Cancer Chemotherapy

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Modalities of Cancer Chemotherapy

Curative:

Only in 10-15% of cases.

In certain disseminated neoplasms.

Palliative:

Given only to relieve the symptoms temporarily and enhance the overall quality of life, not to cure the cancer.

Adjuvant:

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

Cancer Chemotherapy

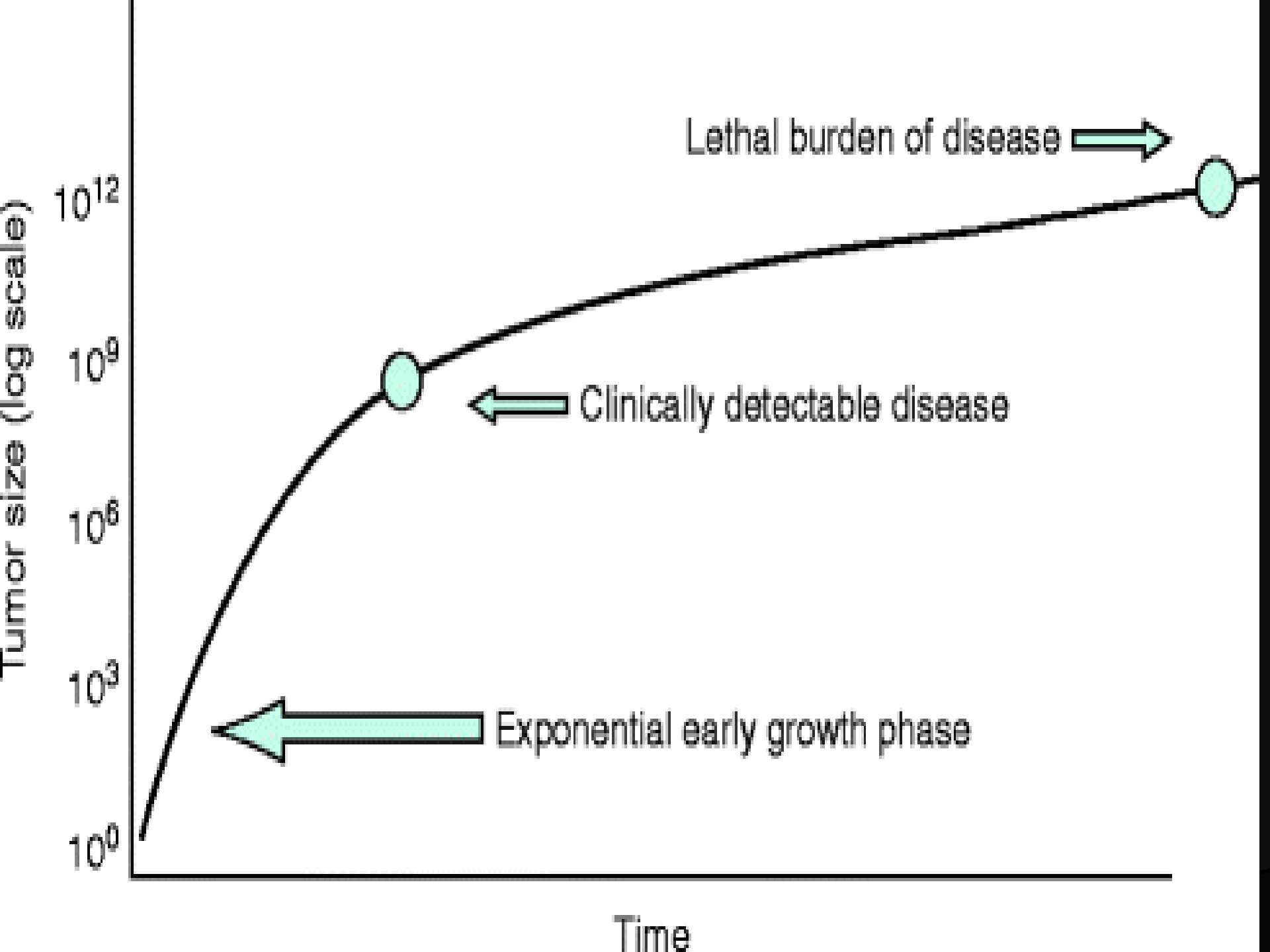
- **Classes of Anticancer Drugs:**
- Signal Transduction Inhibitors.
- Microtubule Inhibitors.
- Differentiation agents.
- Antimetastatic Drugs.
- Antiangiogenic drugs.
- Hypoxic Tumor Stem Cell- specific.
- Tumor Radiosensitizing.
- Normal Tissue Radioprotecting Drugs.
- Cytoprotective Agents.
- Biologic Response Modifiers.

Current Anticancer Drugs

- Carcinogenic.
- Mutagenic.
- Teratogenic.
- Immunosuppressive.
- Very toxic but tolerance develops.

The Ideal Anticancer Drugs

- Exploits the differences between normal and tumor cells.
- Broad spectrum of activity.
- Good distribution through the body.
- Non-immugenic.
- Adequate biological half life.
- Reasonably priced.


Lethal burden of disease
Clinically detectable disease
Exponential early growth phase
Tumor size (log scale)
10^{12}
10^{9}
10^{6}
10^{3}
10^{0}
Time

Gompertzian Tumor Growth

- The growth rate of a tumor is not constant and peaks when the tumor is about one third of its maximum size.

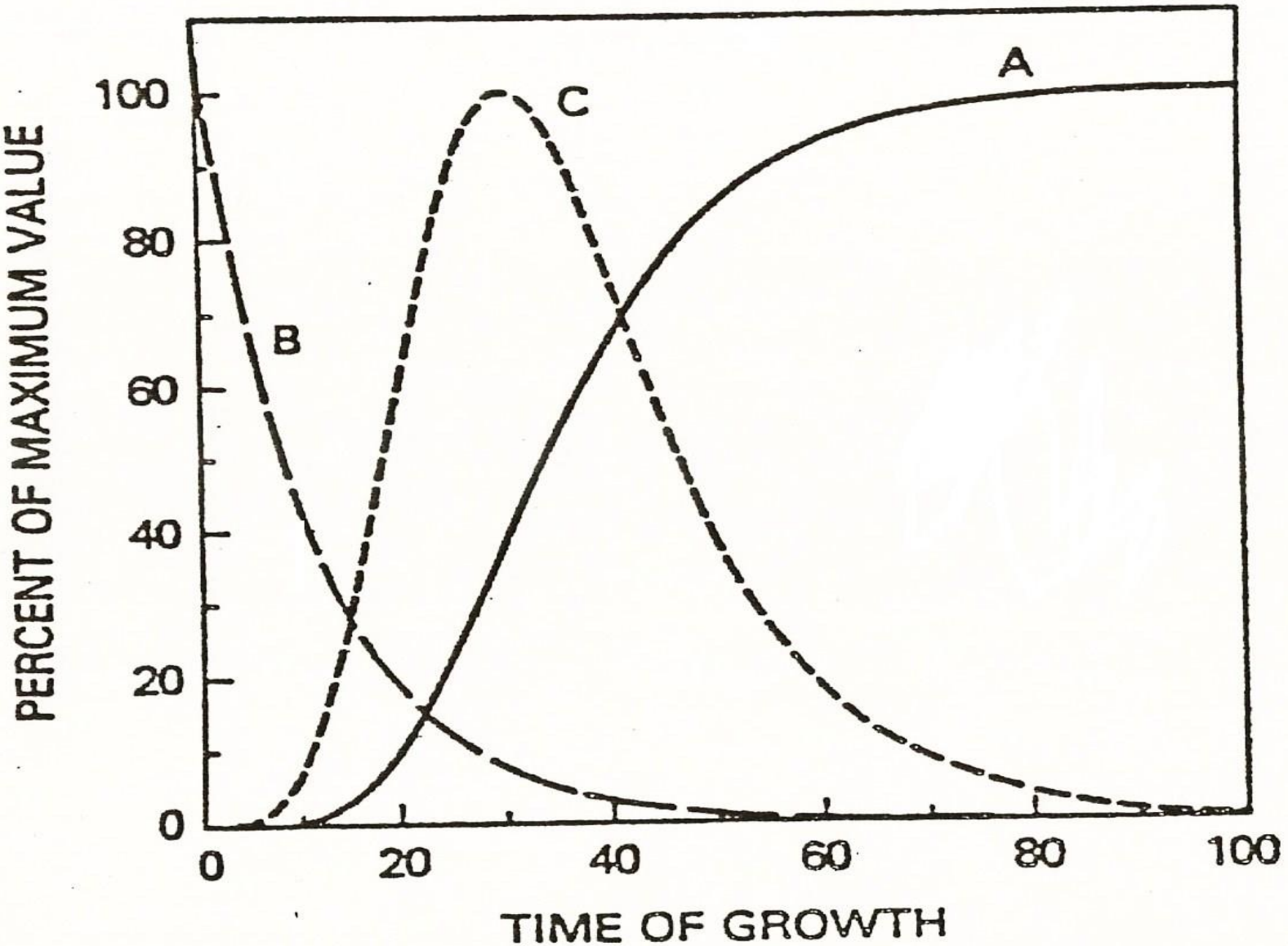


Fig. 7. Norton-Simon relationship between tumor size (A), instantaneous growth fraction (GF) (B), and growth rate (C) for unperturbed Gompertzian growth. While the GF is maximum at the time of initiation of growth the growth rate is maximum when the tumor is about 37 percent of its limiting size.[3] (Reproduced from Cancer Treat Rep.[13])

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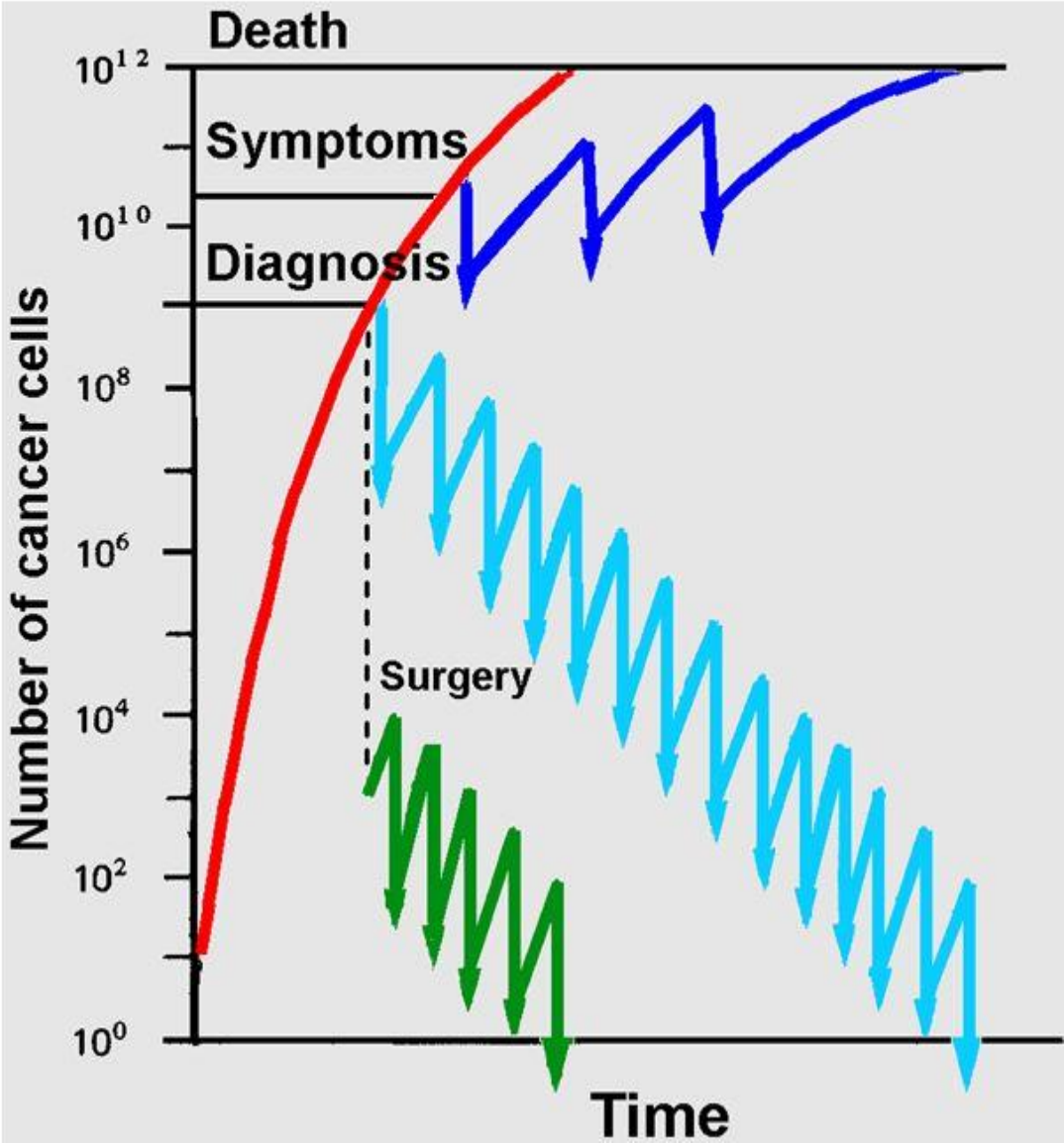
Log-Kill Hypothesis (Exponential Cell Kinetics)

In acute leukemias and aggressive lymphomas:

- 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 for the drug (CNS, testes), and cells in the G_0 phase.

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.



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.**
- **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).
- Toxicity appears at different times.
- Myelosuppressant & nonsuppressant.

Cancer Chemotherapy

- "**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.

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.
- Vomiting:
  - Lorazepam for anxiety.
  - Dexamethasone, Domperidone.
  - Ondansetron: $5HT_3$ antagonist.
- Teratogenesis.
- Bone Marrow suppression.
- Immunosuppression leading to severe infection.

Relative Chemosensitivity of Tumors

- **Highly Sensitive:**
- ***May be cured by chemotherapy.***
  - **Teratoma of Testis.**
  - **Hodgkin's and high grade non- Hodgkin's Lymphomas.**
  - **Wilm's Tumor.**
  - **Embryonal Rabdomyosarcoma.**
  - **Choriocarcinoma.**
  - **Acute Lymphoblastic Leukemia in children.**
  - **Ewing's Sarcoma.**

Relative Chemosensitivity of Tumors

- **Moderately Sensitive:**
- ***Chemotherapy my 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.**
  - **Myeloma.**

Relative Chemosensitivity of Tumors

- **Relatively Insensitive:**
- ***Chemotherapy may sometimes produce palliation.***
  - **Gastric carcinoma.**
  - **Bladder carcinoma.**
  - **Squamous cell carcinoma of head and neck.**
  - **Soft tissue sarcoma.**
  - **Cervical carcinoma.**

Relative Chemosensitivity of Tumors

- **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.

- **Like 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.**

Resistance to Cytotoxic Drugs

- 2. <u>Multidrug-Resistance(Pleiotropic):</u>
- Resistance to a variety of natural product anticancer agents of different structures developing after exposure to a single agent.
- Associated with increased expression of a normal gene(*the MDR1gene*) for a cell surface glycoprotein (P-glycoprotein) involved in drug efflux.

Resistance to Cytotoxic Drugs

- 2. <u>Multidrug-Resistance(Pleiotropic): cont…</u>
- This glycoprotein requires ATP to expel a variety of foreign molecules and not limited to anticancer drugs.
- Reversed by calcium channel blockers.
- 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.

Complicatins of Chemotherapy

- **Immediate Complications:**
  - Nausea and vomiting.
  - Mucosal ulcerations.
  - Bone marrow depression.
  - Alopecia.

Complicatins of Chemotherapy

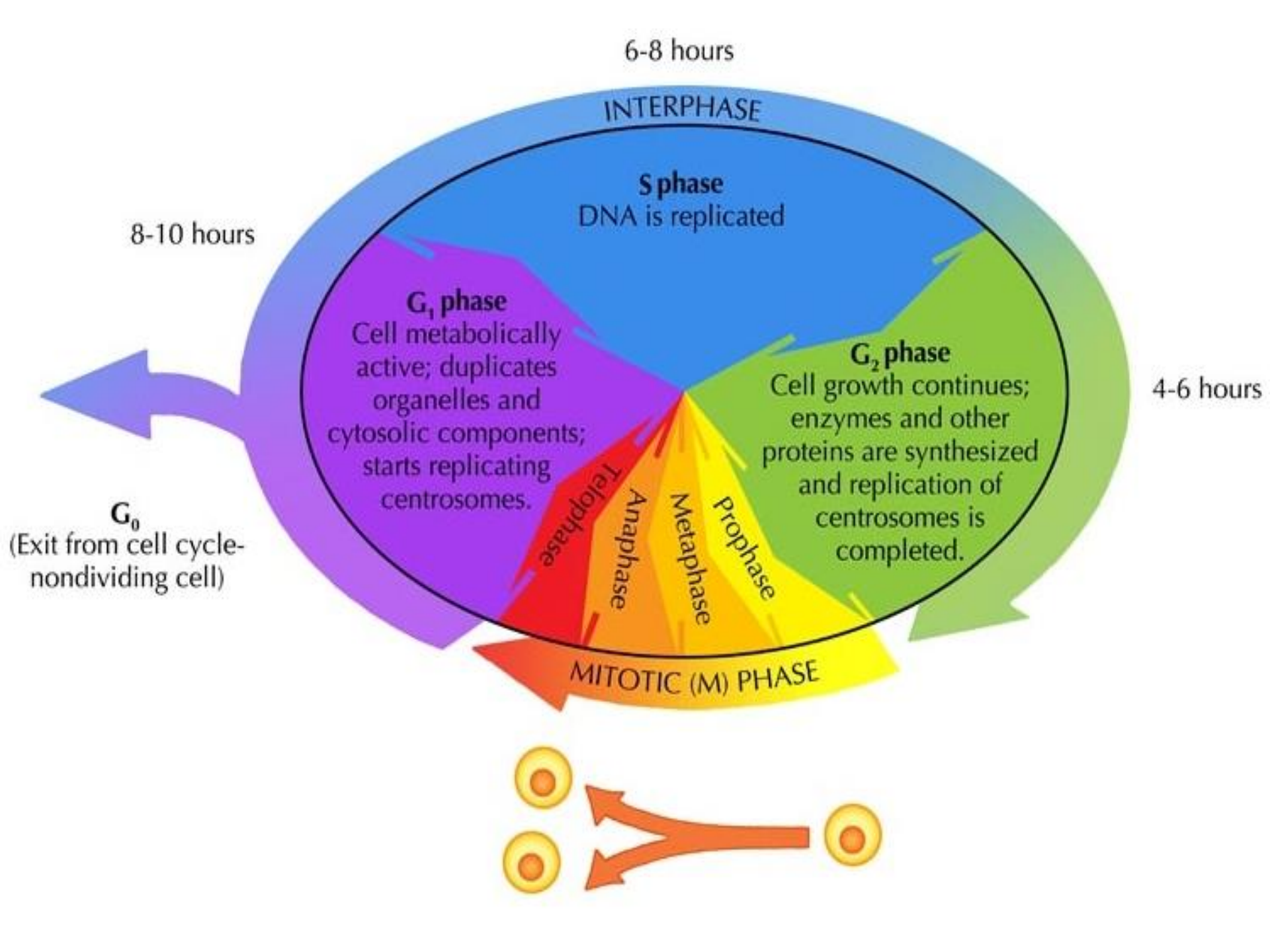
- **Long term complications:**
  - Infertility.
  - Secondary cancers.
  - Pulmonary fibrosis.
  - Cardiomyopathy.
  - Nerve damage.
  - Loss of hearing.
  - Renal impairment.

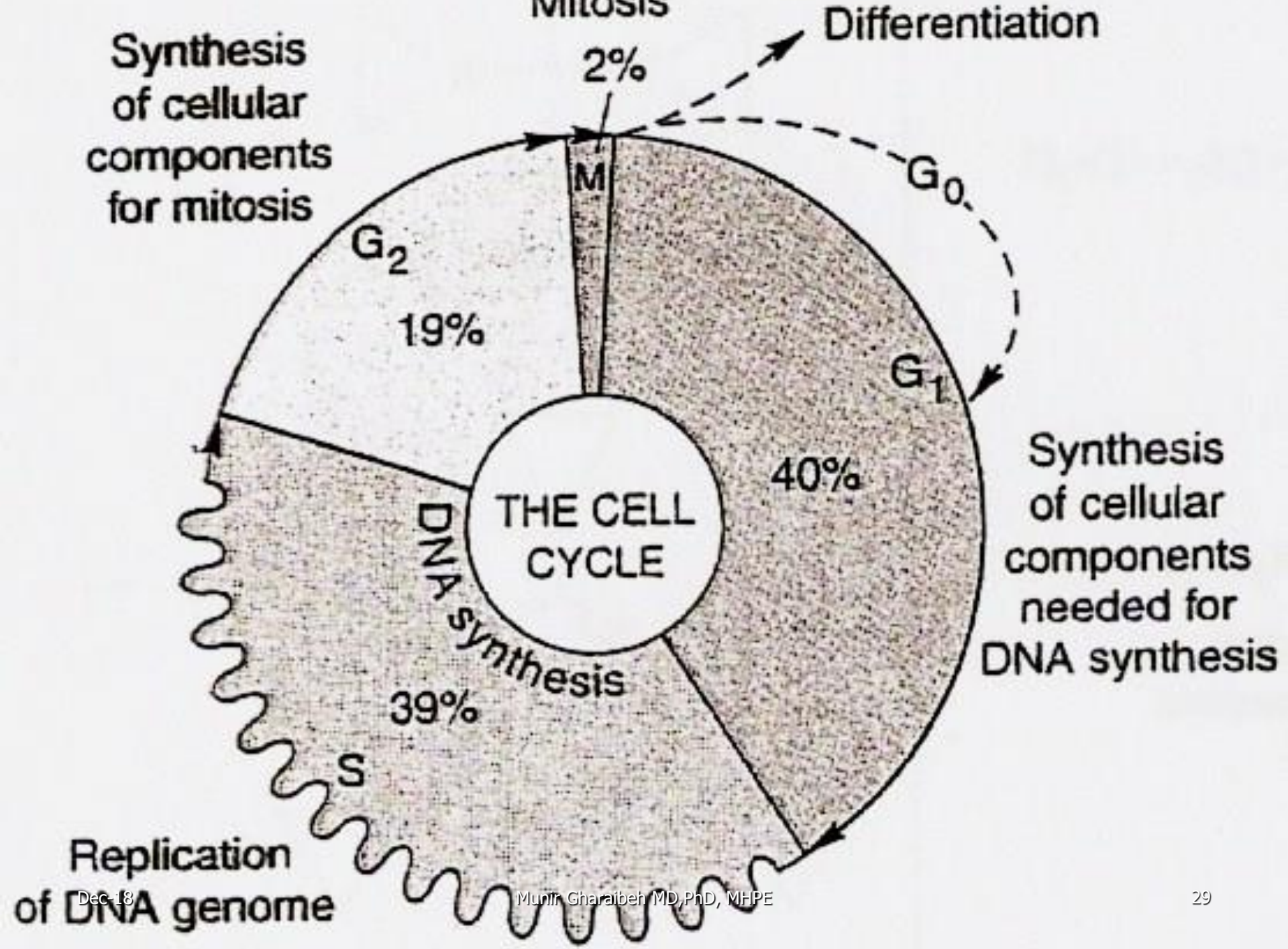
Cancer Chemotherapy

- Cells, normal and cancerous, pass through a series of phases during its life.
- Cancer cells in the G_o will be in the resting phase, and they will be least sensitive to chemotherapy.
- Cytotoxic drugs interfere with DNA or RNA and thus have profound effects on cells, normal and malignant.

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.


6-8 hours
INTERPHASE
S phase
DNA is replicated
8-10 hours
G1 phase
Cell metabolically active; duplicates organelles and cytosolic components; starts replicating centrosomes.
G2 phase
Cell growth continues; enzymes and other proteins are synthesized and replication of centrosomes is completed.
4-6 hours
G0
(Exit from cell cycle-nondividing cell)
Telophase
Anaphase
Metaphase
Prophase
MITOTIC (M) PHASE


Mitosis
2%
Differentiation
Synthesis
of cellular
components
for mitosis
M
G0
G2
19%
G1
40%
THE CELL
CYCLE
DNA synthesis
39%
S
Synthesis
of cellular
components
needed for
DNA synthesis
Replication
of DNA genome

The Cell Cycle and Anticancer Drugs

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

A second group of agents called cell cycle–nonspecific (CCNS) drugs 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).

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)

- **Antimetabolites:**
  - Capecitabine.
  - Cladribine.
  - Cytarabine.
  - Fludarabine.
  - 5-Fluorouracil(5-FU).
  - Gemcitabine.
  - 6-Mercaptopurine(6-MP).
  - Methotrexate.
  - 6-Thioguanine(6-TG).

Cell-Cycle-Specific Drugs (CCS)

- **Antitumor Antibiotics:**
  - Bleomycin.
- **Epipodophyllotoxins:**
  - Etoposide.
  - Teniposide.

Cell-Cycle-Specific Drugs (CCS)

- **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.

Cell-Cycle-Nonspecific Drugs (CCNS)

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

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

Cell-Cycle-Nonspecific Drugs (CCNS)

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