Cancer Incidence and Mortality

- **Cancer is a common disease. One in three people in the Western World contract cancer and one in four die from it.**

- **The cure rate is 50%**

- **Cancer is strongly age-related, the incidence rising rapidly at age 50.**

- **Cancer is a collection of about 200 different diseases. About 10% are leukaemias and lymphomas and the remaining 90% are solid tumours, mostly epithelial carcinomas.**

Abolishing cigarette smoking would lower cancer mortality by about 40% in America/Europe. Lung cancer is 100% fatal. 95% of sufferers are smokers. 1 in 7 smokers succumb. In 1900 lung cancer was virtually unknown. It was the American cigarette, invented in the late 1800's, and WW 1 that transformed the Western World's cancer patterns. There is currently a smoking epidemic in Asia and Africa and lung cancer is sure to follow. Bladder and cervical cancer are also linked to smoking.

Tumour Biology

- **Cancer is a genetic disease that results from the accumulation of mutations that**

(1) Activate dominant oncogenes in the growth proliferative pathways send false positive signals that constitutively drive the proliferative cycle.

(2) Inactivate tumour suppressor genes which function in various biochemical processes.

Tumour Biology

(3) Damage is also done to DNA repair genes so that, over time, giving rise to hypermutability and tumour heterogeneity.

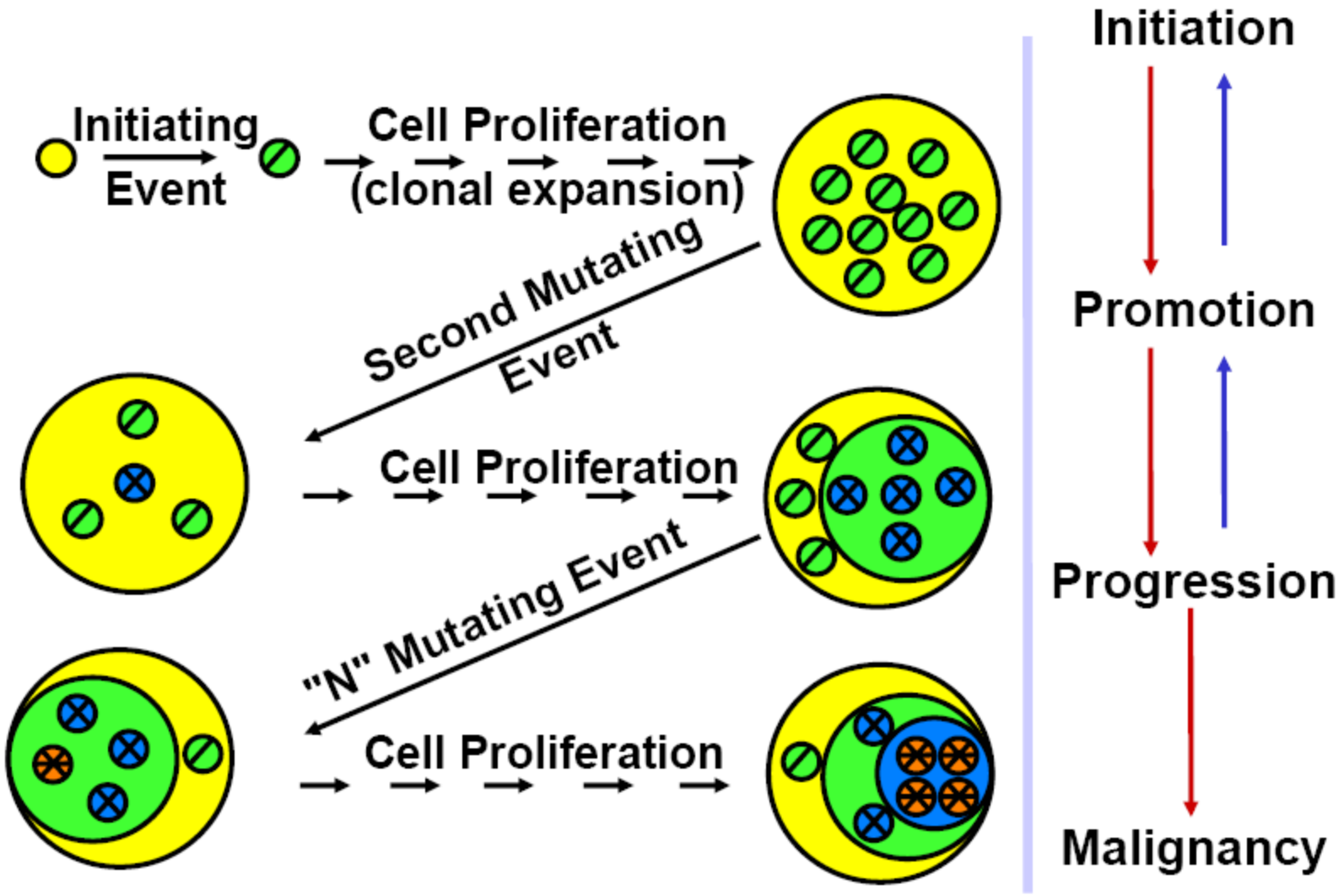
The outcome is that tumour cells relentlessly drive through the proliferative cell cycle and generally loose the capacity to differentiate.

(4) To become MALIGNANT

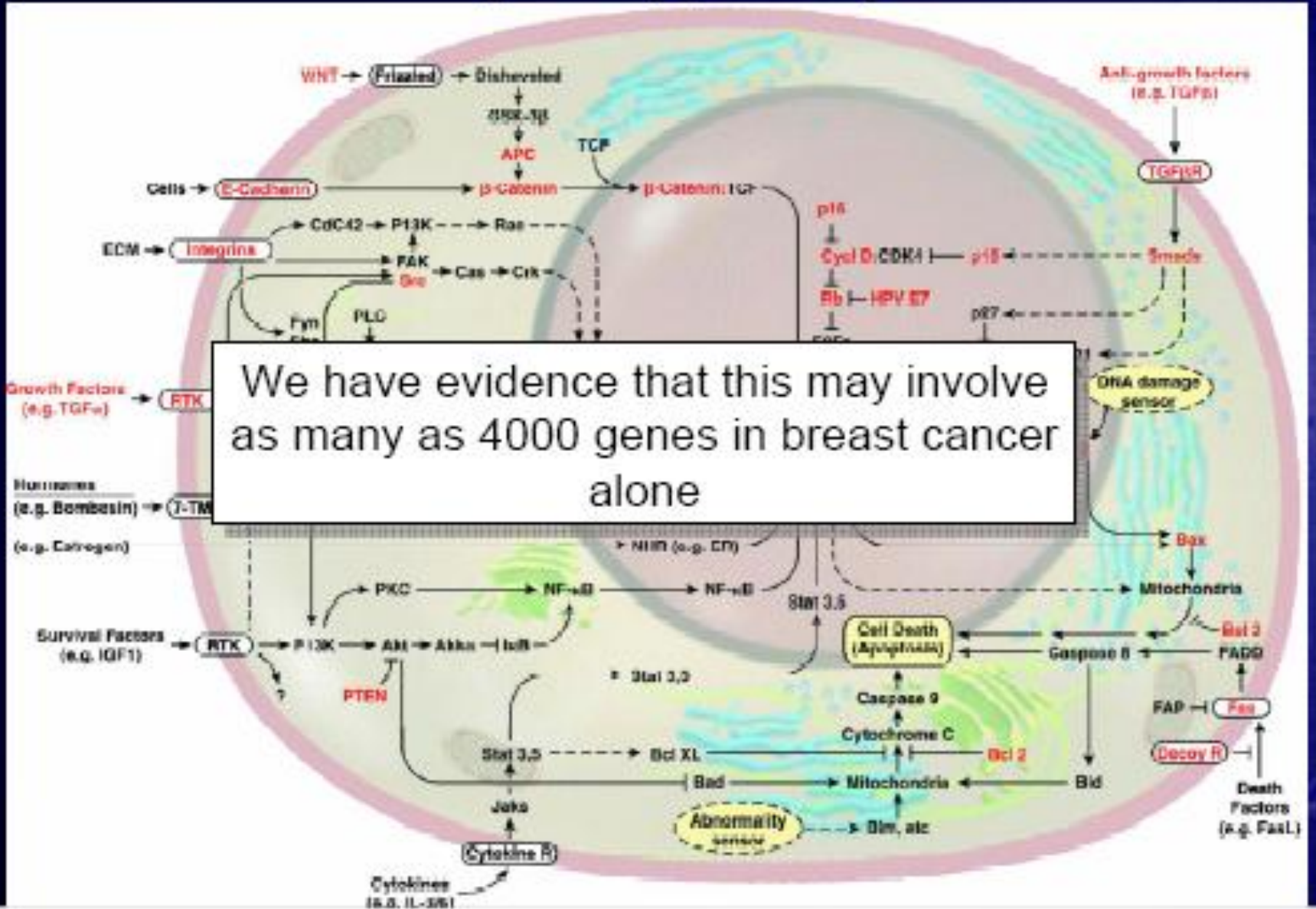
a. The mutated cells have to acquire the capacity to avoid immune detection to metastasise and

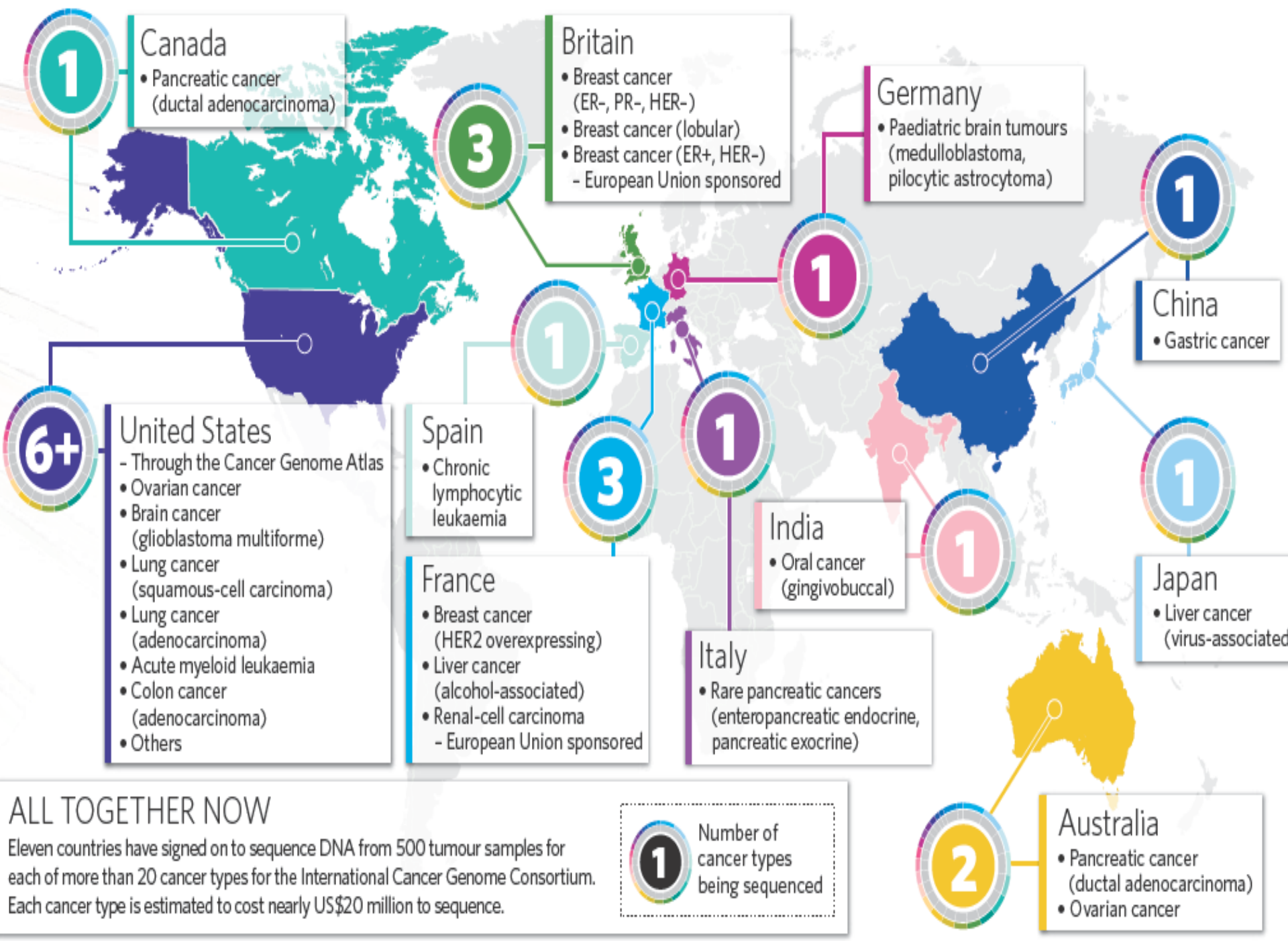
b. to be able to induce angiogenesis in order to provide themselves with a blood supply.

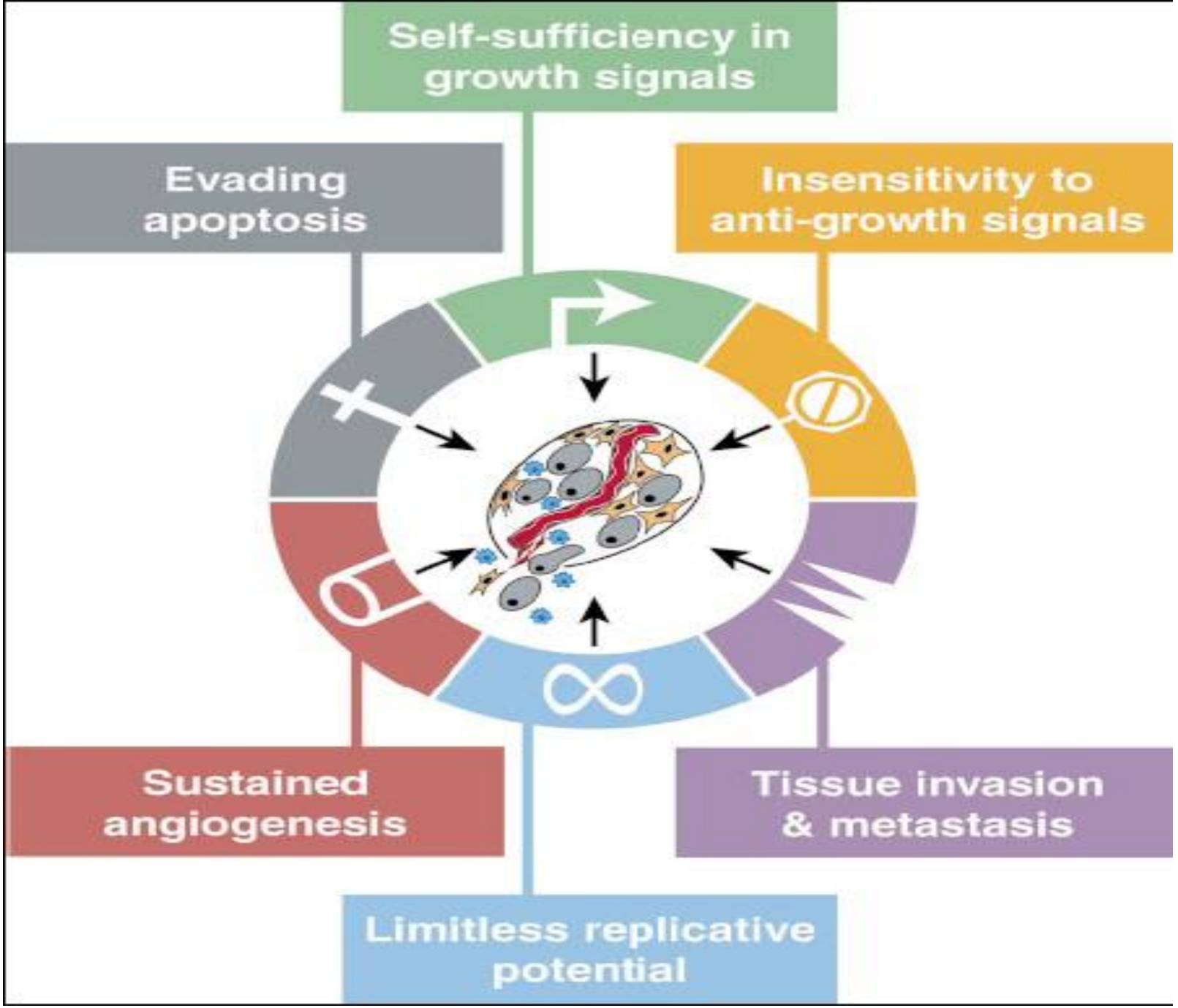
Stages of Carcinogenesis



This happens through deregulation of complex regulatory pathways




1
Canada
• Pancreatic cancer (ductal adenocarcinoma)
3
Britain
• Breast cancer (ER-, PR-, HER-)
• Breast cancer (lobular)
• Breast cancer (ER+, HER-)
– European Union sponsored
Germany
• Paediatric brain tumours (medulloblastoma, pilocytic astrocytoma)
1
1
1
China
• Gastric cancer
6+
United States
– Through the Cancer Genome Atlas
• Ovarian cancer
• Brain cancer (glioblastoma multiforme)
• Lung cancer (squamous-cell carcinoma)
• Lung cancer (adenocarcinoma)
• Acute myeloid leukaemia
• Colon cancer (adenocarcinoma)
• Others
Spain
• Chronic lymphocytic leukaemia
3
1
1
India
• Oral cancer (gingivobuccal)
1
1
Japan
• Liver cancer (virus-associated
France
• Breast cancer (HER2 overexpressing)
• Liver cancer (alcohol-associated)
• Renal-cell carcinoma
– European Union sponsored
Italy
• Rare pancreatic cancers (enteropancreatic endocrine, pancreatic exocrine)
2
Australia
• Pancreatic cancer (ductal adenocarcinoma)
• Ovarian cancer
ALL TOGETHER NOW
Eleven countries have signed on to sequence DNA from 500 tumour samples for each of more than 20 cancer types for the International Cancer Genome Consortium. Each cancer type is estimated to cost nearly US$20 million to sequence.
1
Number of cancer types being sequenced


Self-sufficiency in growth signals
Evading apoptosis
Insensitivity to anti-growth signals
Sustained angiogenesis
Tissue invasion & metastasis
Limitless replicative potential

Cancer treatment

- **The are three major approaches to the treatment of the common solid tumours:**
- **SURGERY**
- **RADIOTHERAPY**
- **CHEMOTHERAPY**

The primary tumour is removed by surgery. If it has not metastasised then the surgery may prove curative.

- **Radiotherapy, irradiation with high energy X-rays (4 to 25 MeV), may be applied subsequent to surgery to help prevent regrowth of the primary tumour.**

- **Surgery plus radiotherapy is a common treatment modality.**

- **X-rays kill tumour cells (and healthy normal cells in division) by free radical damage to DNA that results in double strand breaks which are lethal to cells at mitosis.**

- **Tumours that are not resectable may be treated by radiotherapy alone, in which case treatment is largely palliative.**

- **Most of the 50% cure is effected by surgery and radiotherapy on non-metastatic tumours.**

- **If the disease is found to be metastatic then systemic chemotherapy is administered after surgery and radiotherapy.**

Cancer Chemotherapy

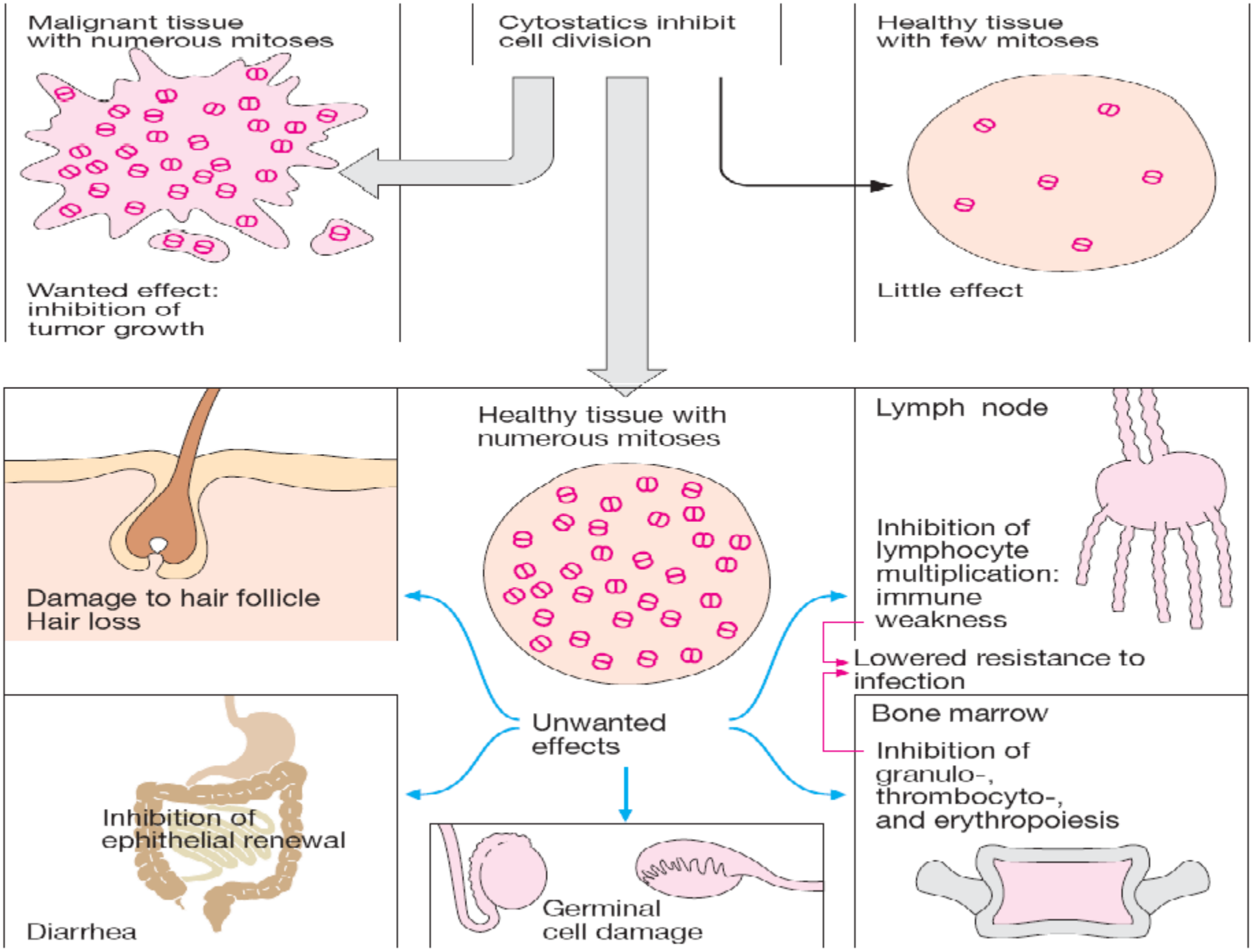
- **Cancer drugs are not specific for cancer cells but are cytotoxic to all proliferating cells in cycle.**

- **Their major unwanted toxicity is damage to bone marrow function and to the epithelial lining of the gut.**

- **Generally speaking, these are the dose-limiting toxicities.**

The Goal of Cancer Treatments

- Curative
  - Total irradication of cancer cells
  - Curable cancers include testicular tumors, Wills tumor
- Palliative
  - Alleviation of symptoms
  - Avoidance of life-threatening toxicity
  - Increased survival and improved quality of life
- Adjuvant therapy
  - Attempt to eradicate microscopic cancer after surgery
  - e.g. breast cancer & colorectal cancer


Malignant tissue with numerous mitoses
Cytostatics inhibit cell division
Healthy tissue with few mitoses
Wanted effect: inhibition of tumor growth
Little effect
Damage to hair follicle
Hair loss
Healthy tissue with numerous mitoses
Lymph node
Inhibition of lymphocyte multiplication: immune weakness
Lowered resistance to infection
Unwanted effects
Bone marrow
Inhibition of granulo-, thrombocyto-, and erythropoiesis
Inhibition of ephithelial renewal
Diarrhea
Germinal cell damage

Reasons for treatment failure

- **Chemotherapy is able to cure only about 10-15 % of all cancer patient.**

- **Either the patient presents**

  (1) with a tumour that is already non-responsive or

  (2) the tumour initially regresses only to return later in a drug-refractory form.

- **The main problem in treatment failure is DRUG RESISTANCE not a lack of selectivity for tumour cells.**

The origins of resistance lie in the following issues

(1) GENOMIC INSTABILITY AND HYPERMUTABILITY

- **The de-regulated genome →→ genetically heterogeneous tumour**
- **Damage to DNA repair genes is critical →→ → more heterogeneousity as the disease progresses.**
- **From a pharmacological perspective at the biochemical level the tumour is a constantly changing target.**
- **Thus, the primary tumour can be biochemically distinct from metastatic deposits**
- **and one person's colon cancer can be biochemically different from another persons.**

(2) Tumour Cells Are Not Immunogenic

Tumour cells evade immune detection by down-regulating their MHC antigens

So they can't be recognised by antigen-presenting and activated killer T-cells.

(3) The Numbers Game

- **1 x 10^8 tumour cells are visible on an X-ray.**
- **1 x 10^9 cells is a palpable lump weighing a gram.**
- **1 x 10^{12} cells weighs a kilogram and the patient is dead.**
- **Cancer is hard to detect in its early stages and may already have grown to 10^{10} - 10^{11} cells at presentation.**

- **You've got to kill every single cell by drug treatment,**

- **No immunological moping-up of residual tumour!**

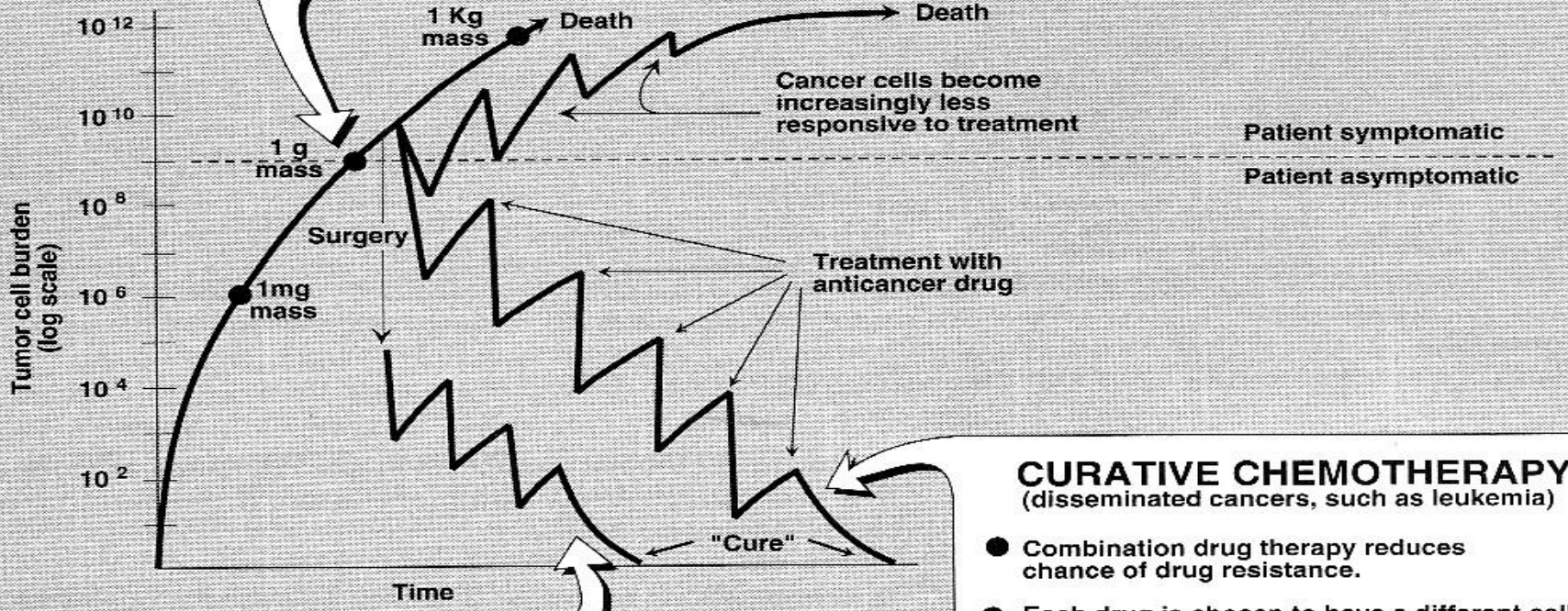
- **If there are 10^{11} tumour cells present (100g), killing 99.99% of them leaves 1 x 10^7 residual cells.**
- **1 L1210 leukaemia cell will kill a mouse.**

SIGNIFICANCE OF 1g TUMOR MASS

- 10^9 Cells is the smallest tumor burden that is physically detectable.
- These 1 billion cells represent a tumor weighing about 1 gram or about the size of a small grape.
- Clinical symptoms usually first appear at this stage.

PALLIATIVE CHEMOTHERAPY

- Initial remissions are transient, with symptoms recurring between treatments.
- Survival is extended, but patient eventually dies of the disease.



CURATIVE CHEMOTHERAPY
(disseminated cancers, such as leukemia)

- Combination drug therapy reduces chance of drug resistance.
- Each drug is chosen to have a different cellular site of action or different cell cycle specificity.
- Each drug is chosen to have a different organ toxicity.

CURATIVE CHEMOTHERAPY
(solid tumors, such as testicular carcinoma)

- Tumor burden is initially reduced by surgery and/or radiation.
- Treatment of occult micrometastases is continued after clinical signs of cancer have disappeared.

(4) Poor Tumour Vasculature

- **Tumour masses can only grow to a diameter of about 200 microns before they run into trouble with nutrient supplies.**

  To grow larger they must develop their own vasculature which they do by producing angiogenic growth factors.

- **However, these blood vessels are of a poorer quality than normal which leaves parts of the tumour without nutrients and oxygen.**

POOR TUMOUR VASCULATURE

- This generates regions of hypoxia in the tumour mass where cells come out of the growth cycle and sit, alive but non-proliferating, in G_0.

- Unfortunately, hypoxic cells in G_0 are resistant to all anticancer drugs.

- Thus, hypoxic cells become a pharmacological sanctuary from which the tumour can be re-populated after a round of drug treatment when surviving cells may get the opportunity to be re-oxygenated.

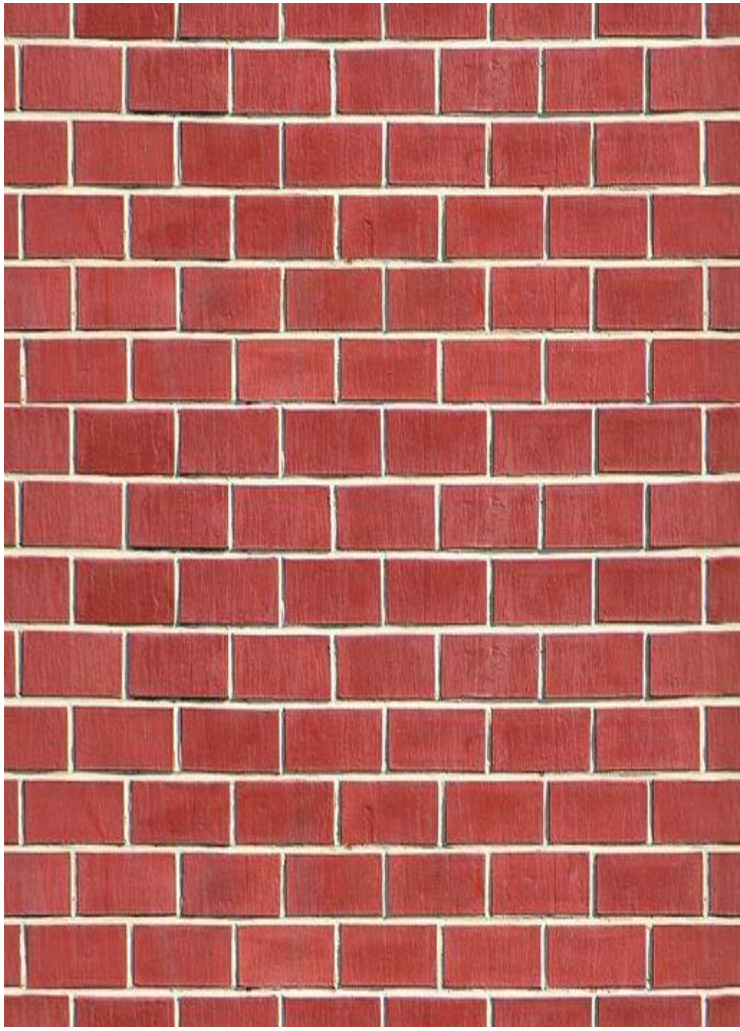
(5) Deregulation of apoptosis

THIS IS THE BIG DADDY OF THEM ALL!

The genomic instability of tumour cells inevitably leads to deregulation of the apoptotic pathways.

This results in a generalised reduction in the sensitivity to all forms of cellular insult.

THE REAL BRICK WALL.



CANCER DRUG CLASSES

- **The classes of drugs currently used in the cancer clinic are**

1. **Antimetabolites (anti-folates, pyrimidine and purine analogues)**

2. **Mitotic Spindle Inhibitors (modulators of tubulin polymerisation)**

3. **DNA Binding Agents (intercalating and alkylating agents)**

4. **Hormones and Hormone Antagonists**
5. **Miscellaneous anticancer drugs**

Breast Cancer Systemic Therapies

- Drug treatments that can attack cancer cells throughout the body
  - Endocrine therapy
  - Chemotherapy
  - Biologically-targeted therapy

Treatment of Early Stage Breast Cancer

- Breast cancer most curable when detected early
  - Micrometastases (undetectable) can exist at time of diagnosis in many patients, leading to eventual recurrence
- Multidisciplinary care critical for best outcomes
  - Surgery
  - Radiation therapy
  - Adjuvant systemic (drug) therapy reduces risk of recurrence and death.

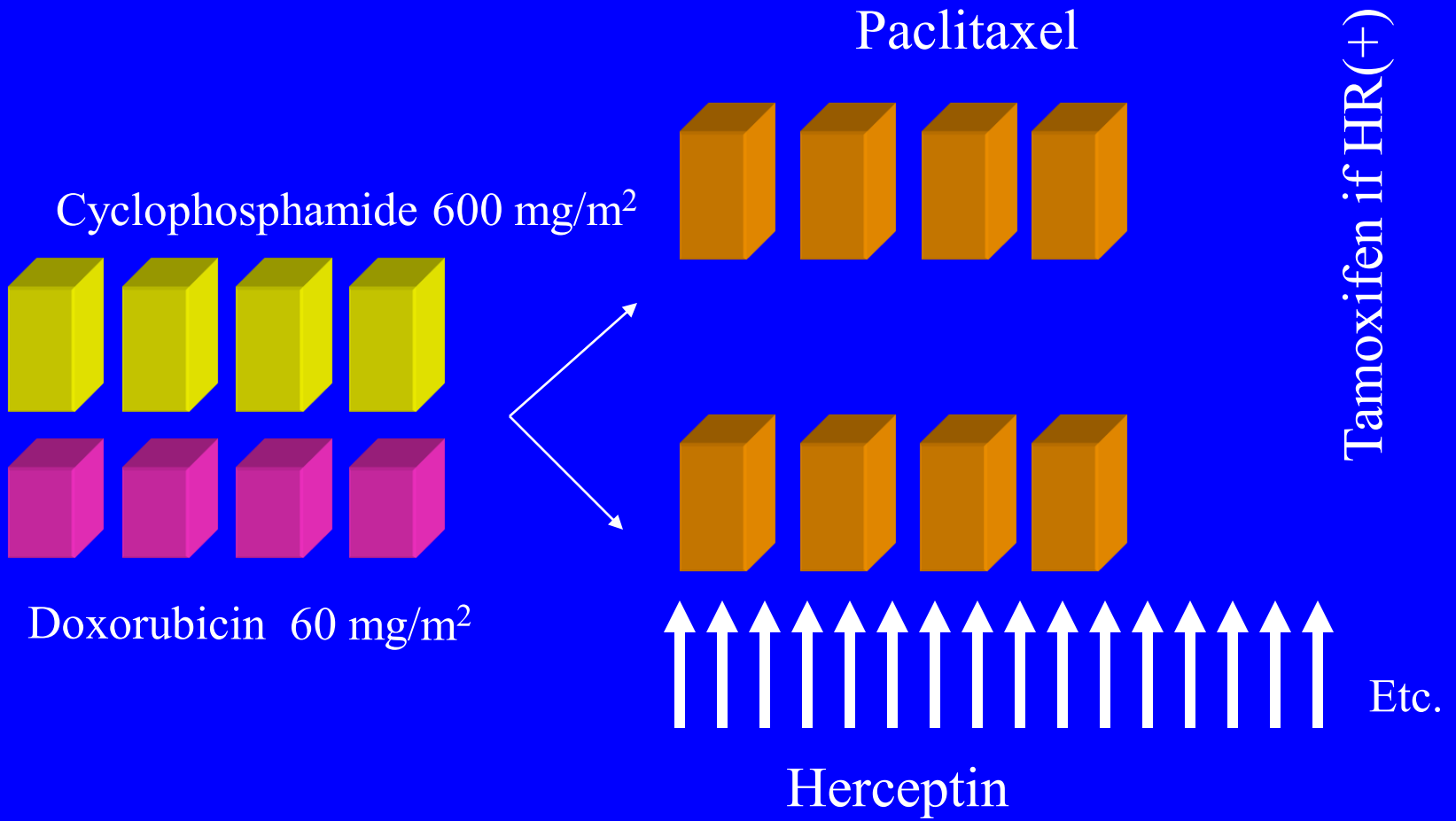
Treatment of Metastatic Breast Cancer

- Metastatic breast cancer is not curable, but can be very treatable
- Goals:
  - Control and regression of disease
  - Prolongation of life
  - Improvement in symptoms and quality of life

Medicine List

- Antineoplastics relevant to treatment of breast/cervical cancer
  - Tamoxifen
  - Doxorubicin (Adriamycin)
  - Cyclophosphamide (Cytoxan)
  - Paclitaxel (Taxol)
  - Trastuzumab (Herceptin)`

Stage II Trial
HER2 (+)



Doxorubicin

- **DNA strand scission via effects on Top II enzyme (topoisomerase poisons)**
- **High-affinity binding to DNA through intercalation, resulting in blockade of DNA and RNA synthesis.**
- **Binding to membranes and altering fluidity**
- **Generation of the free radical and oxygen radicals**

Anthracyclin

- **Their main toxicities are**

  - Bone marrow depression

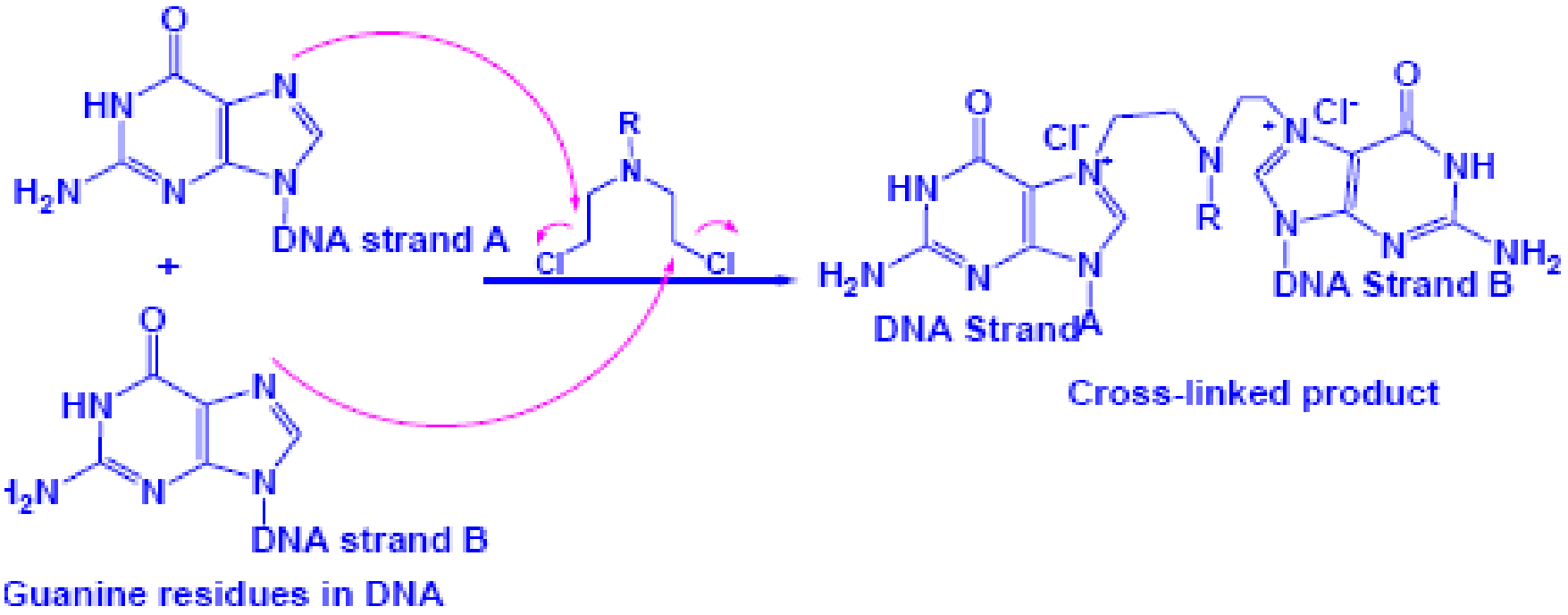
  - Total alopecia

- **BUT the anthracyclines have a strange dose-limiting irreversible and lethal cardiomyopathy.**

- **This cardiotoxicity may be a result of the generation of free radicals and lipid peroxidase.**

ALKYLATING AGENTS

- **Alkylating agents bind irreversibly to DNA and function by crosslinking the two Watson-Crick strands, thereby inhibiting strand separation and preventing DNA replication.**



Nitrogen mustards

Cyclophosphamide

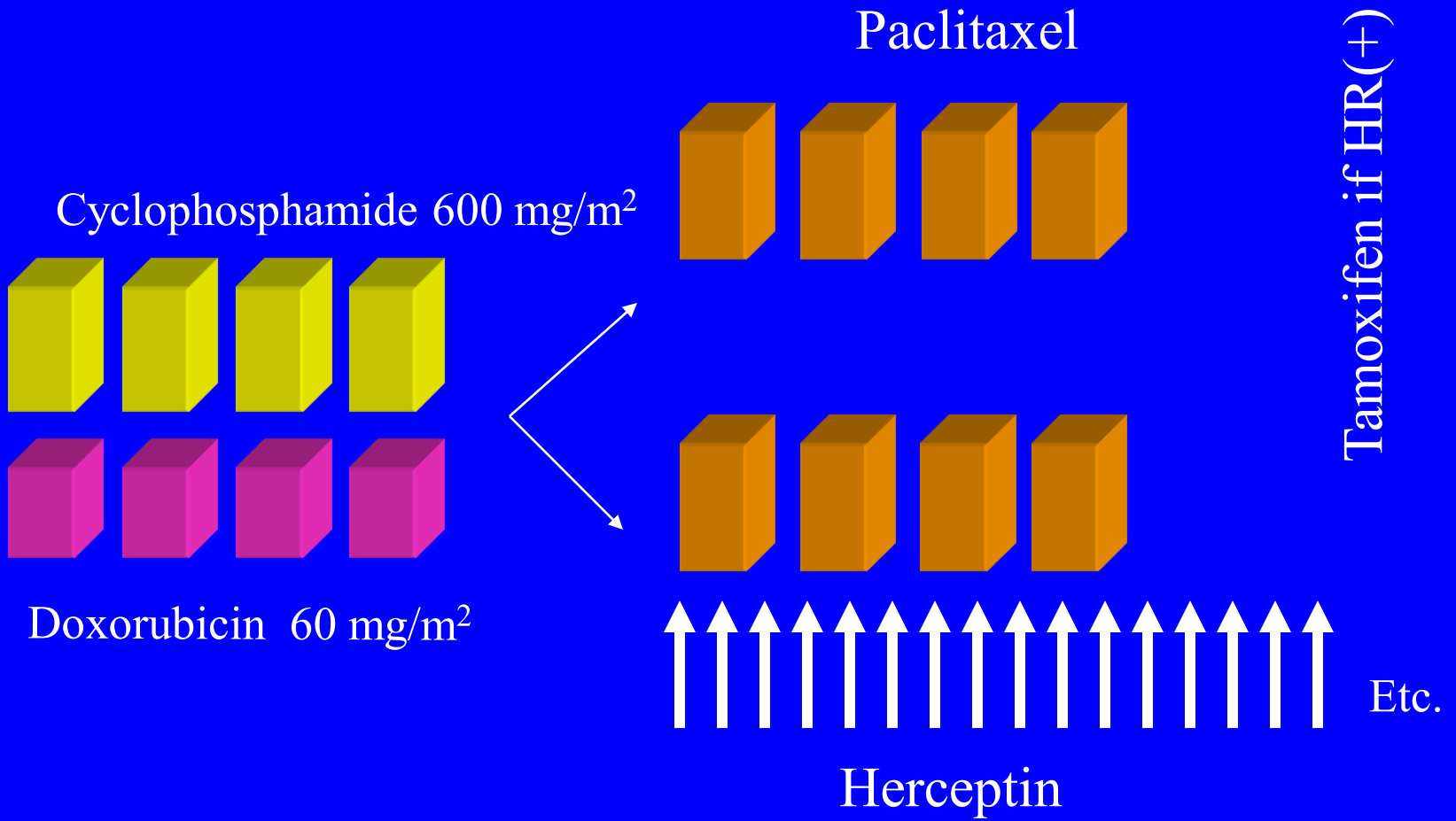
1. most commonly used alkylating agent

used in lymphomas, leukemias, sarcomas, carcinomas of breast or ovary, as well as childhood malignancies.

2. has a special place in the maintenance therapy for breast cancer.

4. Cystitis (inflammation of the urinary bladder) may result. co-administered with N-acetylcystein or 2-mercaptoethanesulfonate (mesna). Both are thiols that neutralized acrolein

Stage II Trial
HER2 (+)



MITOTIC SPINDLE INHIBITORS

Inhibition of formation

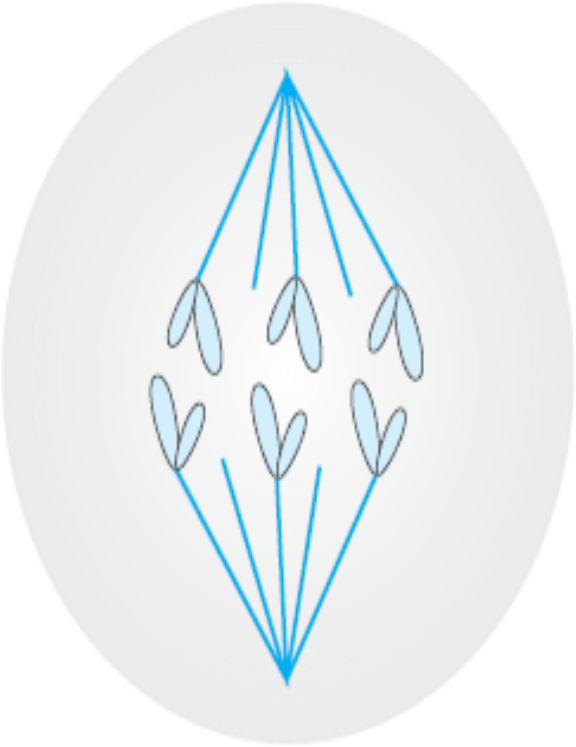
Vinca alkaloids

Microtubules of mitotic spindle

Inhibition of degradation

Paclitaxel

Vinca rosea



Western yew tree

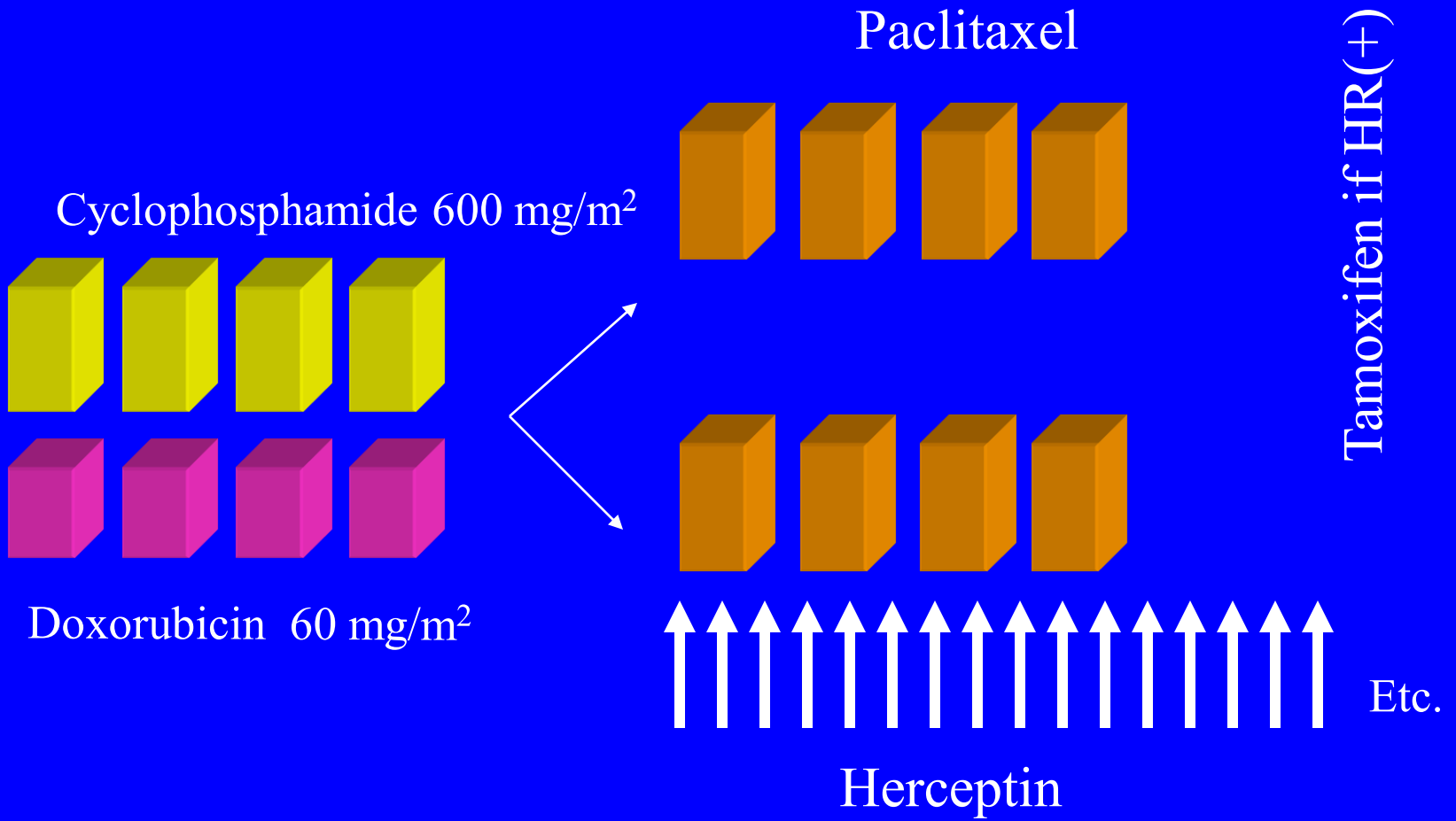
INHIBITORS OF TUBULIN DE-POLYMERISATION

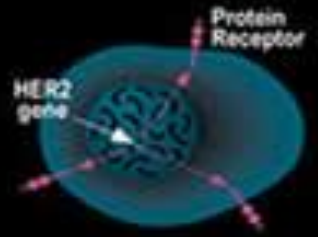
- **The TAXANES, of which Taxol is the best known example, are isolated from the yew tree.**

- **They also bind to tubulin but have the opposite effect to the Vinca alkaloids and stabilise microtubules to de-polymerisation. (mitotic spindle poison)**

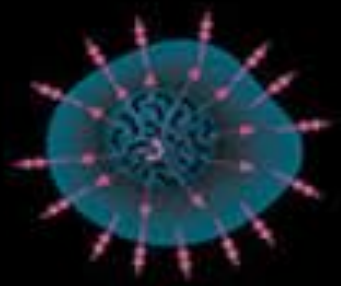
- **The taxanes are generally more toxic than the Vinca alkaloids and side-effects include myelosuppression and Peripheral neuropathy.**

Stage II Trial
HER2 (+)





In a normal breast tissue cell, the Her-2 gene is expressing cell surface receptor required for normal cell growth.



In certain types of breast cancers, the Her-2 gene is over-expressing this cell surface receptor, contributing to cancerous cell growth.
This is the case in ~30% of breast cancers.

Herceptin (trastuzumab) is an antibody that blocks the cell surface receptor and thereby prevents further growth. As a result, disease progression is slowed down.

Her-2 overexpression in breast cancer-

- About 20-30% of breast cancers overexpress HER-2 protein (usually because of gene amplification)
- Monotherapy with anti-HER-2 monoclonal antibody (trastuzumab or Herceptin) has a 30% response rate in HER-2-positive metastatic breast cancer
- Combination of trastuzumab plus chemotherapy improves time to progression and overall survival in advanced HER-2 positive breast cancer

Reduces recurrence by 1/2 & deaths by 1/3 when added to chemo in early stage breast cancer

- Trastuzumab plus anthracycline results in a 20% incidence of cardiotoxicity

HORMONE ANTAGONISTS

- **Tumours derived from hormone-sensitive tissues may be hormone-dependent.**

- **Their growth can be inhibited by**

(1) hormones with opposing actions,

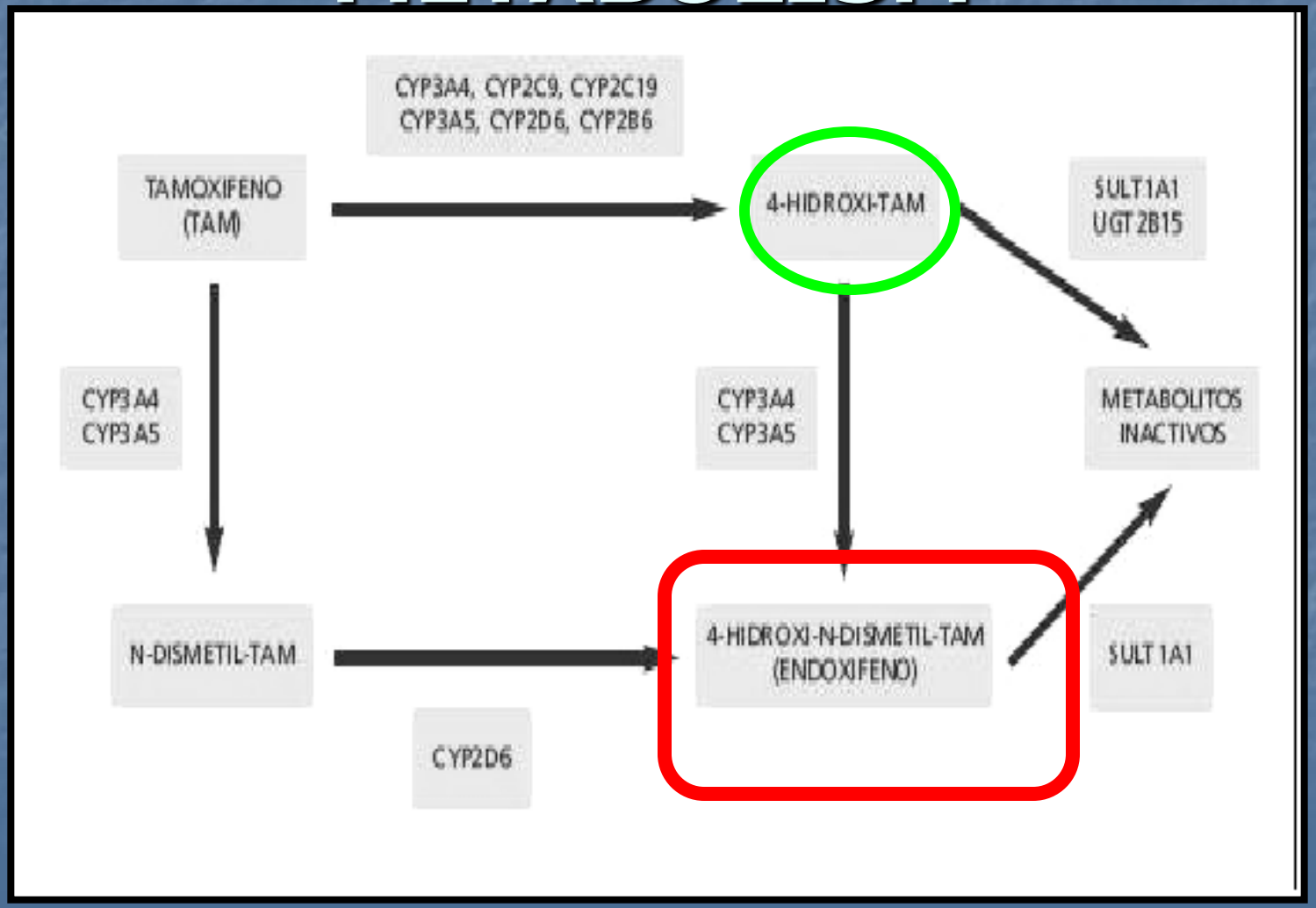
(2) hormone antagonists

(3) inhibit hormone synthesis.

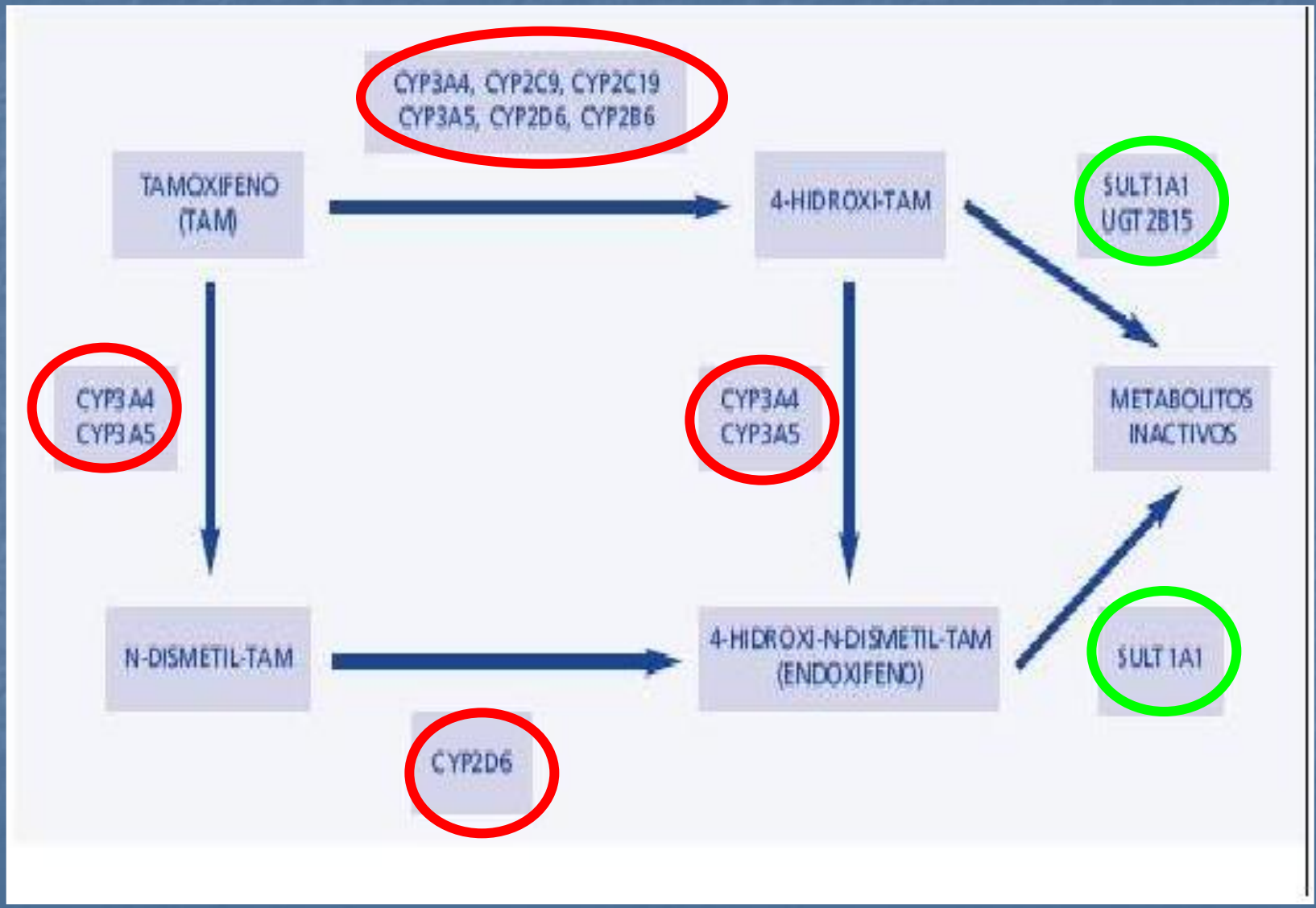
Tamoxifen

- Selective estrogen receptor modulator (SERM), have both estrogenic and antiestrogenic effects on various tissues
- When used prophylatically, tamoxifen has been shown to decrease the incidence of breast cancer in women who are at high risk for developing the disease
- Side effects include hot flashes, depression, increased risk of uterine cancer and blood clots
- Taken daily by mouth for 5 years.

PHARMACOGENETIC AND METABOLISM



PHARMACOGENETIC



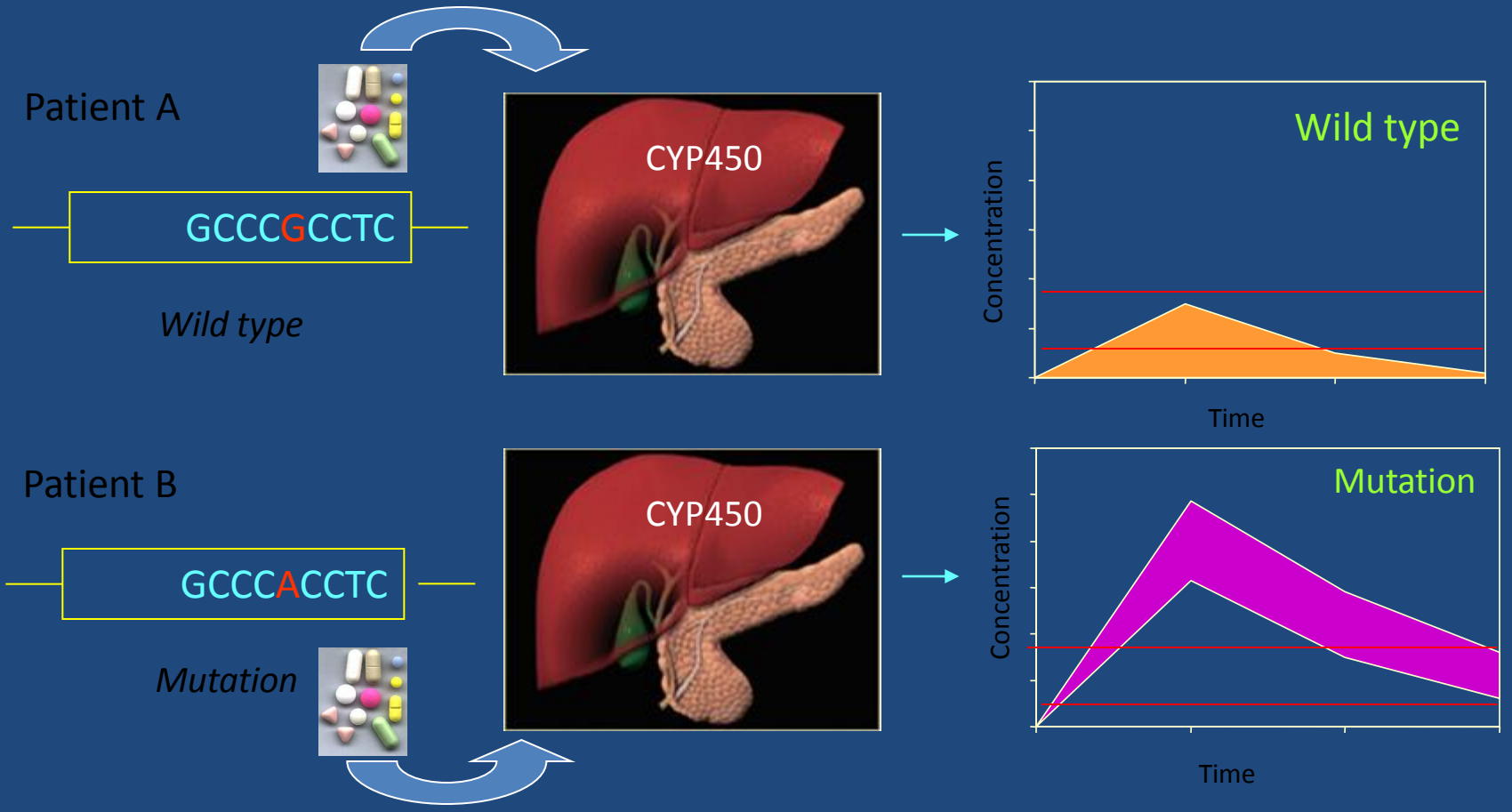
Tamoxifen Metabolism

- Tamoxifen is converted to endoxifen principally by a noninducible P450 enzyme that is coded for by the most polymorphic, and most studied, gene in the cytochrome P450 system: CYP2D6.

- In one study, **breast cancer** patients treated with tamoxifen who were homozygous for a poor metabolizer genotype (*4/*4) had significantly lower serum concentrations of endoxifen than those with the active.

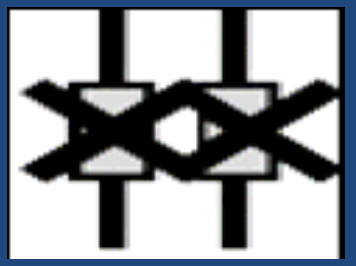
Pharmacogenetics and Drug Metabolism

Same dose but different plasma concentrations

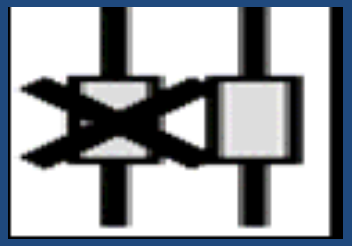


Phenotypes of CYP450

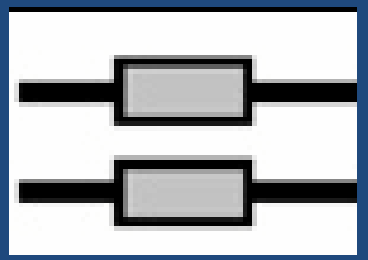
1. Poor metabolizer (PM)
- has low metabolic capacity
- has two mutant alleles



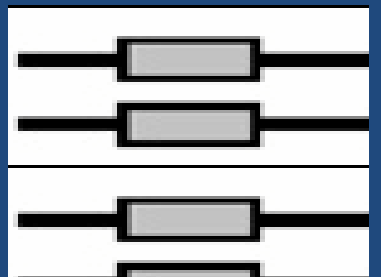
2. Intermediate metabolizer (IM)
- has metabolic capacity between PM and EM
has one reduced activity allele and one null-



3. Extensive metabolizer (EM)
- has regular metabolic capacity
- has at least one and no more than two
normal functioning alleles

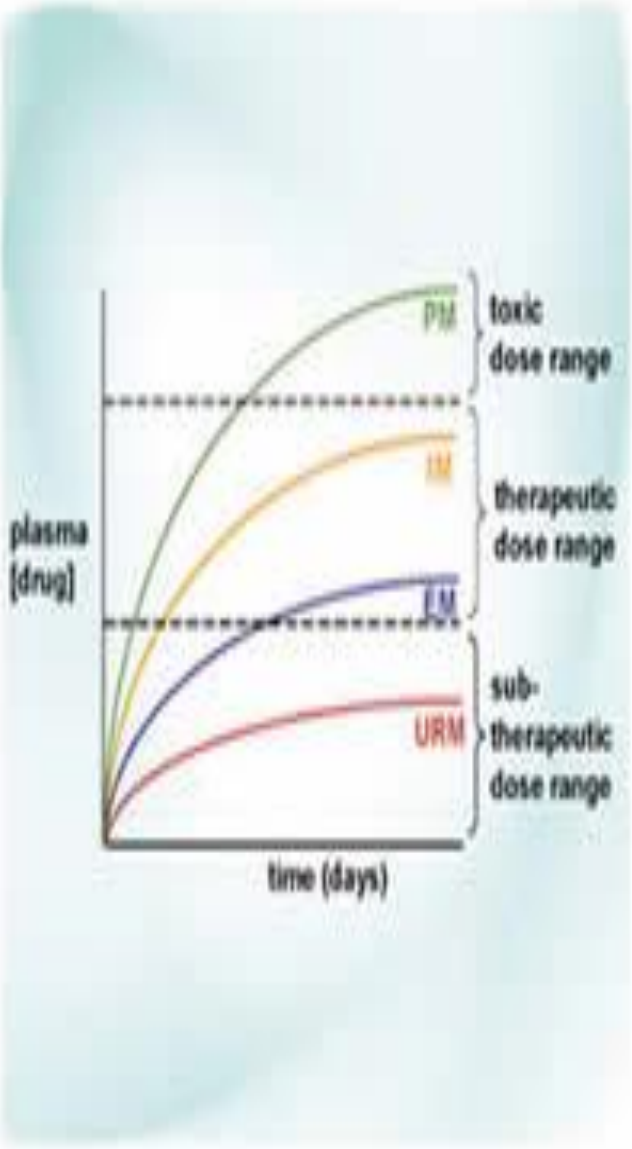


4. Ultrarapid metabolizer (UM)
- has higher metabolic capacity than EM
- has multiple copies of functional alleles



Classification of Drug Metabolism

- Drug metabolism is arbitrarily classified into 3 or 4 classes, depending on the enzyme involved
- These classifications may represent genetic polymorphism or groups of polymorphism
- The classes include:
  - PM = poor metabolizers
  - IM= intermediate metabolizer
  - EM = extensive metabolizers
  - URM = ultrarapid metabolizers



Frequencies of the CYP2D6 genotypes and in Jordan Zihlif et al 2012

Predicted Phenotype	Count (192)	Frequency (%)
Poor metabolism	5	2.6
Intermediate metabolism	41	21.1
Extensive metabolism	120	62.5
Ultra-rapid metabolism	**26**	**13.5**

Zihlif et al 2012

Genetic testing and molecular biomarkers 16 (10), 1201-1205


1-2% UMs
3.6% UMs
7-10% UM
10% UMs
13 % UMs
20% UMs
29% UMs
ALGERIA
LIBYA
EGYPT
SUDAN
KAZA
Springer

Chemotherapy as adjuvant in CRC

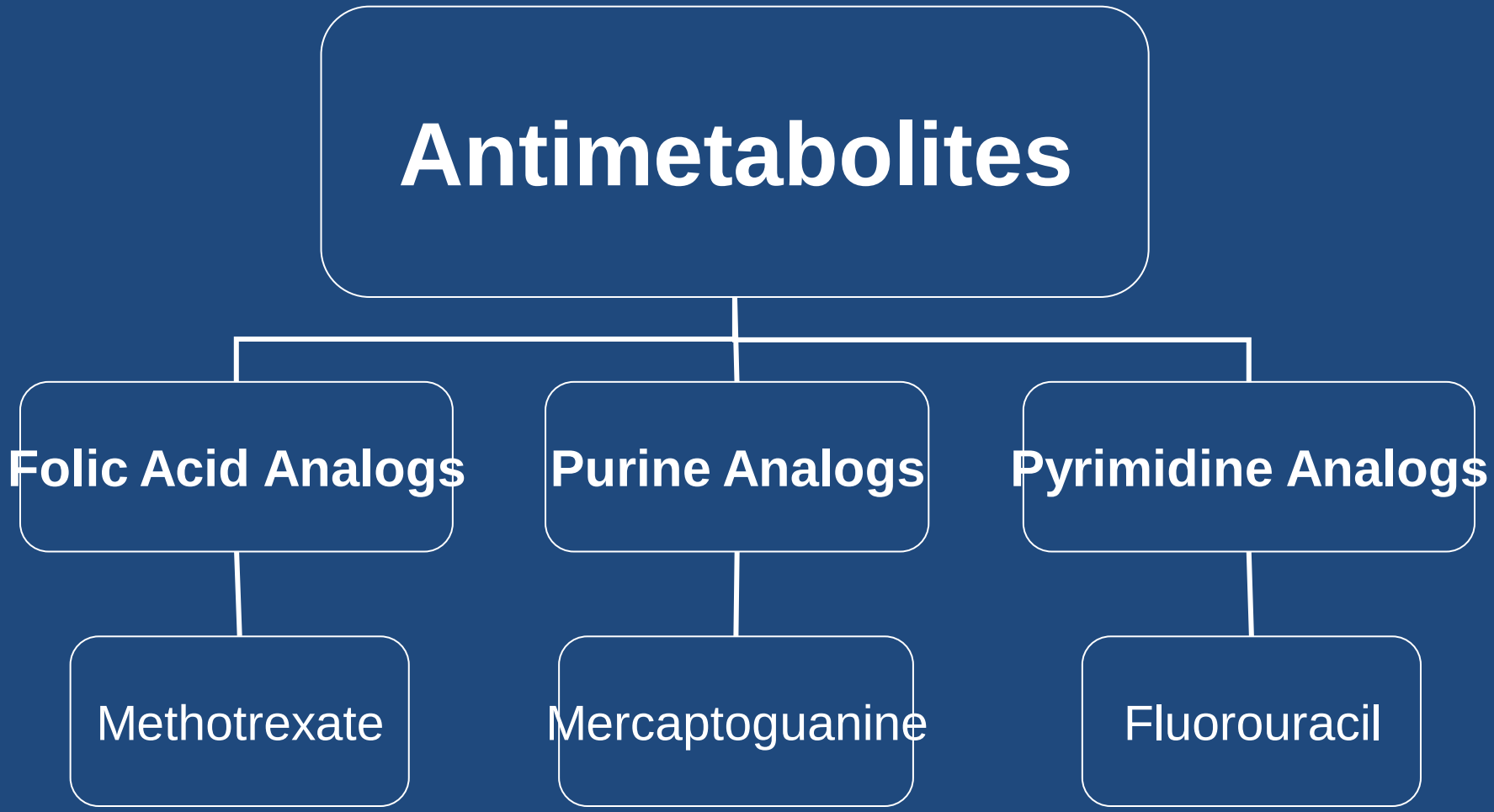
Oxaliplatin + 5-Fluorouracil + Leucovorin (mFOLFOX7)

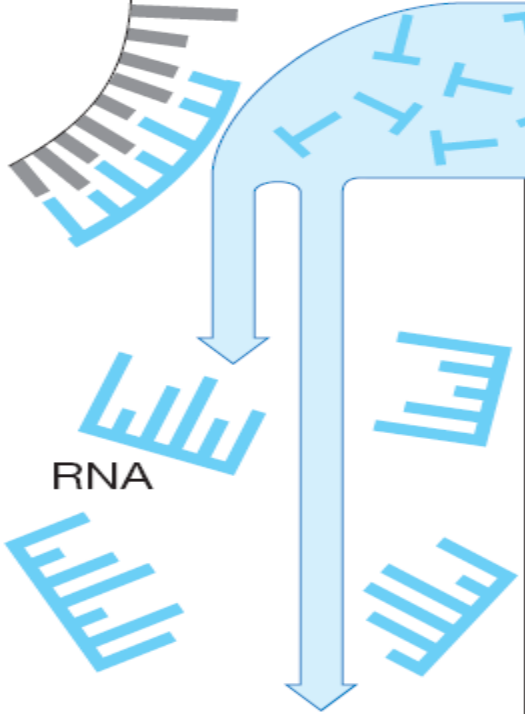
Oxaliplatin: 100 mg/m² IV on day 1

5-Fluorouracil: 3000 mg/m² IV continuous infusion on days 1 and 2 for 46 hours

Leucovorin: 400 mg/m² IV on day 1 as a 2-hour infusion before 5-fluorouracil

Repeat cycle every 2 weeks


Antimetabolites
Folic Acid Analogs
Purine Analogs
Pyrimidine Analogs
Methotrexate
Mercaptoguanine
Fluorouracil



Inhibition of nucleotide synthesi

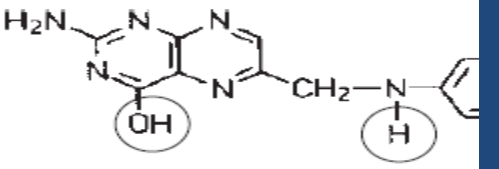
Purines

Thymine Nucleotide

Tetrahydro-folate

Dihydrofolate Reductase

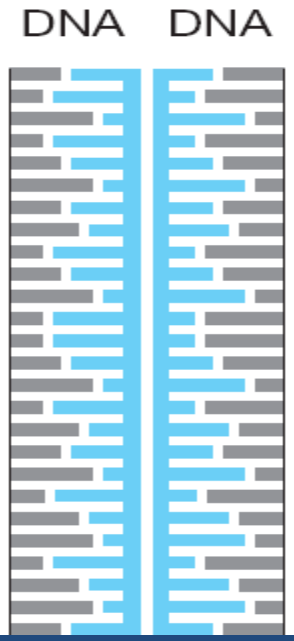
Folic acid



Inhibition by

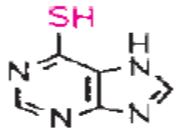
Aminopterin
Methotrexate

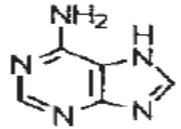
2



Insertion of incorrect building block

Purine antimetabolite





6-Mercaptopurine from Azathioprine — instead of — Adenine

Pyrimidine antimetabolite

5-Fluorouracil — instead of — Uracil

Cytarabine: Cytosine + Arabinose — instead of — Cytosine + Desoxyribos

Folate Antagonists

- Folates are essential for the synthesis of both purine nucleotides and thymidylate which are required for DNA synthesis and cell division.
- Folic acid is a coenzyme used in the one-carbon transfer step in these metabolic pathways.
- In order to function as a coenzyme folic acid must be reduced to tetrahydrofolic acid by the enzyme dihydrofolate reductase (DHFR), first to dihydrofolic acid and then to the tetrahydro form.

Folate Antagonists

- **Methotrexate is a derivative of folic acid which antagonises DHFR with a high affinity.**
- **Methotrexate is widely used clinically, usually administered orally. It is used against acute lymphocytic leukemia.**
- **Main toxicity is myelosuppression**
- **Rescue method: calcium leucovorin (**Folinic acid)

Pyrimidine antagonists

- The best known example is Fluorouracil, 5FU, incorporated into DNA and RNA, finally inducing cell cycle arrest and apoptosis by inhibiting the cell's ability to synthesize DNA.
- It is widely used in colon cancer.
- 5-FU is effective in palliative management of carcinoma of breast, colon, pancreas, rectum and stomach in patients who can not be cured by surgery or other means.
- Its main toxicities are myelosuppression and gut epithelial damage.

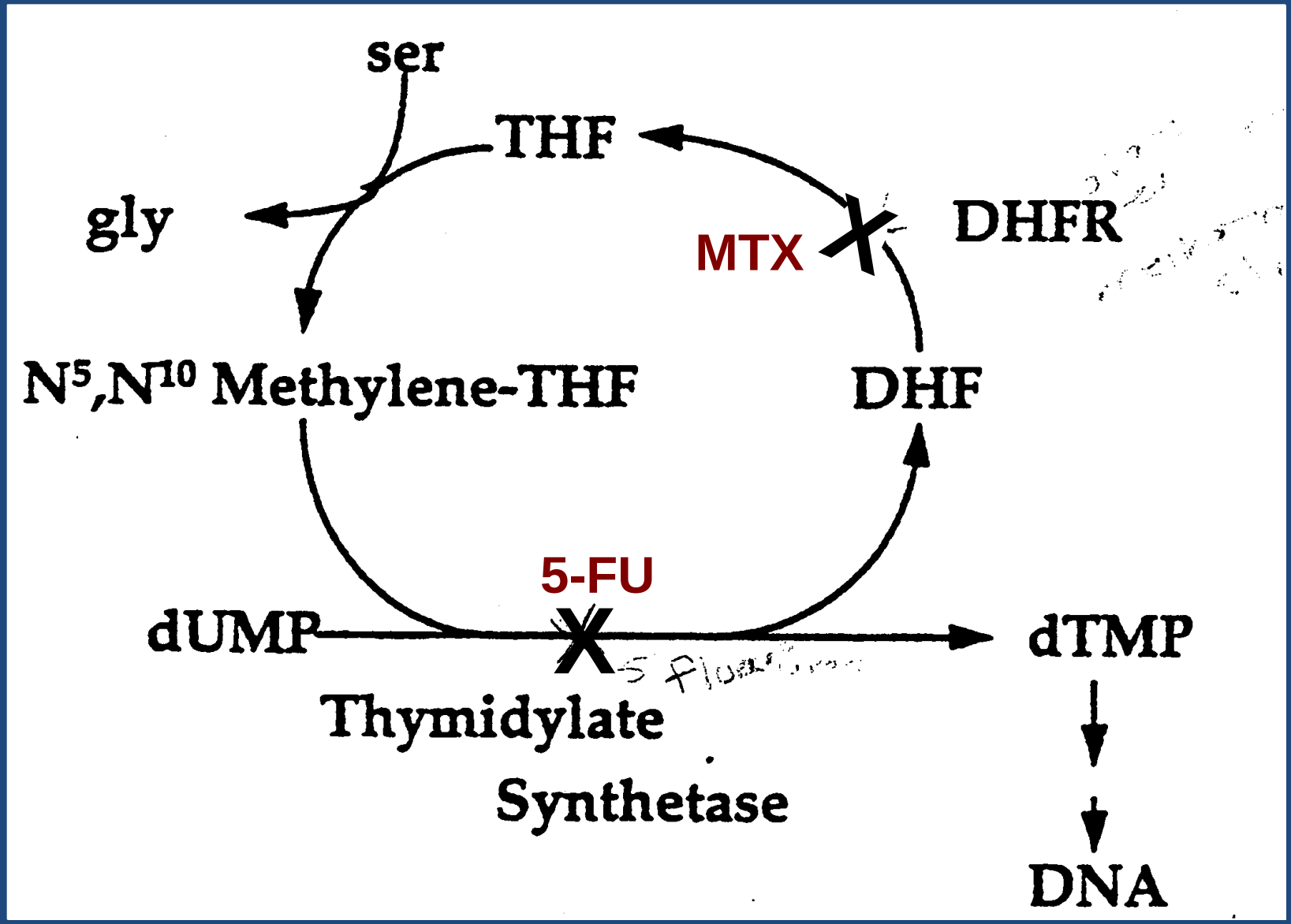
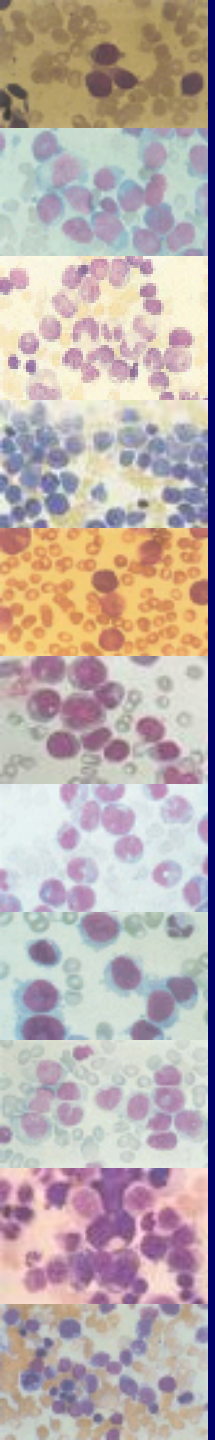


Figure 2. This figure illustrates the effects of MTX and 5-FU on the biochemical pathway for reduced folates.



Leucovorin

- Derivative of FH_4
- Given as “rescue” by repleting intracellular FH_4 pools
- Selective for rescuing normal cells more than malignant cells

Platinum analogs

- **In the clinic, cisplatin behaves very similarly to the organic alkylating agents and finds widespread use.**
- **Cisplatin has efficacy against a wide range of neoplasms.**
- **It is particularly effective in germ cell tumours (testicular cancer and ovarian tumours) and in breast cancer.**
- **Its use in combination chemotherapy has revolutionised the treatment of testicular and ovarian tumours, frequently leading to complete cure of testicular cancers in young men.**

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Platinum analogs

- **Its main toxicities are to the kidney and to the ear,**
- **produces relatively little myelosuppression but can cause severe nausea, vomiting.**
- **Carboplatin is a second generation platinum analog that has less renal toxicity and gastrointestinal toxicity.**
- **Though Carboplatin has widely replace cisplatin in chemotherapeutic regimen.**

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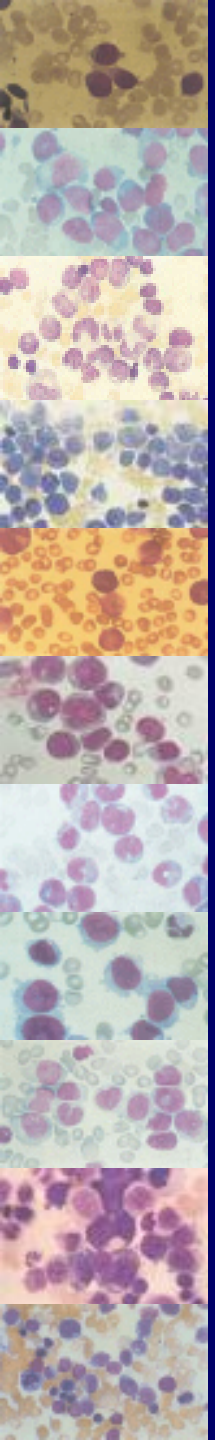

Comparison of Platinum Toxicity

Table 5. Comparative adverse effect profiles of platinum drugs			
Adverse effect	**cisplatin**	**carboplatin**	**oxaliplatin**
Nephrotoxicity	++	+	-
Gastrointestinal toxicity	+++	+	+
Peripheral neurotoxicity	+++	-	++
Ototoxicity	+	-	-
Hematologic toxicity	+	++	+
Hypersensitivity	-	+	-

Bevacizumab

inhibits the action of VEGF, a blood vessel growth

Factor When VEGF is bound to Bevacizumab, it cannot stimulate the formation and growth of new blood vessels

- **prevents VEGF from binding to its receptor**
- **adds to the effects of chemotherapy in cancers like bowel and lung**
- **FDA approved for:**
  - **First-or second-line Colorectal cancer treatment in combination with 5-fluorouracil-based chemotherapy**
  - **Unresectable, locally advanced, recurrent or metastatic nonsquamous non-small-cell lung cancer in combination with carboplatin and paclitaxel**

Bevacizumab

Serious side effects include:

- bowel perforation
- impaired wound healing
- bleeding
- kidney damage

More common side effects of Are:

high blood pressure

- tiredness/weakness
- clots in veins
- diarrhea

- The probability of developing impaired myocardial function based on a combined index of signs, symptoms, and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m2 of Doxorubicin, 3 to 5% at a dose of 400 mg/m2, 5 to 8% at 450 mg/m2, and 6 to 20% at 500 mg/m2. The risk of developing CHF increases rapidly with increasing total cumulative doses of Doxorubicin in excess of 400 mg/m2.