessory sex organs and pituitary

may increase FSH and LH secretion

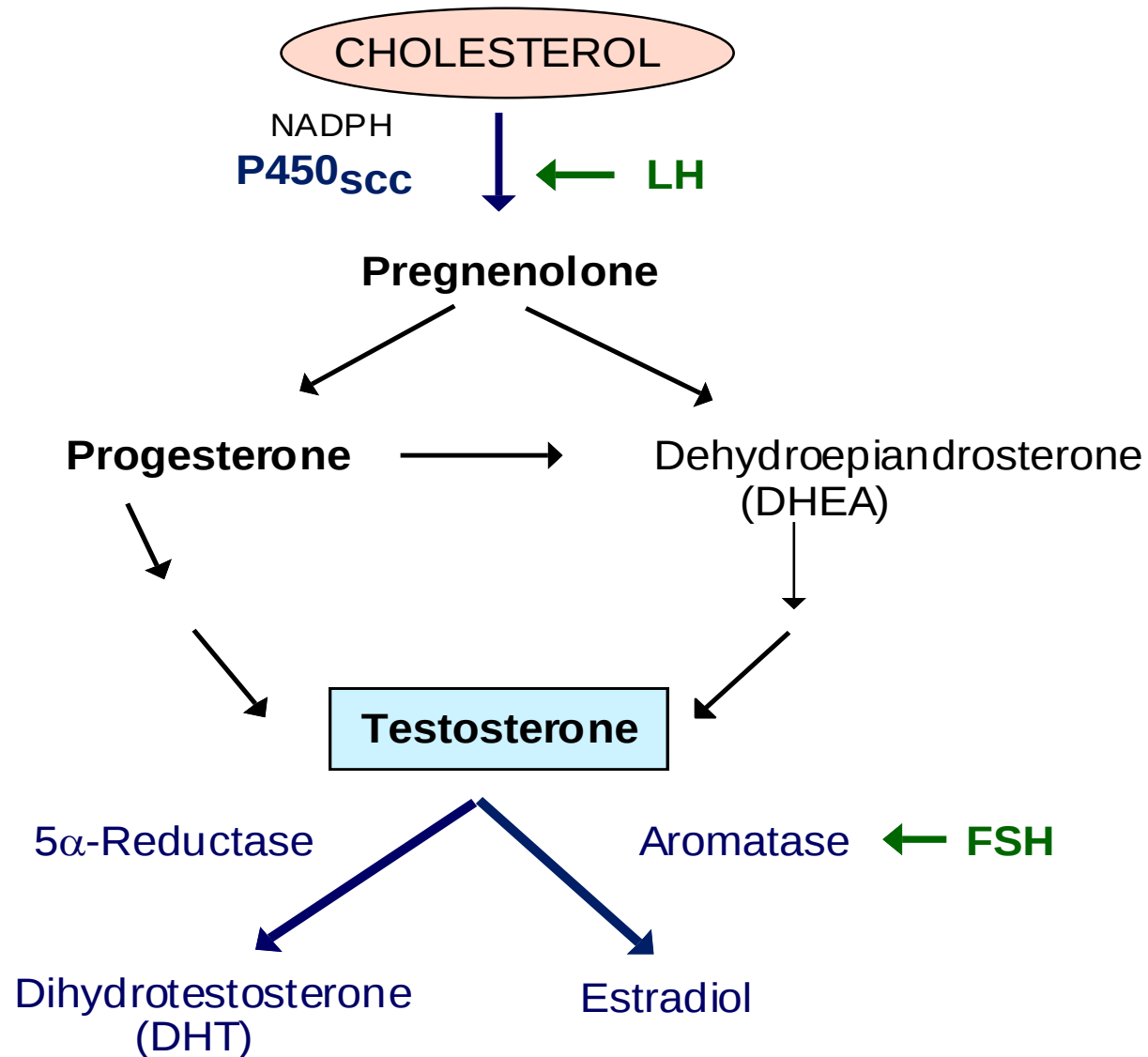
Combine with GnRH agonist

Causes hepatotoxicity

Bicalutamide- more potent, long acting , less hepatotoxic

It is used in the treatment of disseminated prostate ca

Androgen Synthesis



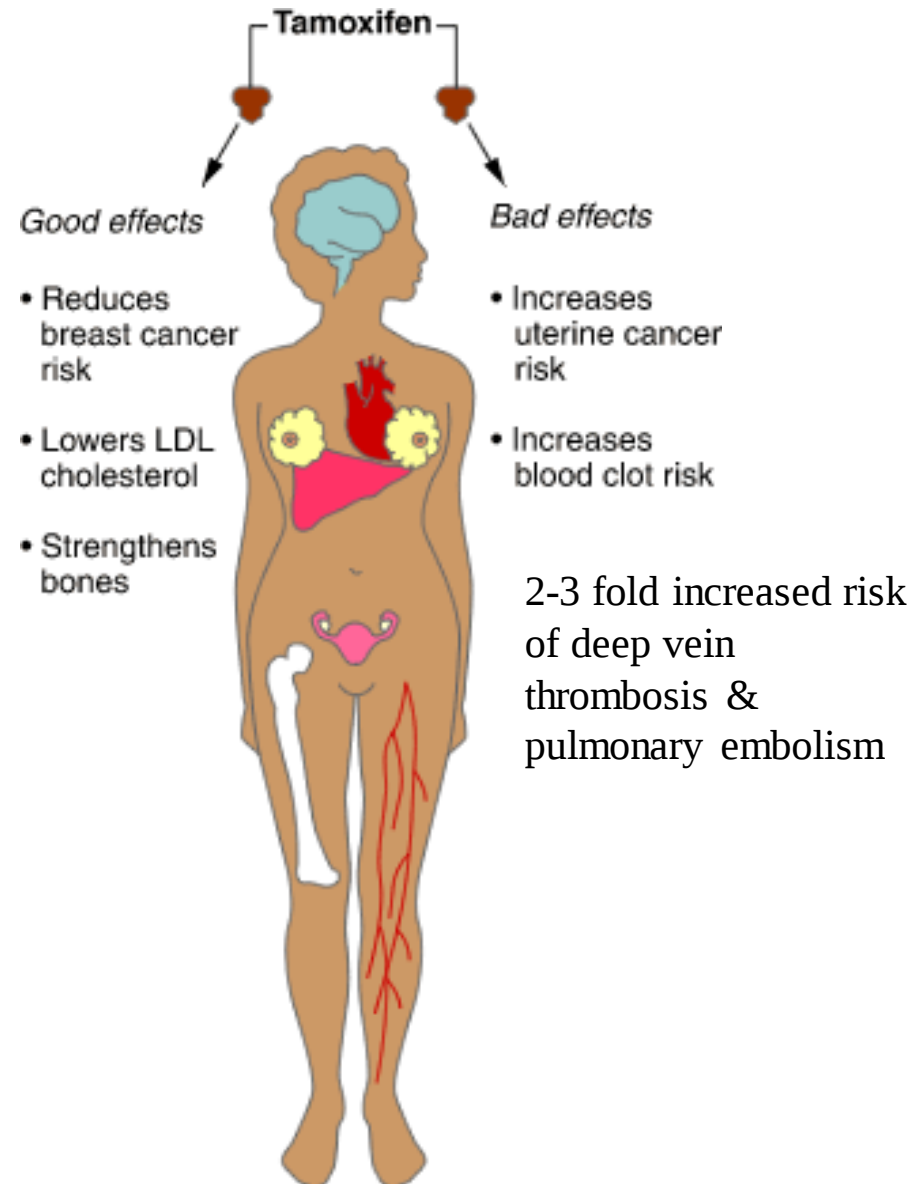
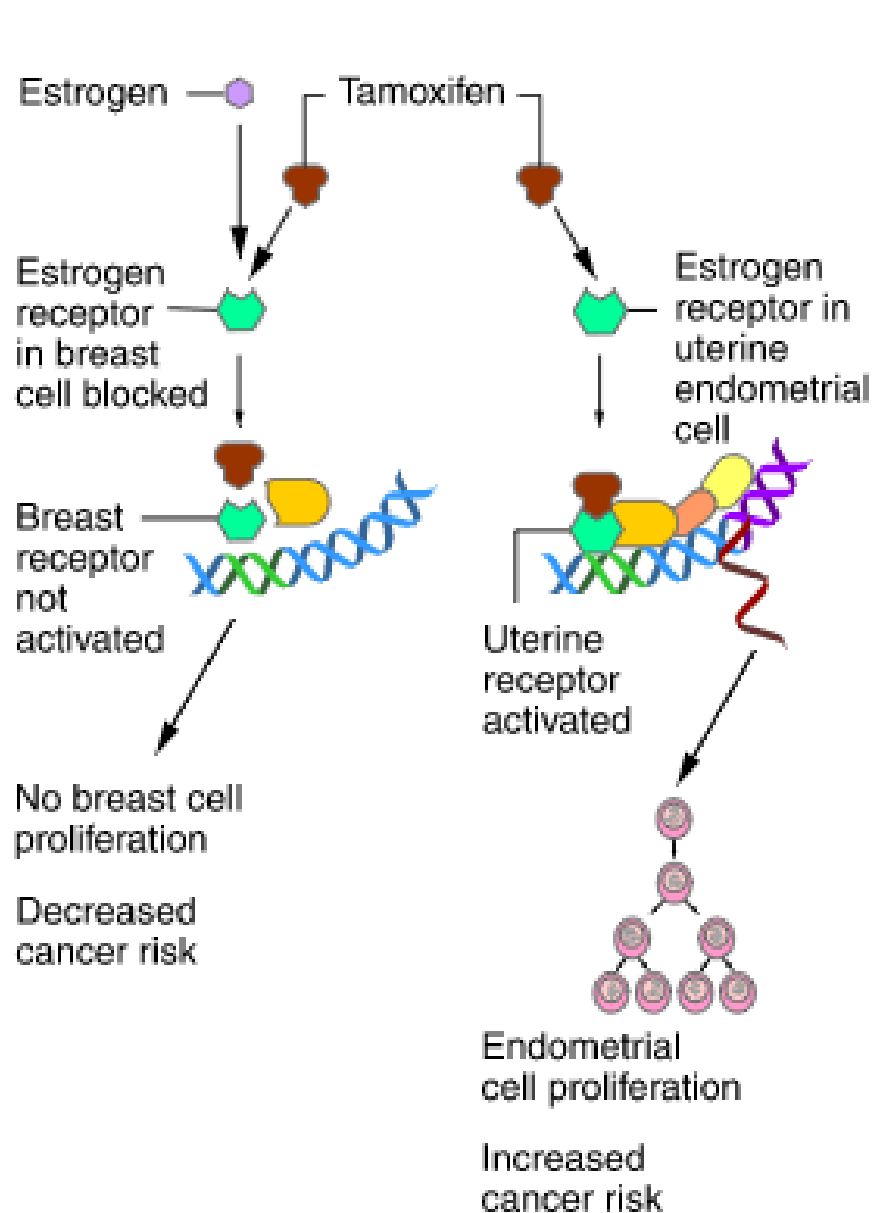
5 alpha reductase inhibitor

- Competitive inhibitor of 5 alpha reductase enzyme
- Testosterone $\longrightarrow$ dihydrotestosterone
- Which is more active and produces androgenic action in few tissues including prostate
- Finasteride, Dutasteride- can be used as palliative therapy

Estrogen dependant malignancy

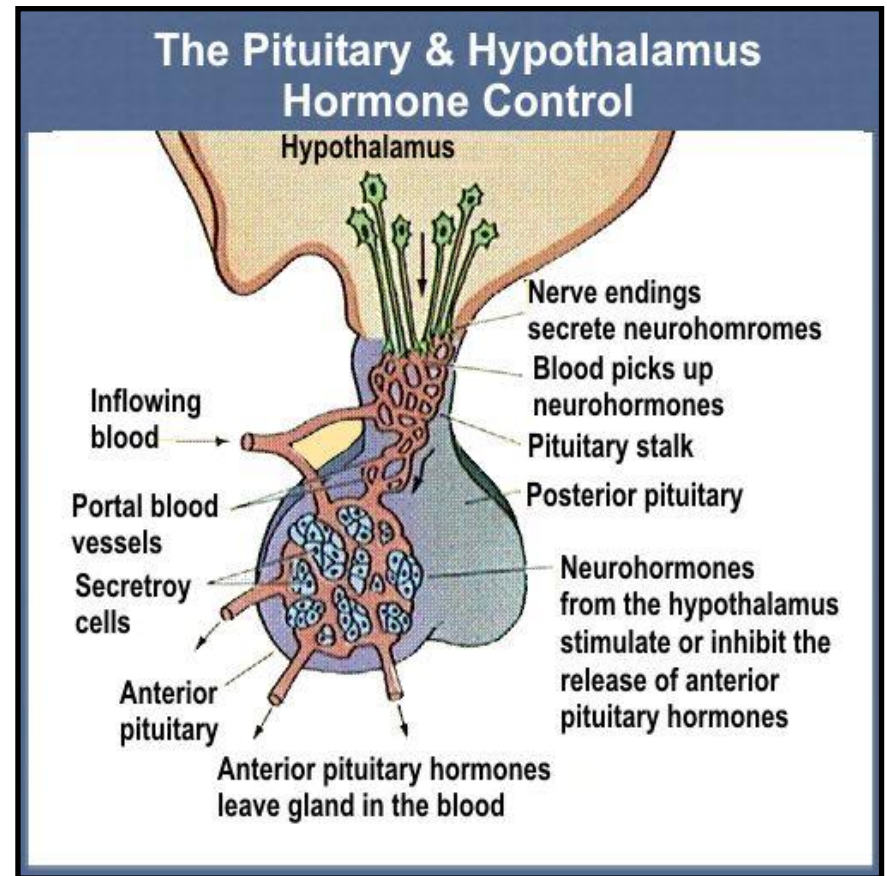
- SERM- exerts estrogenic antagonistic effect with tissue selectivity
- Tamoxifen-potent antagonist to breast tissue, but partial agonist to liver, bone, uterus, and pitutary
- Used for standard hormonal treatment of breast cancer in both pre and post menupausal women as adjuant therapy to mastectomy sp. ER positive tumor- for 5 years can be combine with GnRH agonist

SERMs: Tamoxifen – Breast Cancer



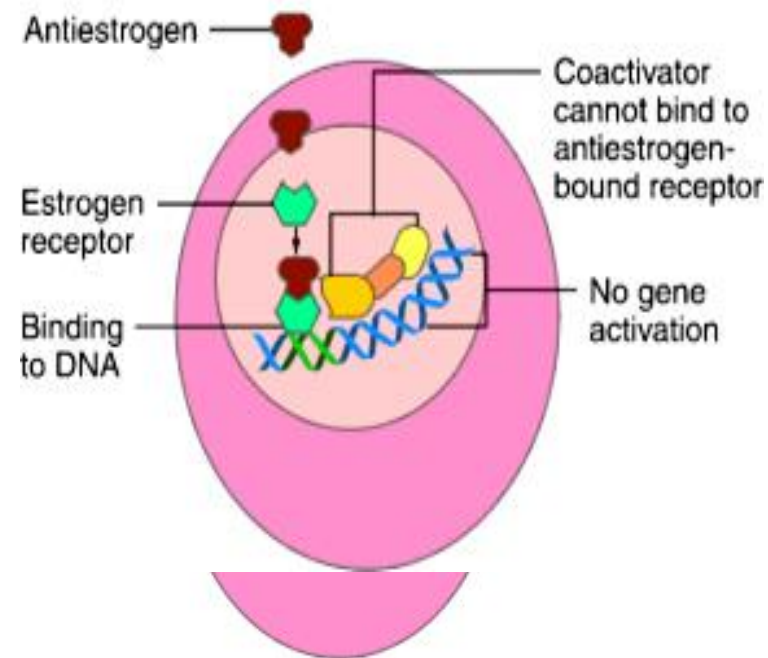
Hypothalamus and Pituitary Hormones

- Progesterin and estrogen have (-) feedback GnRH at hypothalamus.
- FSH releases estrogen and LH releases progesterin effect at.



Selective estrogen receptor down regulator

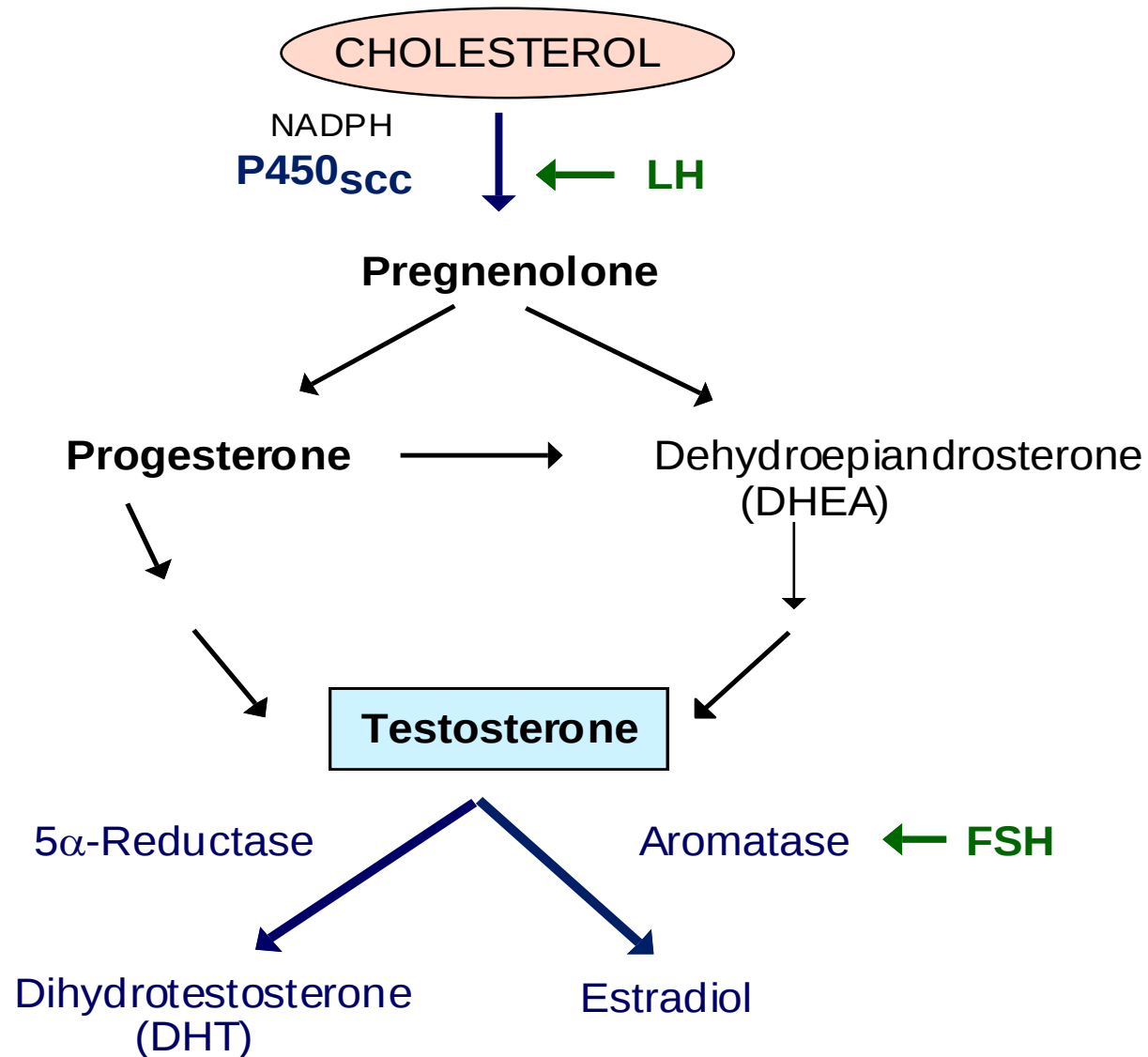
- It is pure estrogen antagonist
- Inhibits ER dimerization
- So estrogen can not bind to receptor and receptor degradation is enhanced
- Causes complete suppression of ER responsive gene useful in tamoxifen resistant breast cancer
- Fulvestrant



Aromatase inhibitor

- used to prevent the recurrence of breast cancer in postmenopausal women.
- These drugs, such as anastrozole and letrozole , prevent estrogen production. More effective than SERM
- First line therapy as adjuvant to mastectomy in postmenopausal ER + case
- Efficacy continues beyond 5 years
- No risk of endometrial hyperplasia,

Androgen Synthesis



Decision regarding hormonal therapy

- Hormone receptor tests measures the amount of hormone receptors in cancer tissue.
- Hormones (such as estrogen and progesterone) can attach to these receptors.
- If the test is positive, it is indicating that the hormone is probably helping the cancer cells to grow.
- negative test indicates that hormone does not affect the growth of the cancer cells,.

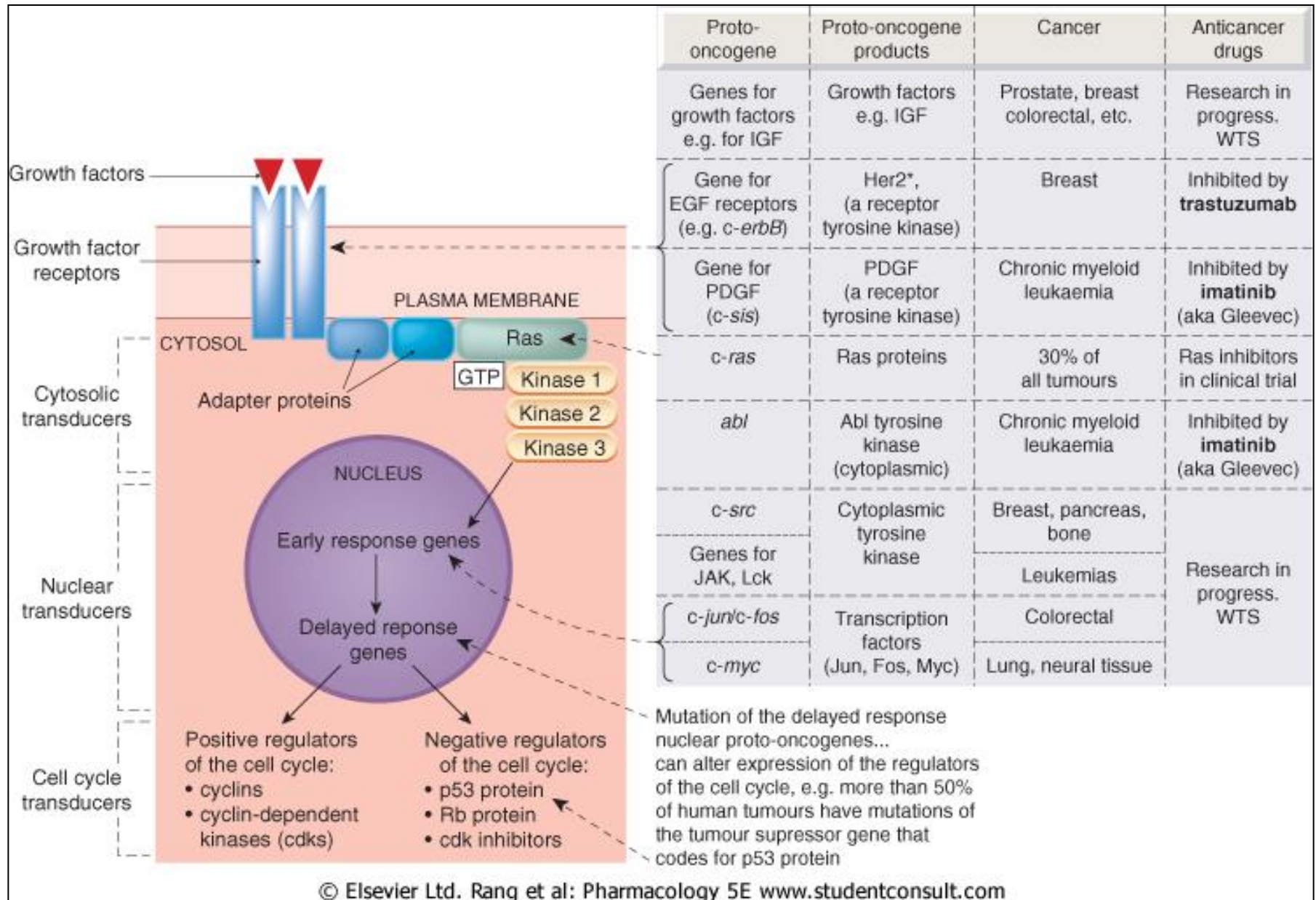
Progestins

- Temporary remission after surgery in endometrial cancer
- Palliative treatment of metastatic breast cancer unresponsive to estrogen antagonist

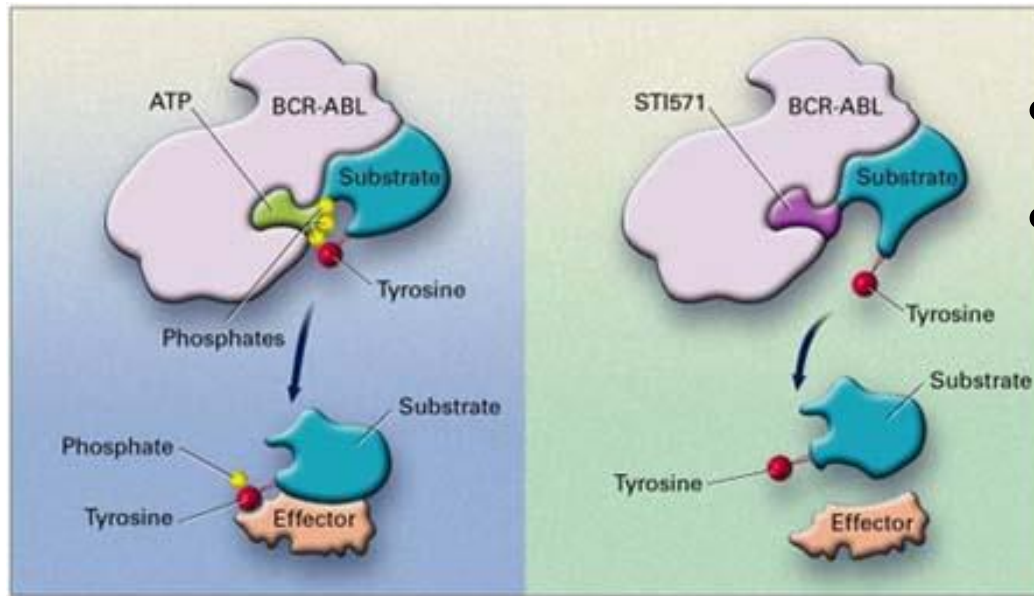
Targeted drug delivery system

- Targets responsible for growth of tumor can be attacked selectively
- These targets are
- Tumor specific enzymes/ proteins/ process

Antitumor Agents Working through Cell Signalling



Tyrosine protein kinase inhibitor- growth factor inhibitor



- Imatinib
- Inhibits Bcr-Abl tyrosin kinase expressed by chronic myloid leukemia cells

EGF receptor inhibitor

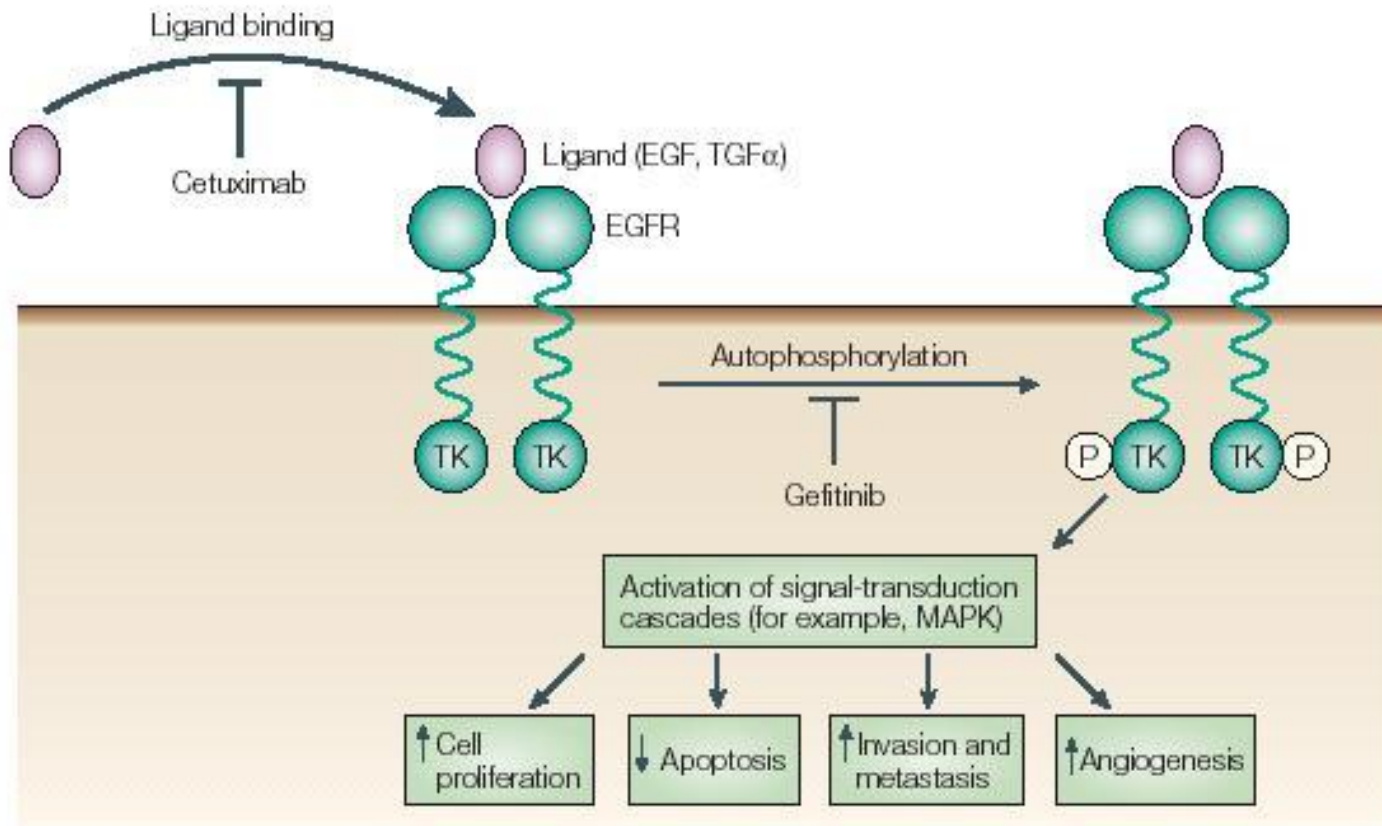
- Epidermal growth factor receptor is a transmembrane tyrosin kinase regulates differentiation of epithelial cells
- Gefitinib / Ertotinib
- binds to tyrosin kinase doman of EGF receptor and prevents phosphorylation of regulatory proteins
- Useful in non-small cell lung cancer

Angiogenesis inhibitor

- Angiogenesis helps in growth and metastasis of tumor
- Vascular endothelial growth factor stimulates neovascularisation in solid tumors
- Its inhibitors are-
- Bevacizumab / Sunitinib

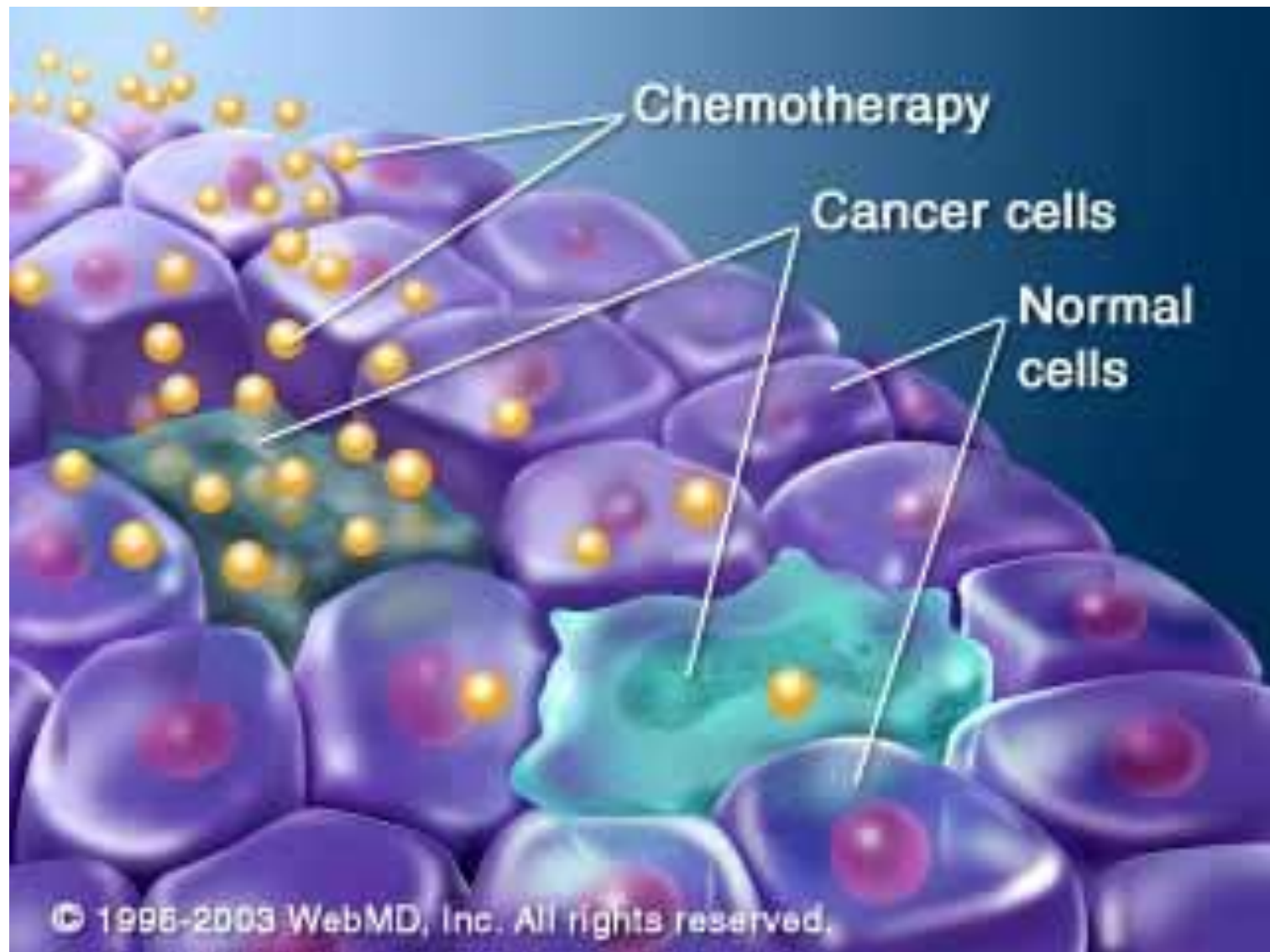
Drugs Targeting Growth Factor Receptors

- Cetuximab-Monoclonal Ab directed against EGFR



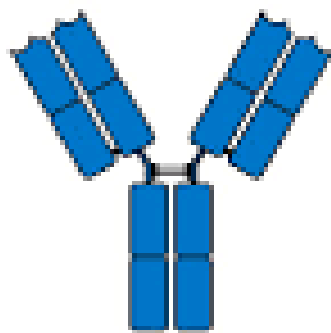
3-Monoclonal Antibodies (MoABs)

- MoABs consist of immunoglobulin sequences that recognize a specific antigen or protein on the surface of cells.
- Two classes of MoABs are
 - unconjugated or naked MoABs
 - immunoconjugates, MoABs conjugated to a toxin (immunotoxin), chemotherapy agent, or radioactive particle (radioimmunoconjugate).

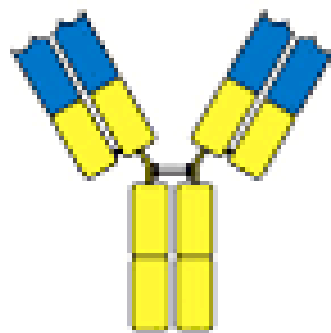


http://www.wvu.edu/depts/healthyliving/PE511info/cancer/My%20Cancer%20Webs/Symptoms%20and%20Therapy_files/image001.jpg

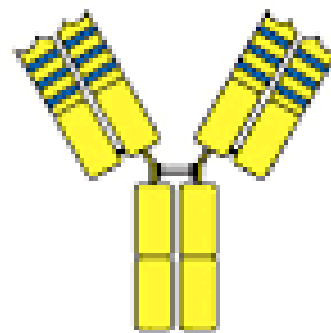
Four types of therapeutic monoclonal antibody



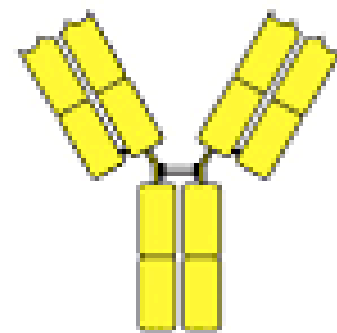
mouse



chimeric



humanized



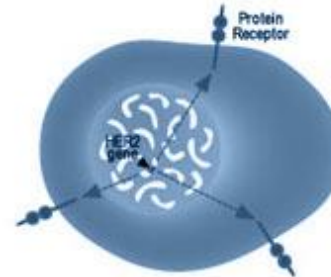
human

Mo ABs

mechanisms by which MoABs may induce death of cancer cells.

- Unconjugated MoABs that target antigens on the cell surface of cancer cells may directly mediate cell killing
- antibody binding may result in the transmission of signals that induce apoptosis, or programmed cell death in the targeted cell.
- immunoconjugates deliver a chemotherapy drug or radioactive particle to the site of disease.

- Trastuzumab
 - “Humanized” monoclonal Ab
 - Binds HER2-structurally similar to EGFR
- Combine with in breast cancer cells
- Cell cycle inhibitors
- Ab can be linked to radioisotopes/ drug



Normal Cell

In normal breast tissue cells, the HER2 gene produces a protein receptor on the cell surface. These growth factor-like receptors are thought to play a role in normal cell growth by signaling the cell to divide and multiply.

HER2 Overexpressing Cancer Cell

Cancerous breast tissue cells that overexpress (or overproduce) the HER2 gene produce extra protein receptors on the cell surface. The higher density of receptors triggers the cell to divide and multiply at an accelerated rate, thus contributing to tumor growth. Approximately 25-30% of all women with metastatic breast cancer overexpress the HER2 protein.



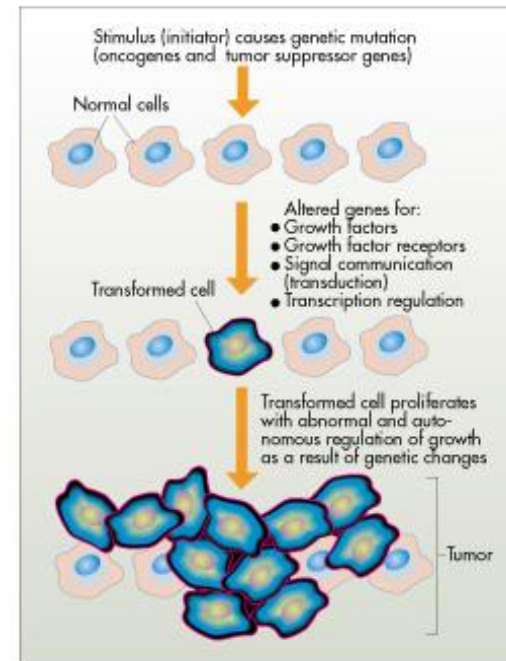
Herceptin® (Trastuzumab)

It is thought that Herceptin (a HER2 antibody) binds to numerous HER2 receptor sites found on the cell surface, blocking the receptor sites and possibly preventing further growth by interrupting the growth signal. As a result, the HER2 antibody may slow progression of the disease.

Biological therapy

The immune system is an effective antitumor defense

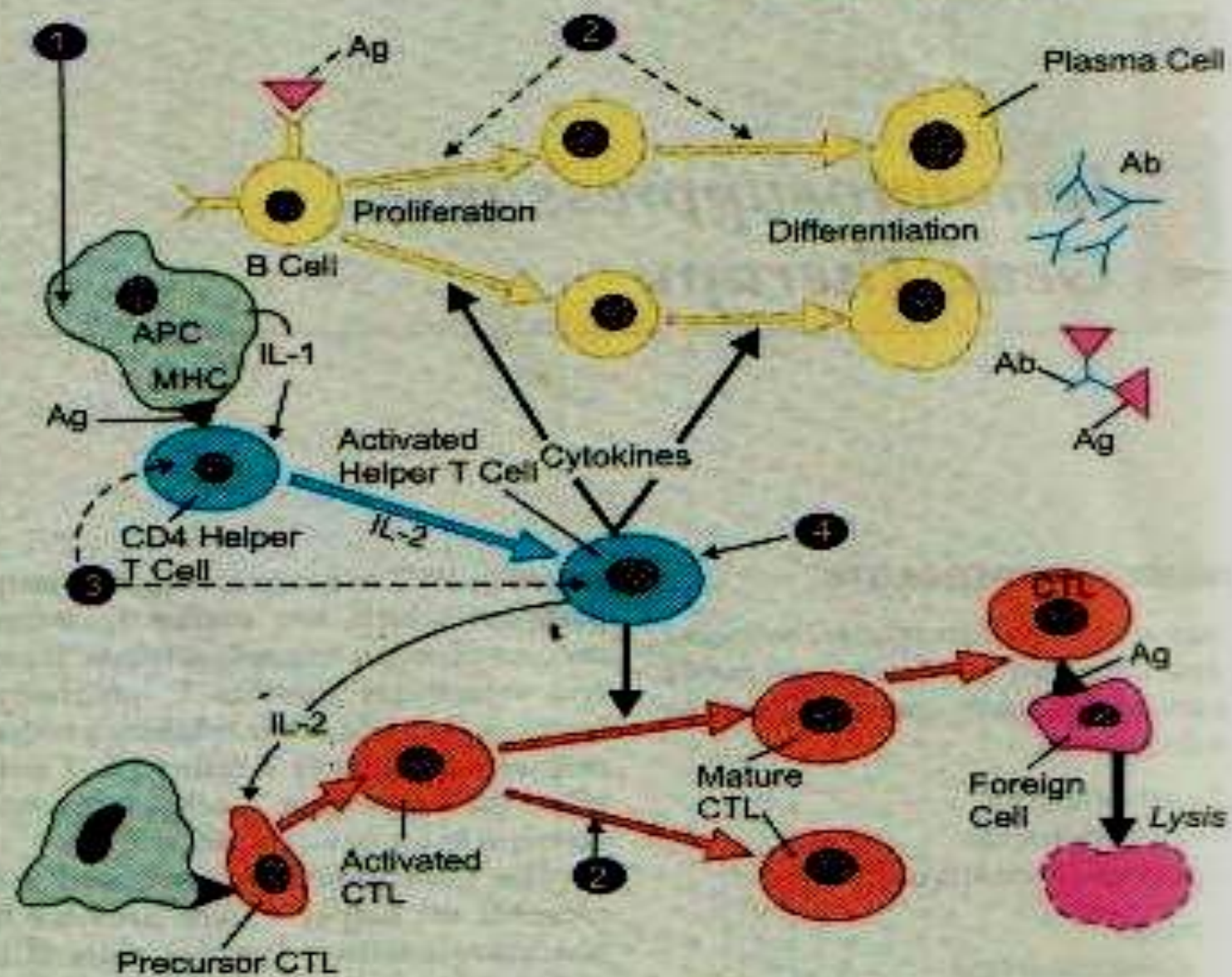
- Malignant cells occasionally arise in healthy bodies as a result of mutations but Not all these cells give rise to clinically evident cancer
- An intact immune system can identify malignant cells and destroy them without negative effects on normal cells.
- Few drug can enhance immune function induced destruction of cancer cells



Biological therapy

- making cancer cells more recognizable by the immune system, and more susceptible to destruction
- boosting the killing power of immune system cells
- changing the way cancer cells grow, so that they act more like healthy cells
- enhancing the body's ability to repair or replace normal cells damaged or destroyed by other forms of cancer treatment, like chemotherapy or radiation

Humoral Immune Response



Cell Mediated Immune Response

Biological therapy

Interferons- A type of BRM that naturally occurs in the body.

improve the way a cancer patient's immune system acts against cancer cells.

may work directly on cancer cells to slow their growth,

may cause cancer cells to change into cells with more normal behavior.

stimulate natural killer cells, T cells, and macrophages.

-Interleukins (IL): Proteins (cytokines)

– stimulate the growth and activity of immune cells, such as lymphocytes, which work to destroy cancer cells

Colony-stimulating factors (CSFs):

- Proteins that encourage stem cells in bone marrow to produce more blood cells.
- Given with chemotherapy, to help boost the immune system.
- With chemotherapy, bone marrow's ability to produce blood cells is suppressed, making patients more prone to infections.

Treatment of drug induced complications

- Colony stimulating factor
- Erythropoietin
- Antiemetic agents
- Corticosteroids
- Treatment of hyperuricemia