Pharmacology - HLS

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Cancer Chemotherapy

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Many cancers can be resected to a great extent, but we still need chemotherapy to eradicate neoplasms furthermore.

شوف هي أيوا 36 سلايد، وفارما وسخام، بس اجمد كدا، اجمد
بقولك ما تعيطش..
أنا مزبطتكم والسلايدز فيها كلام قليل وسهل يا دكترة أومال..
استعين على الشقاء بالله بقى..

Modalities/Objectives of Cancer Chemotherapy

Curative(شفائي):

Only in 10-15% of malignancy cases.

In certain disseminated neoplasms, The more disseminated the easier to tackle by chemotherapeutic agents like in leukemia (since it's freer in the circulation)

Palliative(تسكيني):

Given only to relieve the symptoms temporarily and enhance the overall quality of life, not to cure the cancer, certainly, tumor will progress along the course of the treatment.

Adjuvant(مساعد):

Given as an *adjuvant* to surgery, even if there is no evidence of metastasis,

85-90% of neoplasm cases are treated surgically, and this adjuvant treatment is to eradicate the neoplasms that surgery couldn't get rid of.

Cancer Chemotherapy

Classes of Anticancer Drugs: You don't need to memorize all these classes at the time being

- **Signal Transduction Inhibitors.**
- **Microtubule Inhibitors.**
- **Differentiation agents.**
- **Antimetastatic Drugs.**
- **Antiangiogenic drugs.**
- **Hypoxic Tumor Stem Cell- specific.**
- **Tumor Radio sensitizing.** (To facilitate the activity of radiation on tumor cells).
- **Normal Tissue Radio protecting Drugs.** (To protect healthy tissue).
- **Cytoprotective Agents.**
- **Biologic Response Modifiers.**

The Ideal Anticancer Drugs

Most of the cancer drugs are not ideal, they have many side effects, they don't have a great efficacy and they're not 100% effective, not like other drugs for peptic ulcer or antimicrobials for example..
The ideal anticancer drug should have the following features:

- **Exploit the differences between normal and tumor cells.**
- **Broad spectrum of activity:** having a Spectrum that includes many tumors.
- **Good distribution through the body.**
- **Non-immugenic:** Doesn't cause unnecessary immunological responses and doesn't suppress necessary immunological reactions.
- **Adequate biological half life.**
- **Reasonably priced.**

Current Anticancer Drugs

They have many side effects, examples include:

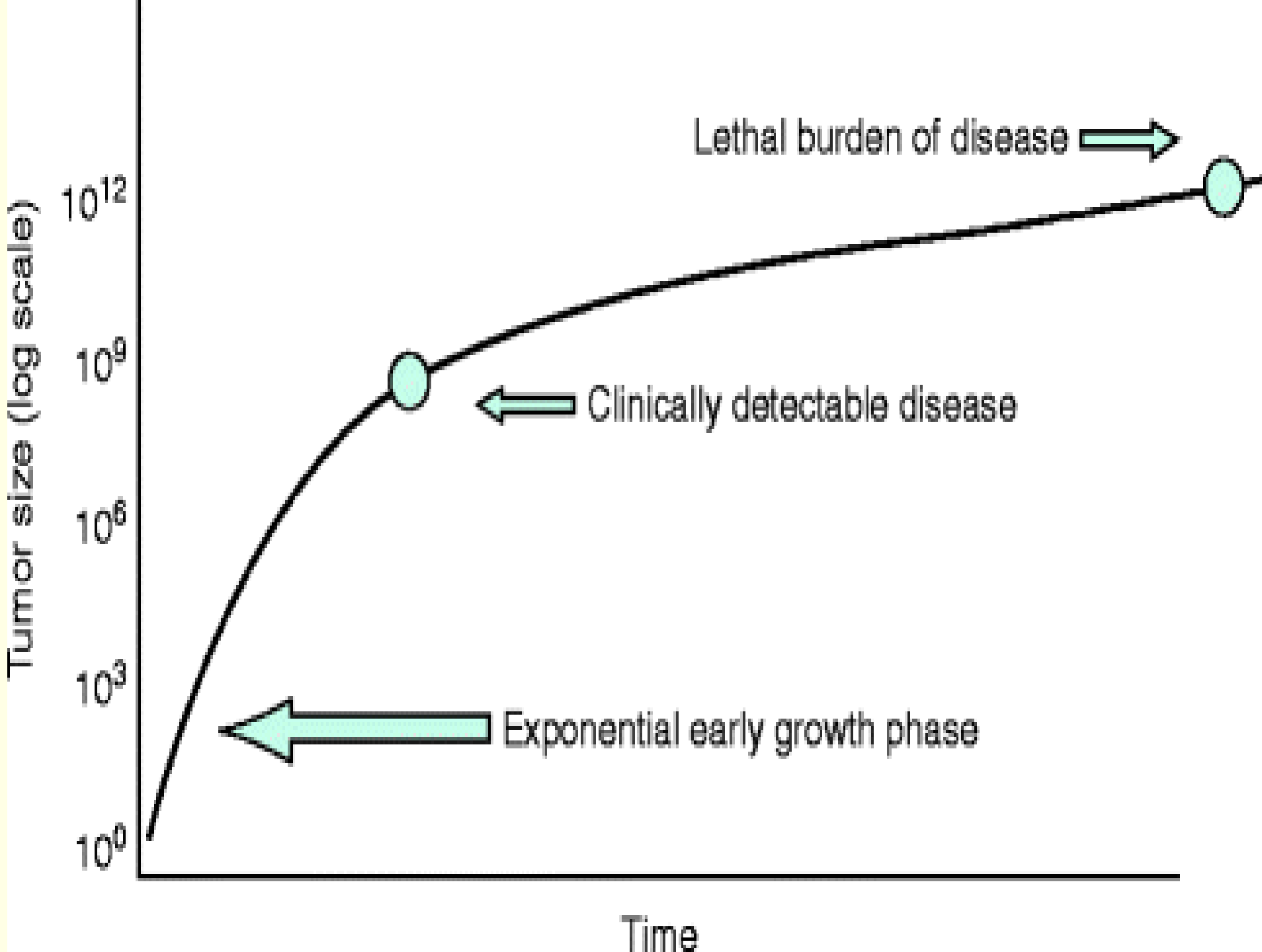
- **Carcinogenic:** They treat cancer and induce cancer at the same time.
- **Mutagenic.**
- **Teratogenic:** Induce birth defects in fetuses.
- **Immunosuppressive;** That's why patients will develop suprainfection.
- **Very toxic, but tolerance can develop.**

Gompertzian Tumor Growth

- The principle that explains tumor growth:
- States that:
- **The growth rate of a tumor is not constant and peaks when the tumor is about <u>one third of its maximum size</u>.**
- **Gompertzian growth curve describes the complex pattern of tumor growth. The curve has an early, almost exponential(متسارع) growth rate followed by slower growth rate which reaches a plateau as tumors grow larger in size.**

عايزني أشرحهولك؟ طيييب..

We can see that in this graph, the growth rate of the tumor rises rapidly and peaks when the tumor reaches 1/3 of its maximal size, and then the growth continues but in a slower rate..



In this graph, the **curve A** is the **size** of a tumor; we can see that in the beginning, it starts to grow rapidly until it reaches third of its maximal size, after that it starts to grow but slowly until it reaches its maximal size.

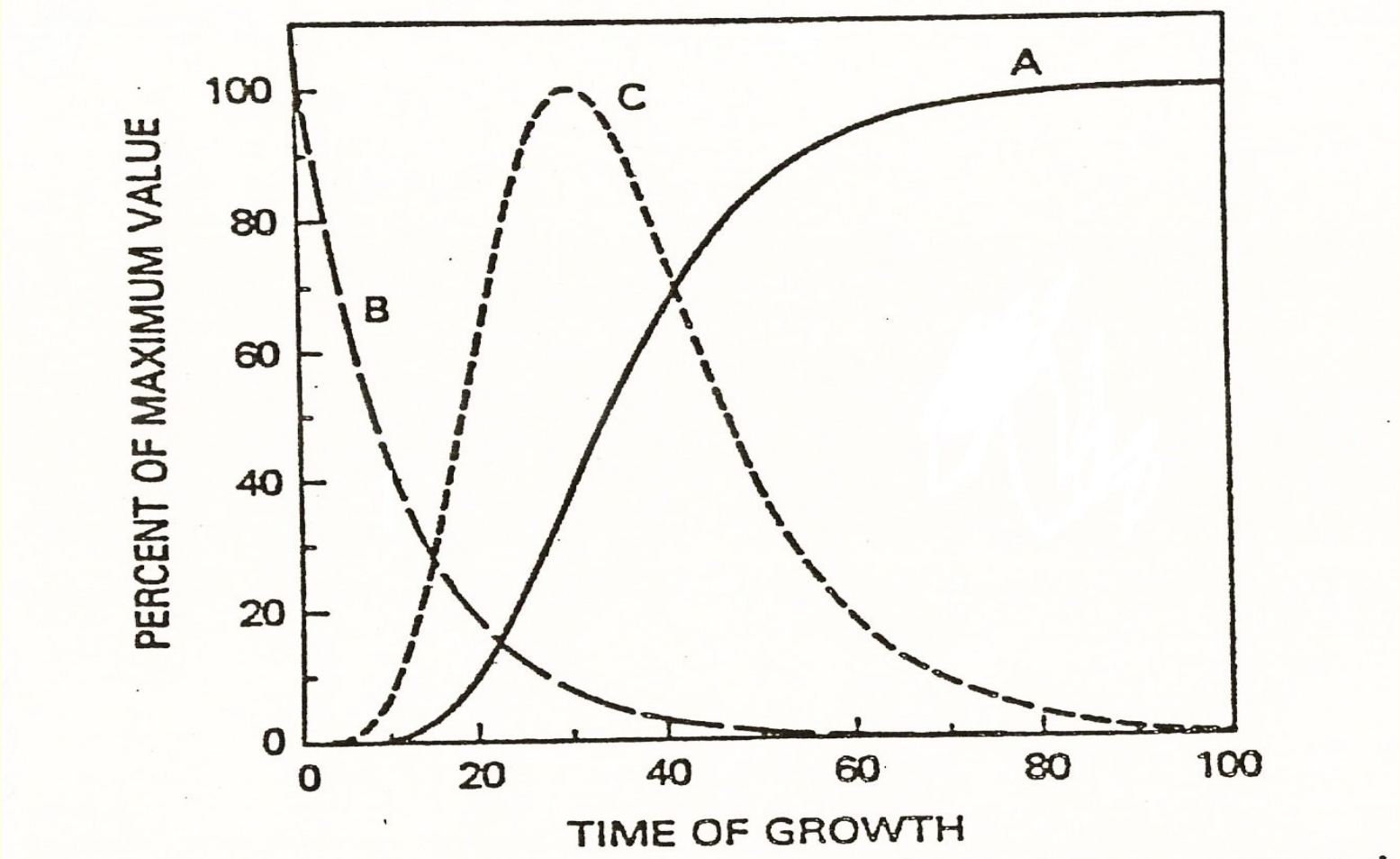
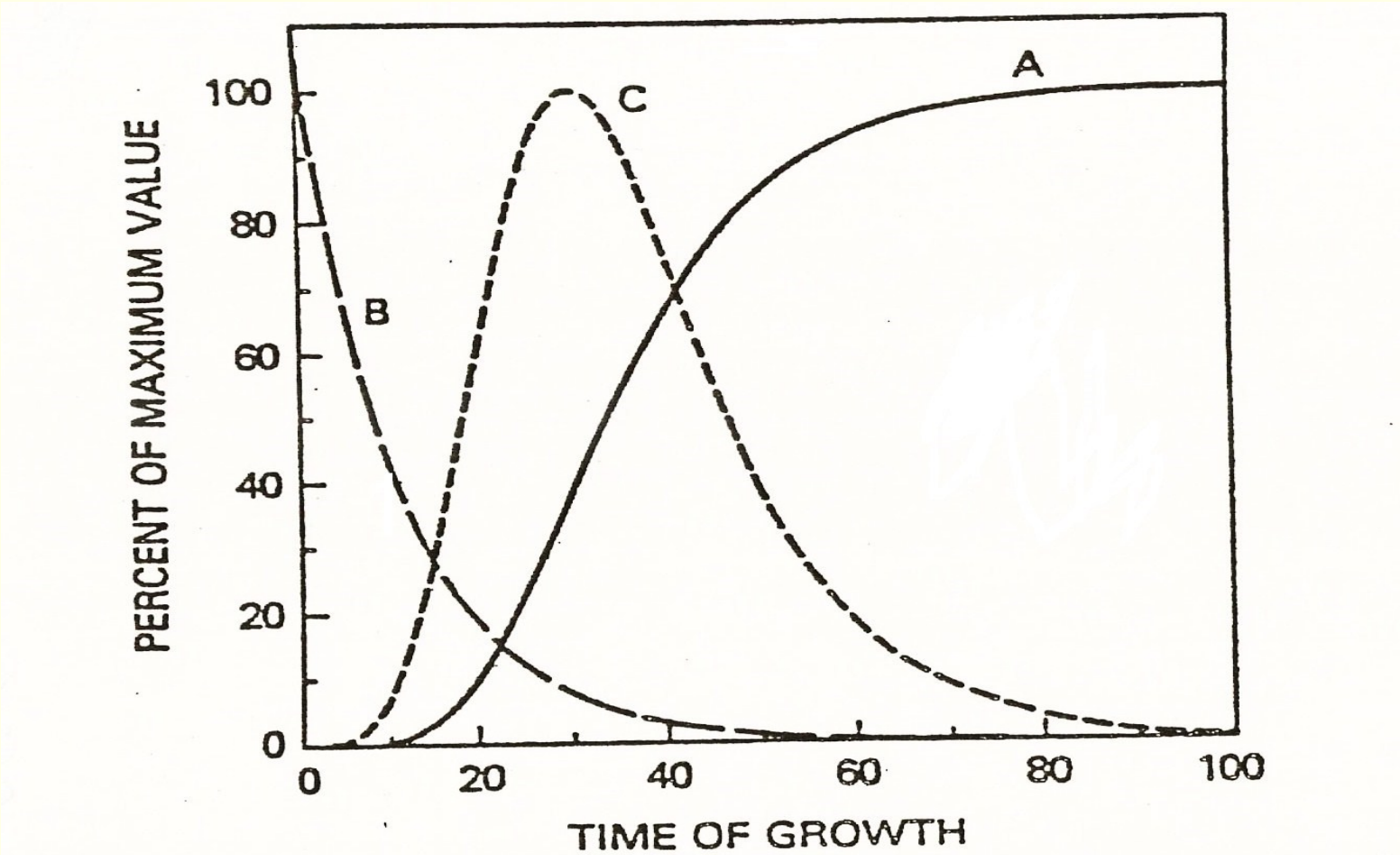


Fig. 7. Norton-Simon relationship between tumor size (A), instantaneous growth fraction (GF) (B), and growth rate (C) for unperturbed Gompertzian growth. While the GF is maximum at the time of initiation of growth the growth rate is maximum when the tumor is about 37 percent of its limiting size.[5] (Reproduced from Cancer Treat Rep.[13])

The **curve B** is the **instantaneous growth fraction** of the tumor; we can see that the instantaneous growth fraction of the tumor is at its highest level in the very beginning when there are zero tumor cells, the fraction continues to be large in the beginning of the tumor life but it decreases gradually until we reach the third of the maximum size of the tumor, then the fraction is at a very low value, this means that the tumor has a higher tendency to grow in the beginning of its life until it reaches the third of its maximum size, and after that the tendency of the tumor to grow is lower, that's why it takes longer time to reach the maximum size.



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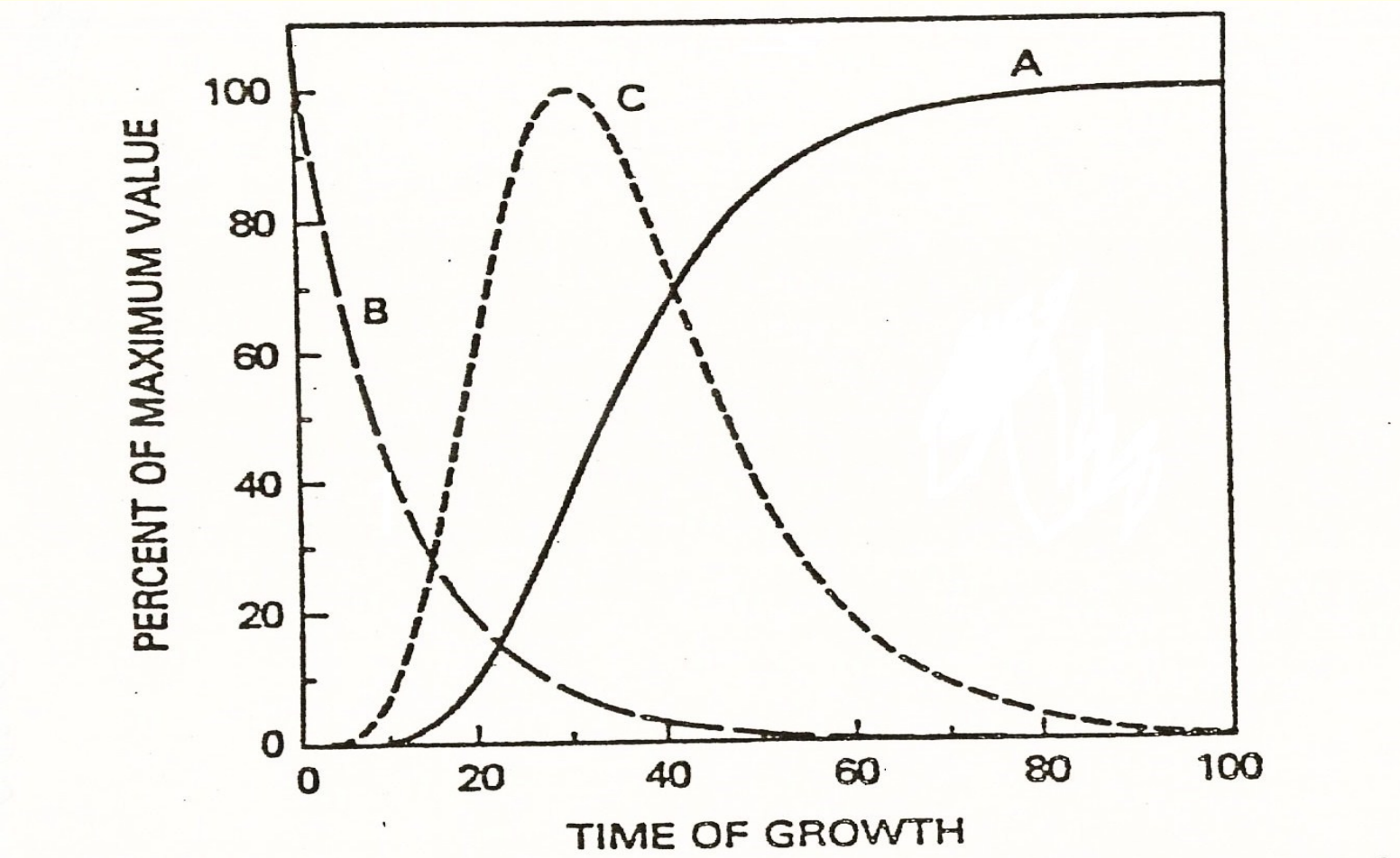
Curve C is the **growth rate** of the tumor; we can see that in the beginning of the life of the tumor, the growth rate increases until it reaches its peak, and again, this is where the thirds of its maximum size is reached, and then it starts to decrease gradually until it is almost zero when we reached the maximum size.



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شفت؟ مش قلتلك سلايدز سهلة؟
هيني حطيتلك سلايد فاضية أهوه..
وهي meme كمان يلا تدلّلوا..

When you can tell which curve is what in the previous graph:

Log-Kill Hypothesis (Exponential Cell Kinetics)

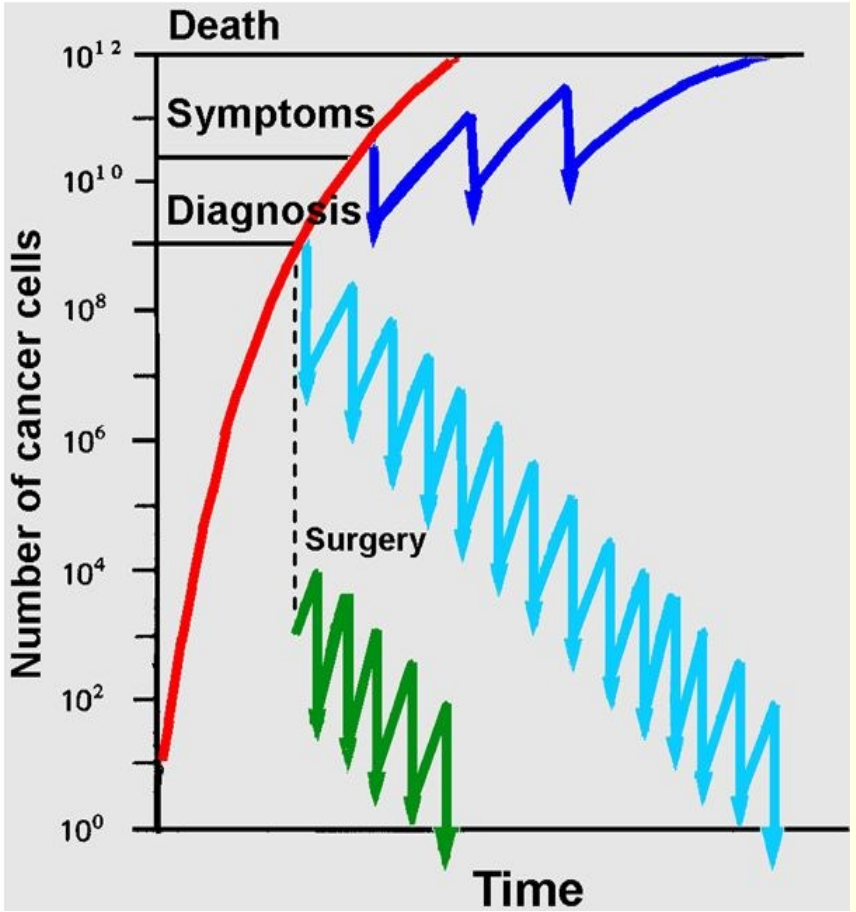
Drugs kill tumor cells at an exponential rate (the curve follows the logarithmic scale), we call it Log-Kill Hypothesis.

In acute leukemias and aggressive lymphomas:

- If we assume that the number of **Cells at time of diagnosis: 10^{12} .**
- **A very effective drug can kill 99.99%.**
- **So, cells in remission: 10^{8}.**
- **Also add, the number of cells that are inherently resistant , cells not available(not exposed)for the drug (CNS, testes), and cells in the G_0 phase** (cells in the G0 phase are not sensitive to chemotherapeutic drugs).
- So, a drug with a 99.99% efficiency rate is still not efficient enough to eradicate the tumor, there will still be many tumor cells

LOG kill hypothesis

- The example shows the effects of tumor burden, scheduling, initiation/duration of treatment on patient survival.
- The tumor burden in an untreated patient would progress along the path described by the RED LINE –
- The tumor is detected (using conventional techniques) when the tumor burden reaches 10^9 cells
- The patient is symptomatic at 10^{10}-10^{11} cells
- Dies at 10^{12} cells.



- **In the following graph, the red line is the size of the tumor; notice that we cannot diagnose the tumor with a size less than 10^9**
- **At the time of diagnosis, if the tumor was accessible to surgery, we can reduce the size of the tumor by surgery to less than 10^3 and then we can continue with chemotherapy until the cancer is cured (green zigzag).**
- **But if the tumor was not accessible to surgery, and chemotherapy starts at the point of diagnosis, it will take much longer time to treat cancer and fully eradicate it (cyan zigzag).**

LOG kill hypothesis

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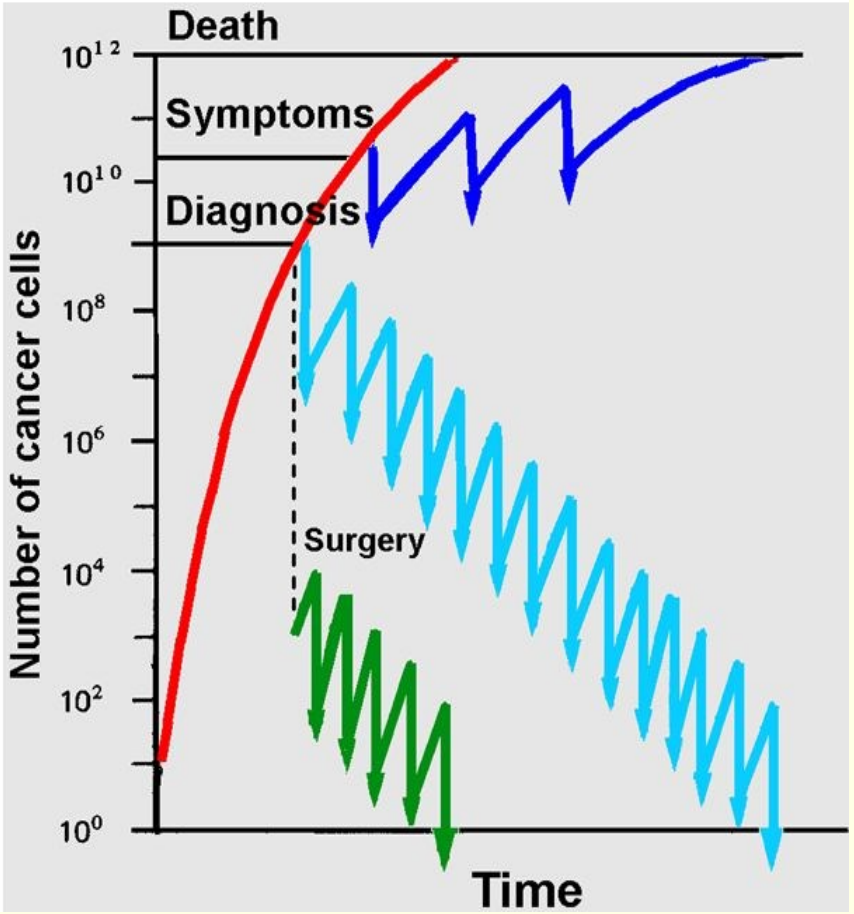
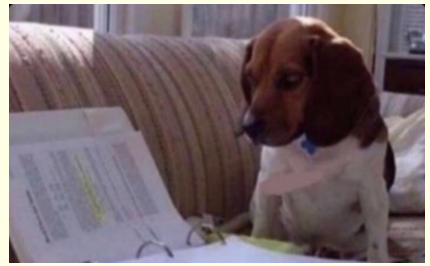


Notice that symptoms start to appear when the size of the tumor is much larger than 10^{10}; once the symptoms have appeared, the treatment cannot treat cancer, so the treatment is only palliative to ensure that the patient has the highest quality of life until the time they pass away when the tumor size reaches the number of cells of 10^{12}.

Oh ummm, this graph wasn't as nice as the one before, was it? 😬



Combination Therapy

- **Anticancer drugs are usually given in combinations to:**
  - **Increase effectiveness.**
  - **Reduce the toxicity.**
- ***Employed to overcome the limited log kill of individual drugs.***
- **The drugs should be effective when used as single agents.**
- **If there is no biochemical basis for synergism, there should be at least additive effects.** But preferably, there should be synergism between the drugs.
- **Where possible, drugs with differing modes of actions are combined.**

Combination Chemotherapy

- **The major toxicity of each drug, should be as different as possible from that of other agents (non overlapping toxicity)**
  To give the patient the opportunity to deal with one toxicity at a time, for example if one drug was **Myelosuppressant,** the other has to be **nonsuppressant.**

- **Toxicity should appear at different times.**

Cancer Chemotherapy

- A "Magic bullet" drug, is a dream that did not materialize yet.
- Cytotoxic drugs are given in repeated courses arranged so that the recovery of normal cells can occur, but little recovery of cancer cells is possible.

شوف السلايد الفاضية يا عبدو.. خمسة وخميسة في عيون الحسود

Toxicity of Cancer Chemotherapy

- Cells of the bone marrow, the lymphatic system, and the lining of the intestinal tract are very sensitive to cytotoxic drug effects.
- Almost all anticancer drugs cause toxicity, e.g. :

  - Bone marrow suppression: Nitrogen mustard.
  - Immunosuppression: Methotrexate.
  - Neuropathy: Vincristine.
  - Cardiotoxicity: Doxorybicin (Adriamycin).

Special Problems/Practical Points

- **Storage .**
- **Preparation.**
- **Administration.**
- **Extravasation of injection:** Drugs taken by injections can cause vasculitis and irritation of blood vessels.
- **Vomiting,** If given orally.. that's why we might give with them the following:
  - **Lorazepam for anxiety.**
  - **Dexamethasone, Domperidone.**
  - **Ondansetron: $5HT_3$ antagonist.**
- **Teratogenesis.**
- **Bone Marrow suppression.**
- **Immunosuppression leading to severe infection.**

Relative Chemosensitivity of Tumors

Tumors are divided according to their chemosensitivity into 4 categories:

Do not memorize examples on these categories, they're for the future only, but just in case we were betrayed, take a look at the ones that have notes beside them ♡♡♡

- **A. Highly Sensitive:**
- ***May be cured by chemotherapy.***
  - **Teratoma of Testis.**
  - **Hodgkin's and high-grade non- Hodgkin's Lymphomas.**
  - **Wilms's Tumor.**
  - **Embryonal Rhabdomyosarcoma.**
  - **Choriocarcinoma.**
  - **Acute Lymphoblastic Leukemia in children,** this one especially was highly reported to have a super high curability rate.
  - **Ewing's Sarcoma.**

Relative Chemosensitivity of Tumors

- **B. Moderately Sensitive:**
- ***Chemotherapy may sometimes contribute to cure and often palliates.***
  - **Small cell carcinoma of the lung.**
  - **Breast carcinoma.**
  - **Low grade non-Hodgkin's Lymphoma.**
  - **Acute Myeloid Leukemia.**
  - **Ovarian cancer.**
  - **Multiple Myeloma.**

Relative Chemosensitivity of Tumors

- **C. Relatively Insensitive:**
- ***Chemotherapy may sometimes produce palliation(تسكين).***
  - **Gastric carcinoma.**
  - **Bladder carcinoma.**
  - **Squamous cell carcinoma of head and neck.**
  - **Soft tissue sarcoma.**
  - **Cervical carcinoma.**
- **D. Resistant Tumors:**
  - **Melanoma.**
  - **Squamous cell carcinoma of the lung.**
  - **Large bowel cancer.**

Resistance to Cytotoxic Drugs

Primary or Inherent Resistance:

- **Absence of response on the first exposure,** Do not respond to chemotherapy, shouldn't be given it anyway.
- **Melanoma, renal cell carcinoma, brain cancer.**

Acquired Resistance:

1. **Highly Specific:**

- **For one single drug.**
- **Based on a change in the genetic apparatus of a given tumor cell with amplification or increased expression (*gene amplification)* of one or more specific genes,** note that the genetic mutation here is **in the tumor cells.**

Resistance to Cytotoxic Drugs

2. Multidrug-Resistance(Pleiotropic متعدد الاتجاهات):

- **Resistance to a variety of natural product anticancer agents of different structures developing after exposure to a single agent,** the agents that resistance develops towards are related to the agent that it was first exposed to.
- **Associated with increased expression of a normal gene(*the MDR1gene*) for a cell surface glycoprotein (P-glycoprotein) involved in drug efflux** (Drug efflux is its ejection out of the cell).
- **This glycoprotein requires ATP to expel a variety of foreign molecules and not limited to anticancer drugs.**
- **Reversed by calcium channel blockers** (That's why Ca channel blockers can be useful in cancer treatment).
- **Could also be due to overexpression of the multidrug resistance protein1 (MRP1) which can function as a drug export pump.**

Resistance to Cytotoxic Drugs

3. Biochemical Resistance:

Decreased drug transport into the cells.

Alteration in the structure of the target enzyme.

Changes in cell DNA repair capability.

Never mind me, just looking for jokes to add to this slide

Complications of Chemotherapy

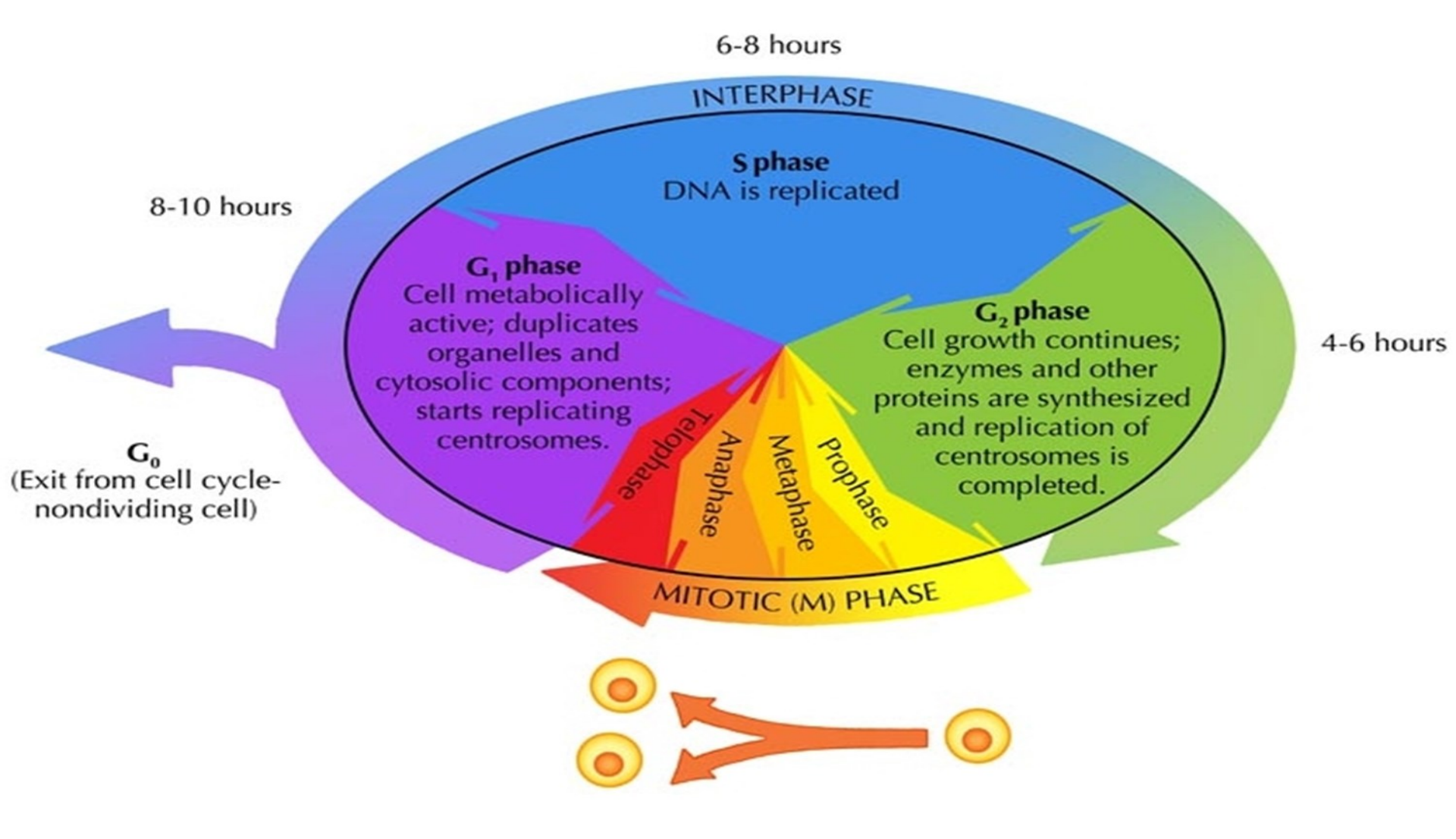
- **Immediate Complications:** Might appear in the first 2 weeks of the chemotherapy course:
  - **Nausea and vomiting.**
  - **Mucosal ulcerations.**
  - **Bone marrow depression.**
  - **Alopecia.**
- **Long term complications:**
  - **Infertility.**
  - **Secondary cancers.**
  - **Pulmonary fibrosis.**
  - **Cardiomyopathy.**
  - **Nerve damage.**
  - **Loss of hearing.**
  - **Renal impairment.**

Cell Cycle

Cells, normal and cancerous, pass through a series of phases during their life.

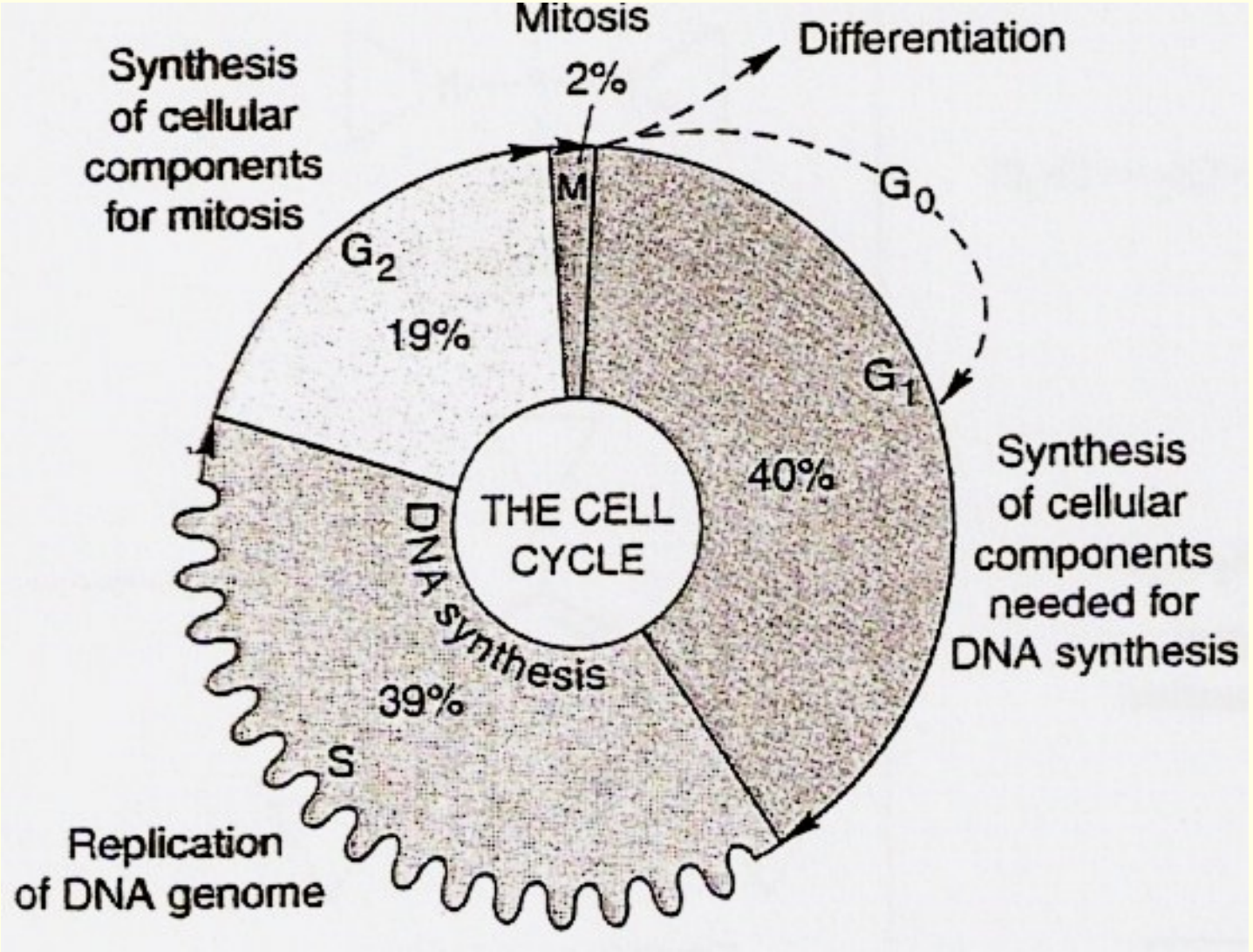
You remember the cell cycle

مش كده يا دكتور؟



Cell Cycle

- G_0 : Resting phase.
- G_1: Initial phase, enzyme synthesis.
- S: DNA synthesis.
- G_2: Synthesis of cellular components required for mitosis.
- M: Mitosis, Cell division phase.



Cell Cycle

- **Cancer cells in the G_o will be in the resting phase, and they will be least sensitive to chemotherapy,** So we must target other phases of tumor cells.
- **Cytotoxic drugs interfere with DNA or RNA and thus have profound effects on normal** Profound effect is only on normal multiplying cells as well as **malignant cells.**
- They have less effects on normal nonmultiplying cells.

The Cell Cycle and Anticancer Drugs

Many of the effective anticancer drugs exert their action on cells traversing the cell cycle and are called <u>cell cycle–specific (CCS) drugs.</u>

A second group of agents called <u>cell cycle–nonspecific (CCNS) drugs</u> can kill tumor cells whether they are cycling or resting in the G_0 compartment. CCNS drugs can kill both G_0 and cycling cells (although cycling cells are more sensitive).

CCNS are more effective, while CCS are more specific in affecting cell cycle.

Cell-Cycle-Specific Drugs (CCS)

- **Exert their action on cells traversing the cell cycle.**
- **Effective only when large proportion of the cells are proliferating or are in the growth fraction.**

Cell-Cycle-Specific Drugs (CCS)

Do not memorize any of the example names ya 7elween ♡♡♡

- **Antimetabolites:**
  - Capecitabine.
  - Cladribine.
  - Cytarabine.
  - Fludarabine.
  - 5-Fluorouracil(5-FU).
  - Gemcitabine.
  - 6-Mercaptopurine(6-MP).
  - Methotrexate.
  - 6-Thioguanine(6-TG).
- **Antitumor Antibiotics:**
  - Bleomycin.
- **Epipodophyllotoxins:**
  - Etoposide.
  - Teniposide.
- **Taxanes:**
  - Docetaxil.
  - Paclitaxil.
- **Vinca Alkaloids:**
  - Vinblastine.
  - Vincristine.
  - Venorelbin.

Cell-Cycle-Nonspecific Drugs (CCNS)

- **Can sterilize tumor cells whether they are cycling or resting or resting in the G_0 compartment.**
- **Useful both in low growth fraction solid tumors as well as in high growth fraction tumors.**
- **Bind to cellular DNA and damage these macromolecules.**

جايتلك بسلايد أمثلة كمان بعد هاد، تدلّل وانت بتعمل سكيب للأسماء 😉

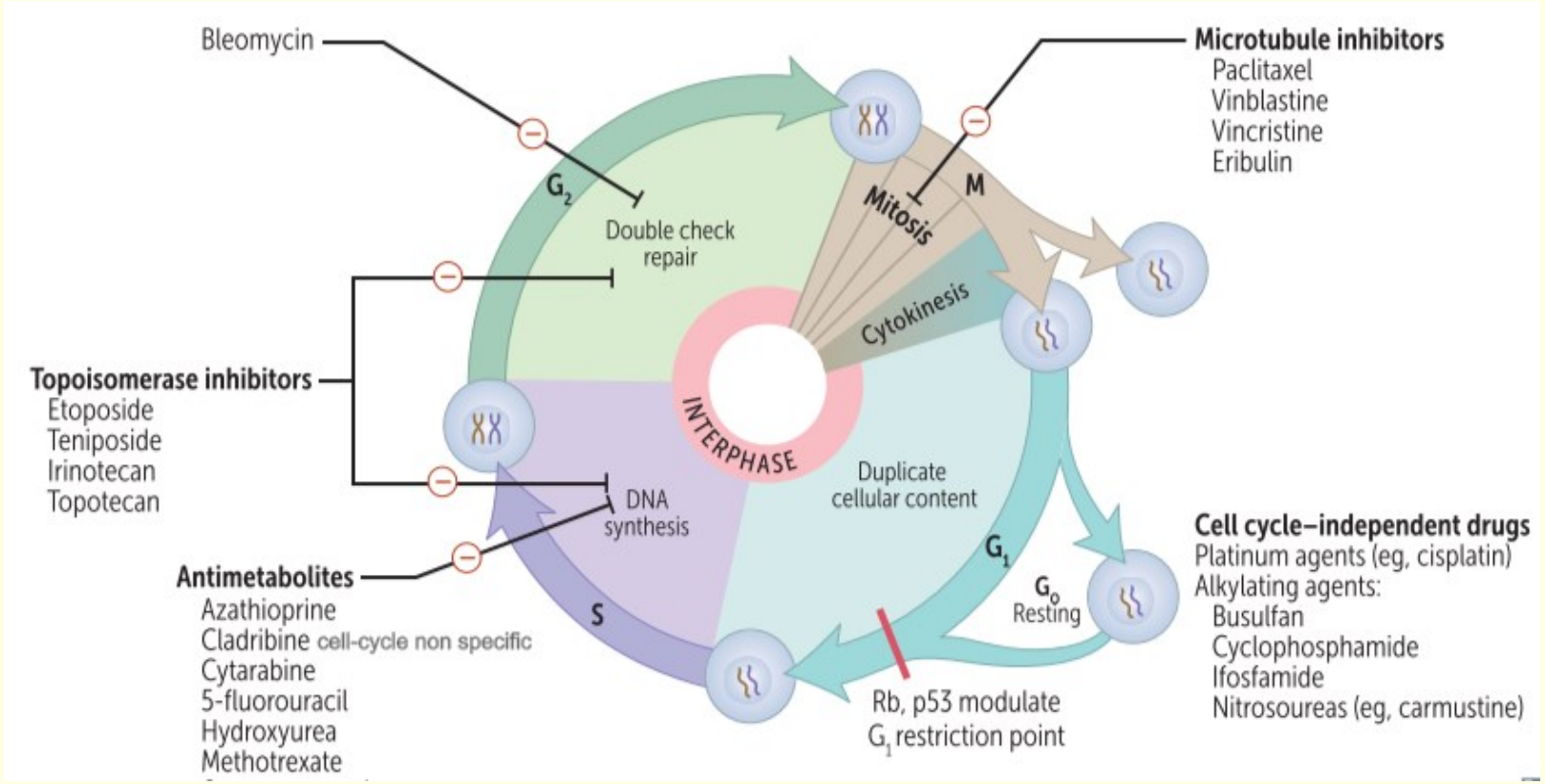
Cell-Cycle-Nonspecific Drugs (CCNS)

- **Alkylating Agents:**
  - Busulfan.
  - Carmustine.
  - Cyclophsphamide.
  - Lomustine.
  - Mechlorethamine.
  - Melphalan.
  - Thiotepa.

- **Anthracyclines:**
  - Daunorubicin.
  - Doxorubicin.
  - Epirubicin.
  - Idarubicin.
  - Mitoxantrone.

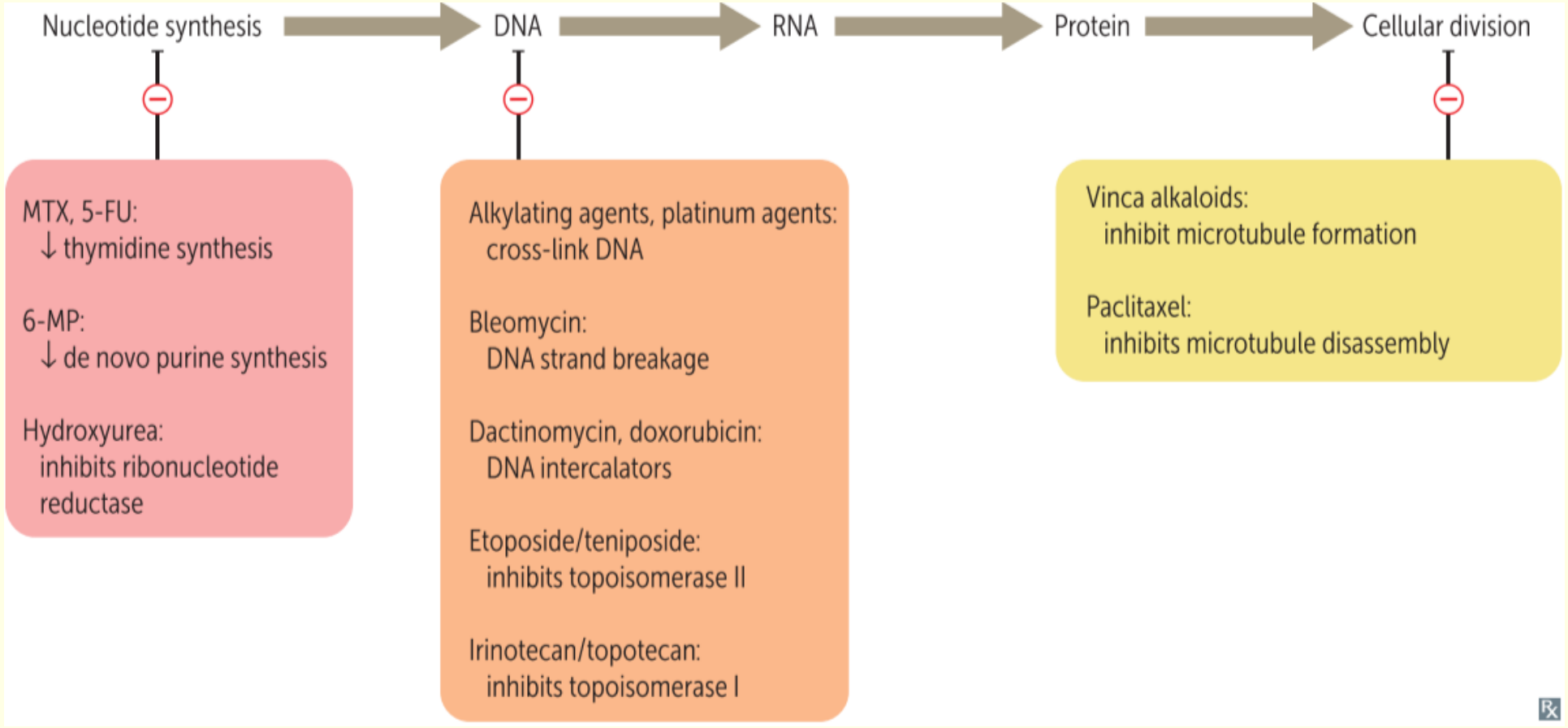
- **Antitumor Antibiotics:**
  - Dactinomycin.
  - Mitomycin.
- **Camptothecins:**
  - Irinotecan.
  - Topotecan.
- **Platinum Compounds:**
  - Carboplatin.
  - Cisplatin.
  - Oxaliplatin.

Cancer drugs—cell cycle



I honestly have no idea why these slides are here; they weren't in the lecture so let's talk about something useful instead..
Do you remember the Kanye – Taylor Swift drama?

Anticancer Drugs Targets



And now we've come to the end of the lecture, go get a sandwich for the effort, have a nice day and happy زنقة! ♡♡♡