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.

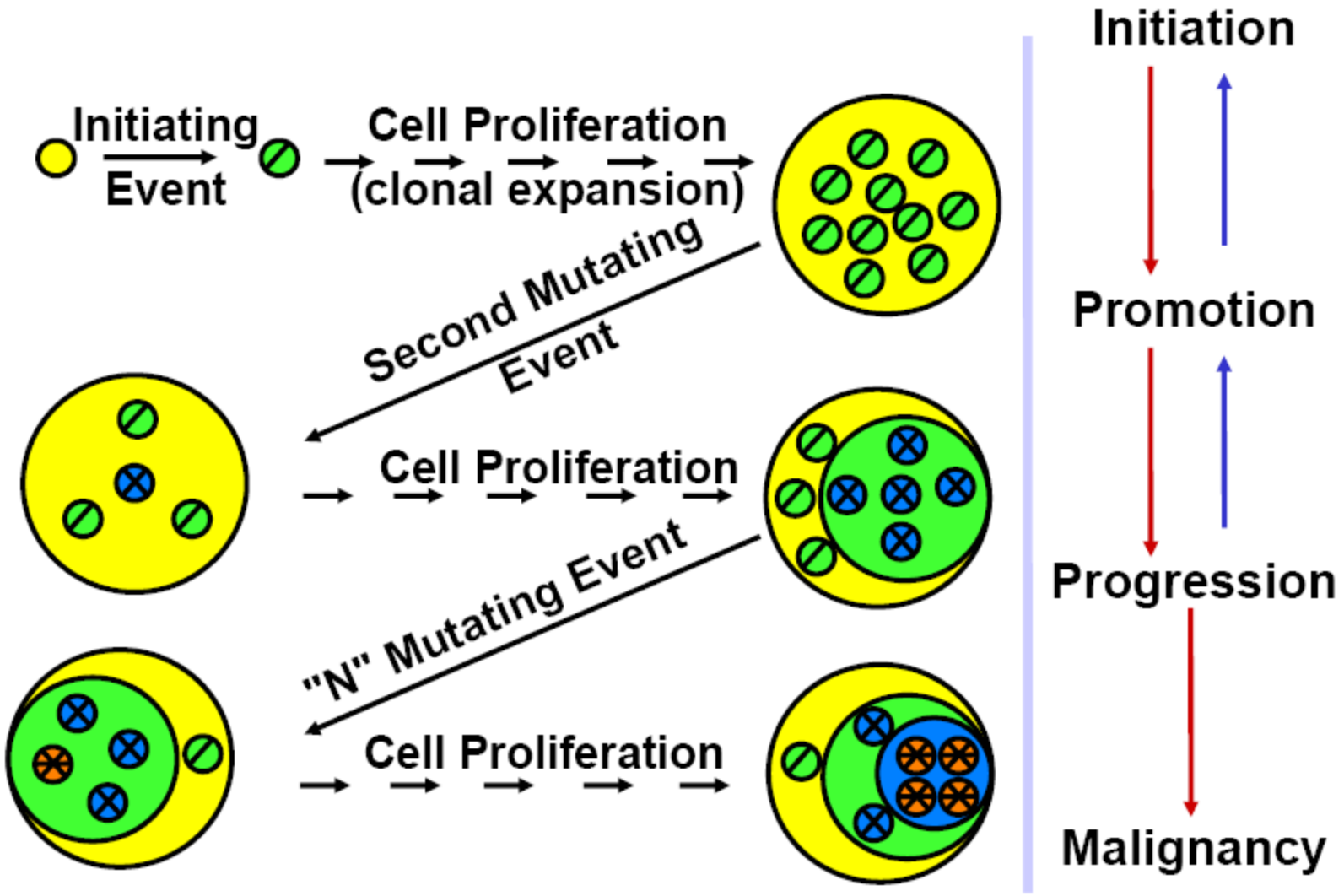
The outcome is that tumour cells relentlessly drive through the proliferative cell cycle and generally loose the capacity to differentiate.

(4) To become MALIGNANT

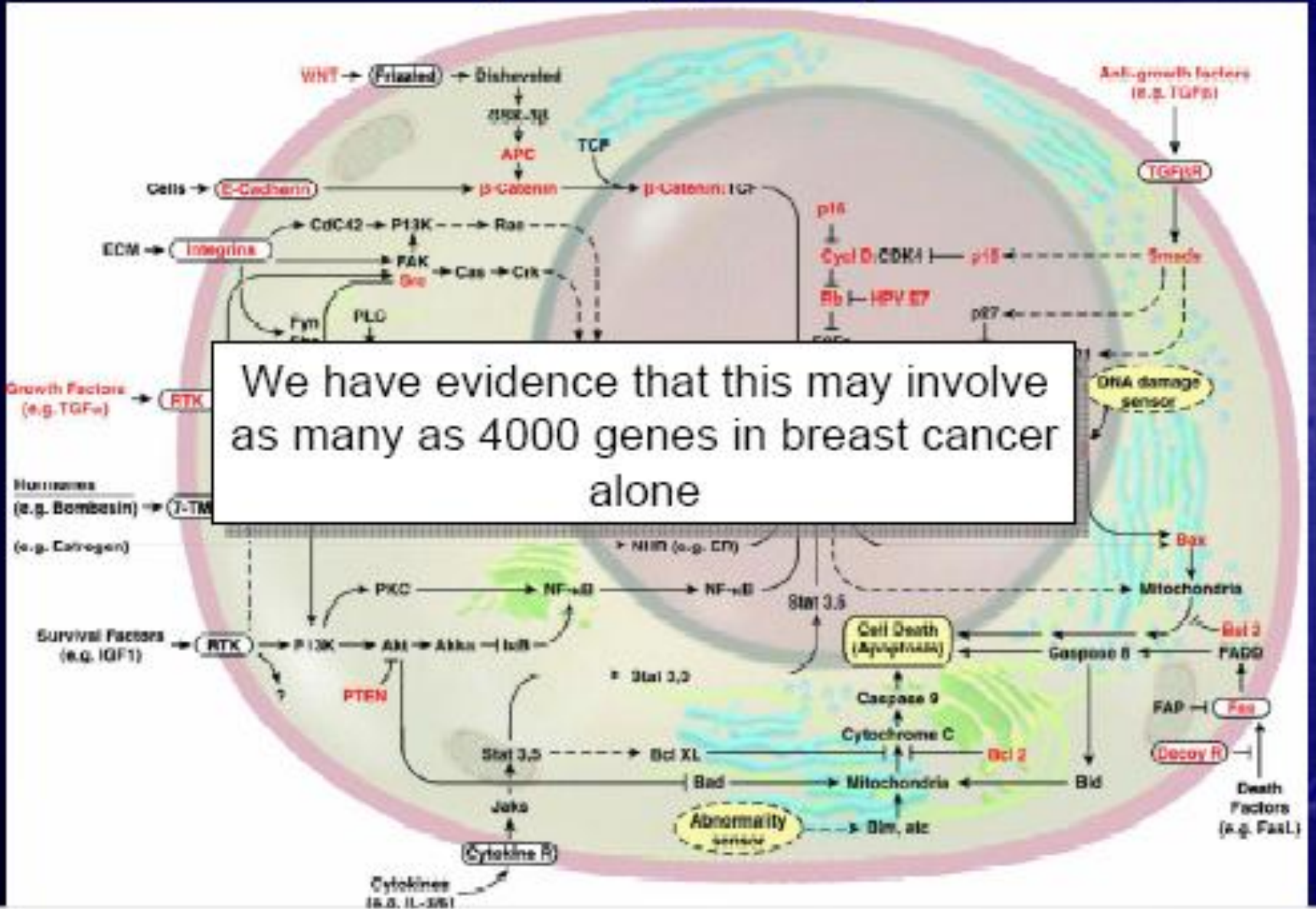
a. The mutated cells have to acquire the capacity to avoid immune detection to metastasise and

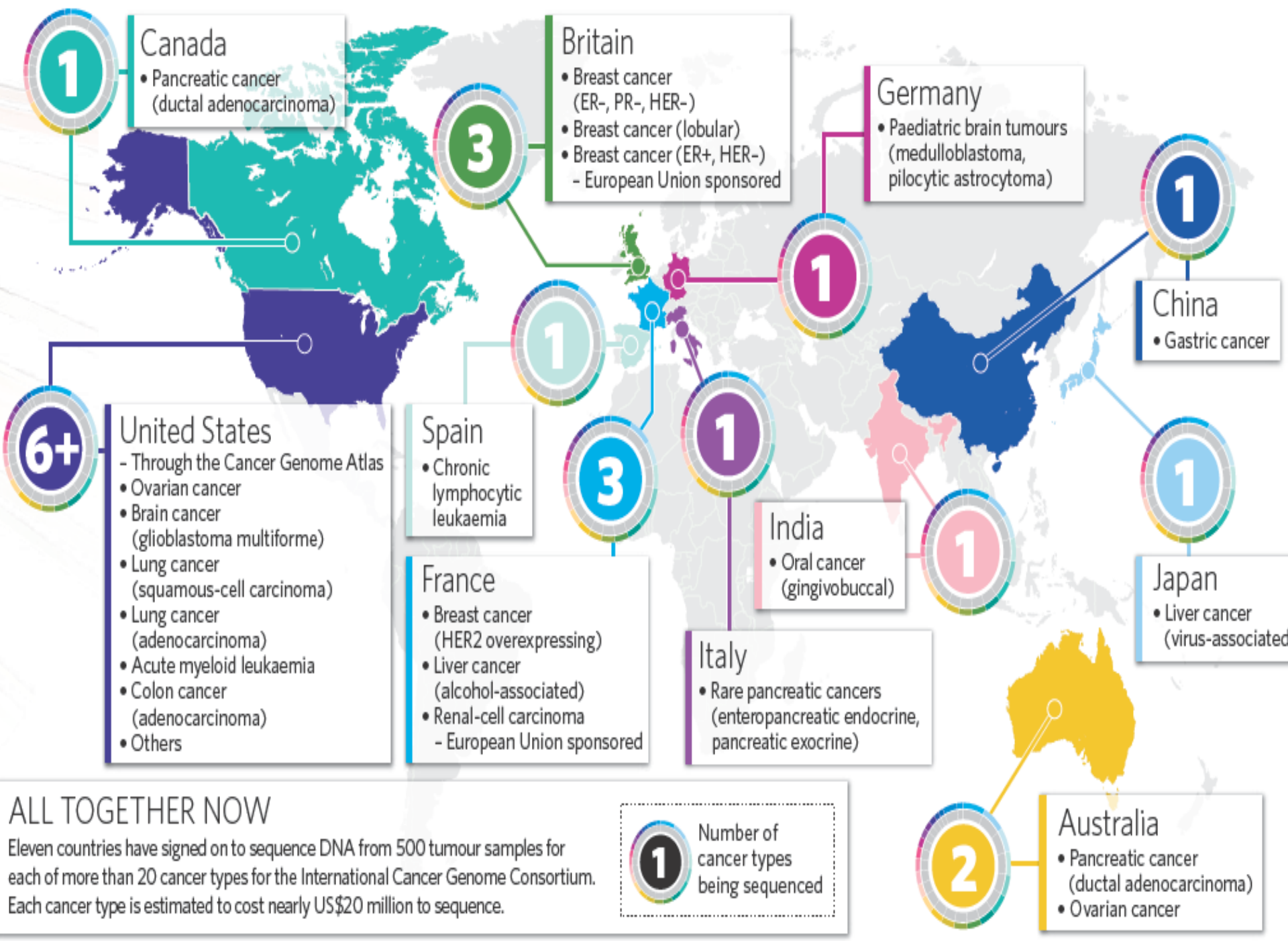
b. to be able to induce angiogenesis in order to provide themselves with a blood supply.

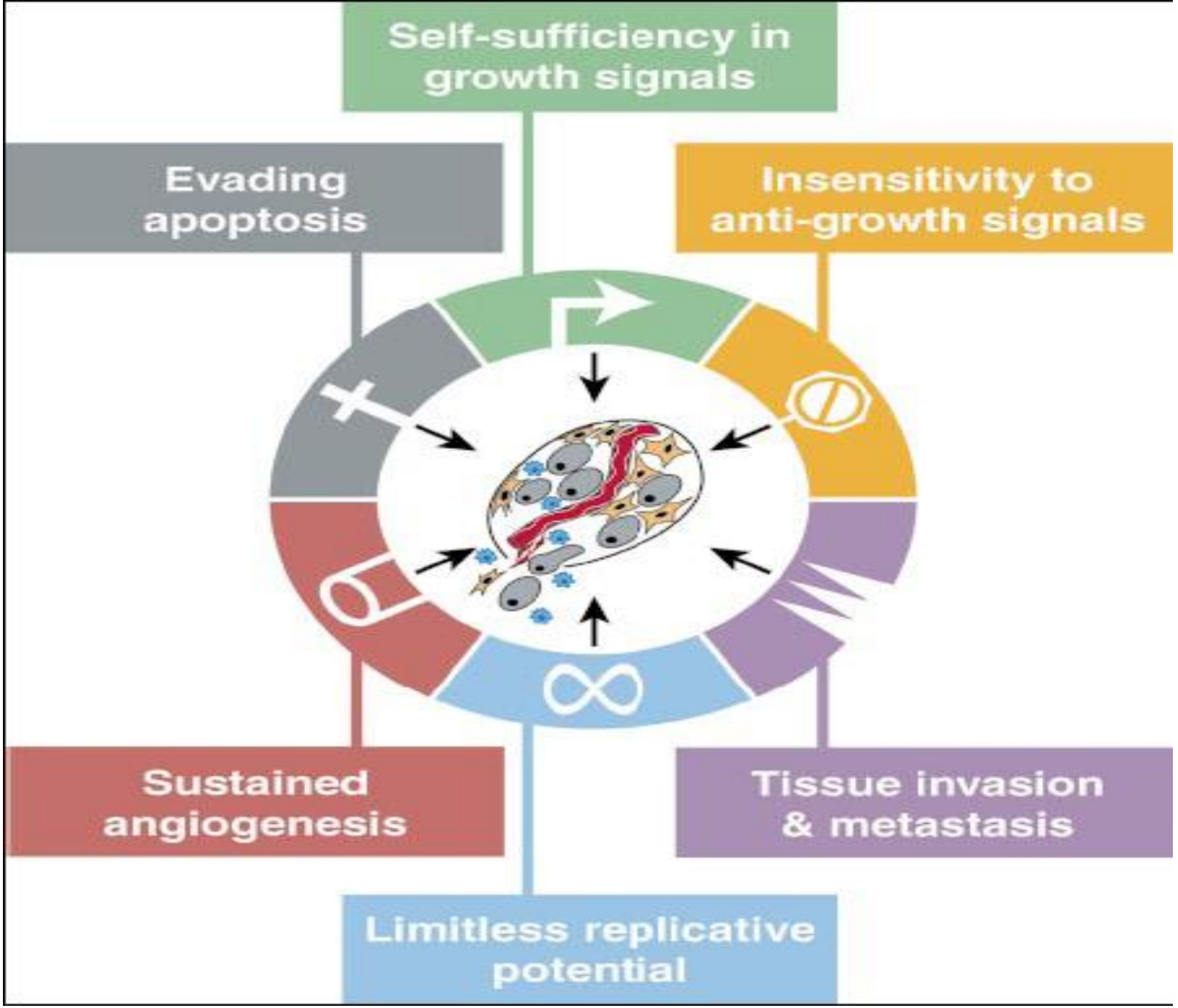
Stages of Carcinogenesis



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

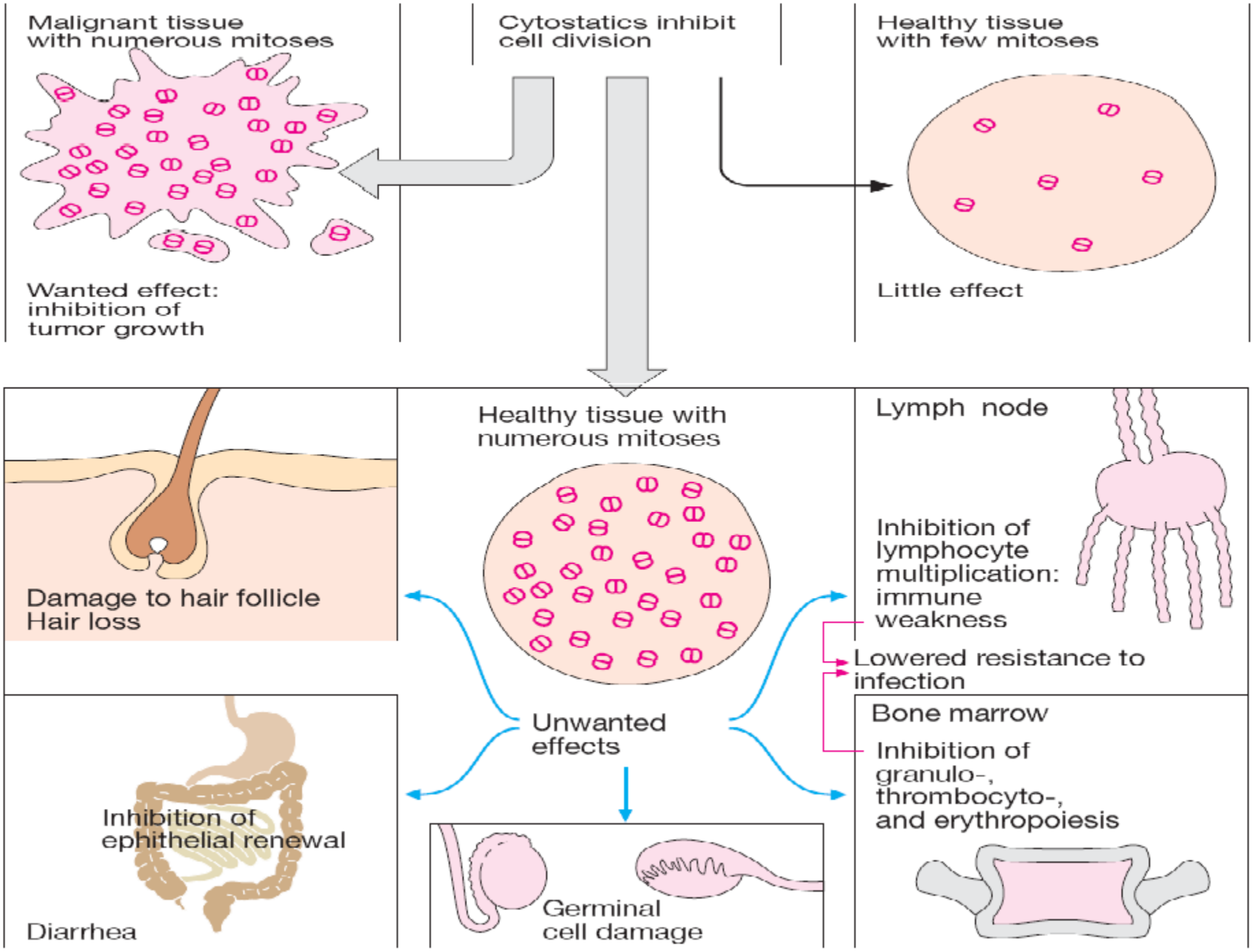
- **Cancer drugs are not specific for cancer cells but are cytotoxic to all proliferating cells in cycle.**

- **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!**

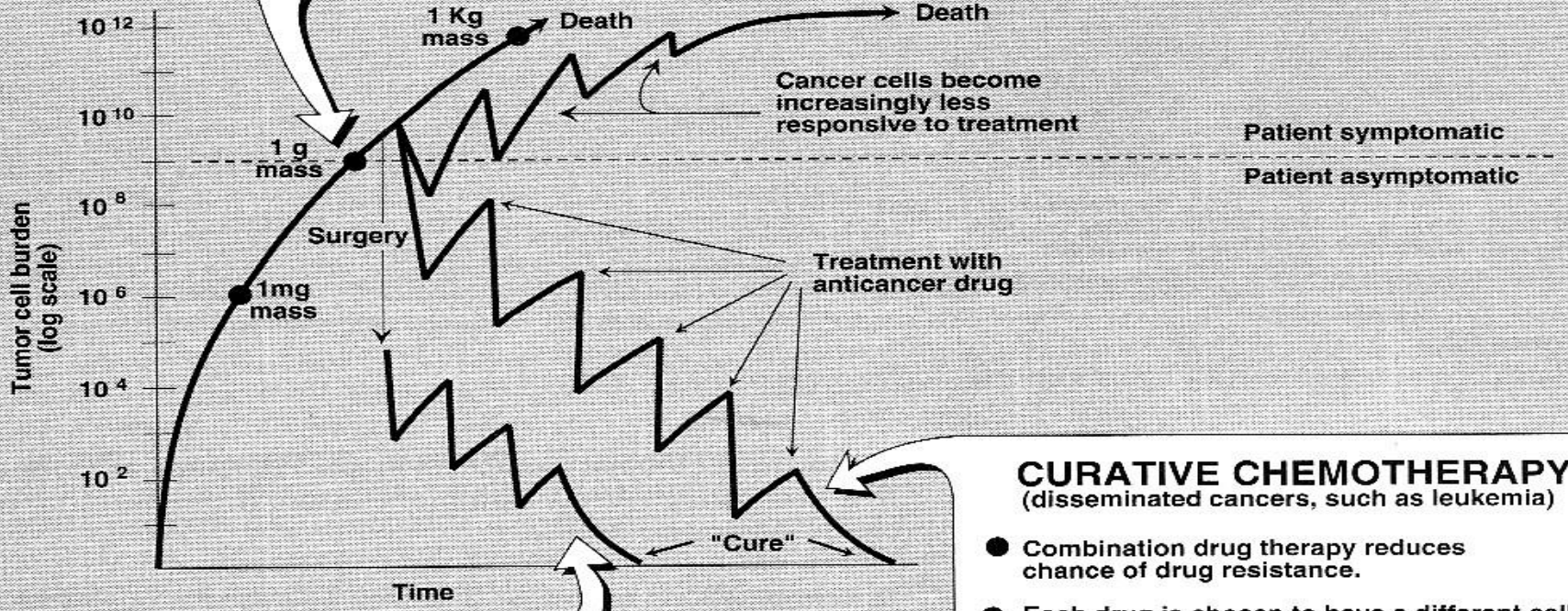
- **If there are 10^{11} tumour cells present (100g), killing 99.99% of them leaves 1 x 10^7 residual cells.**
- **1 L1210 leukaemia cell will kill a mouse.**

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.

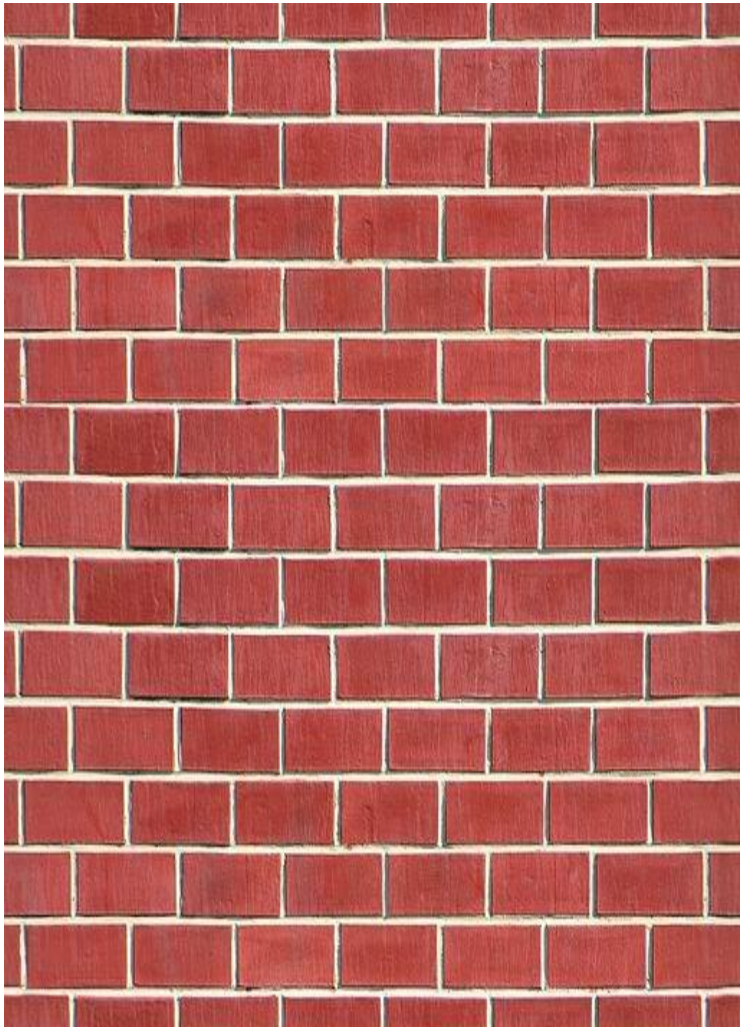
(5) Deregulation of apoptosis

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)**

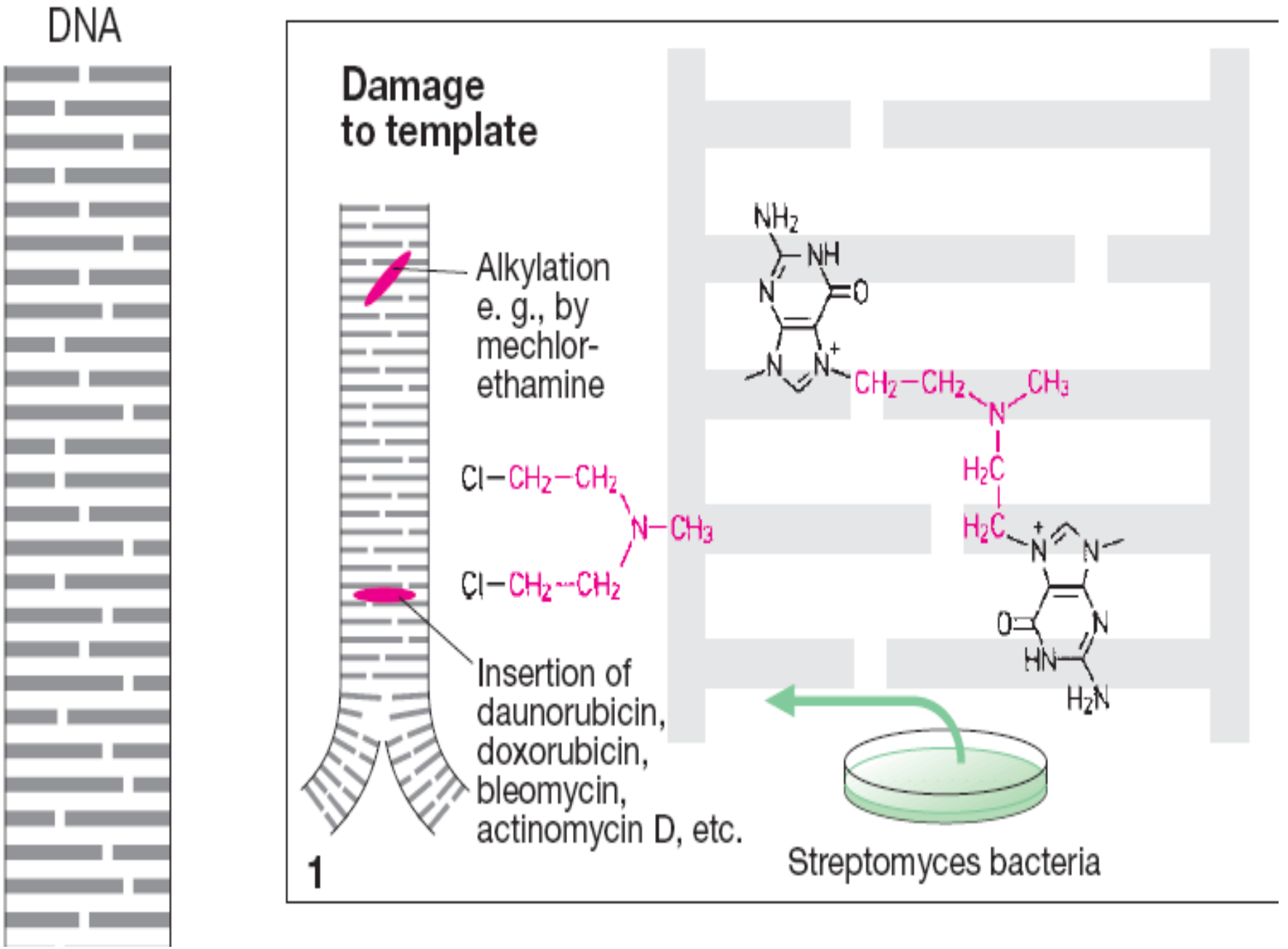
4. **Hormones and Hormone Antagonists**
5. **Miscellaneous anticancer drugs**

DNA BINDING AGENTS
INTERCALATING AGENTS

- **Intercalating agents are flat planar aromatic compounds that insert themselves in between the DNA basepairs.**

- **They either inhibit RNA polymerase activity but not DNA polymerase or exert their action as cancer drugs by poison the activity of topoisomerase II.**

- **Clinically used intercalating agents include ANTHRACYCLINES , MITOXANTRONE and ACTINOMYCIN D.**


DNA
Damage to template
Alkylation e. g., by mechlor-ethamine
Cl–CH2–CH2
N–CH3
Cl–CH2–CH2
Insertion of daunorubicin, doxorubicin, bleomycin, actinomycin D, etc.
1
NH2
NH
N
O
N
N+
CH2–CH2
N
CH3
H2C
H2C
N+
N
O
N
HN
H2N
Streptomyces bacteria

Anthracyclines

- **are the most commonly used anticancer drug,**

- **doxorubicin (adriamycin) having activity against a wide range of solid tumours. (Most common)**

- **Daunorubicin (daunomycin) being used against acute myeloid leukemia (AML)**

- **Idarubicin is a semisynthetic anthracycline that took Daunorubicin place in AML therapy.**

- **Epirubicin doxorubicin analogue used in metastatic breast cancer and gastric gancer**

Anthracyclines

- **High-affinity binding to DNA through intercalation, resulting in blockade of DNA and RNA synthesis**
- **DNA strand scission via effects on Top II enzyme**
- **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 te generation of free radicals and lipid peroxidase.**

Mitoxandrone

- **Treats pediatric and adult acute myeloid leukemia, non-Hodgkin's lymphomas, and breast cancer.**
- **poisons the activity of topoisomerase II. And .....**
- **Myelosuppression is the main side effect.**

  Causes cardiac toxicity.
- **Blue discoloration of finger nails for 1 – 2 days after treatments.**

Actinomycin

- **Actinomycin is a very potent inhibitor of RNA polymerase. Does intercalate in the minor groove of the double helix.**

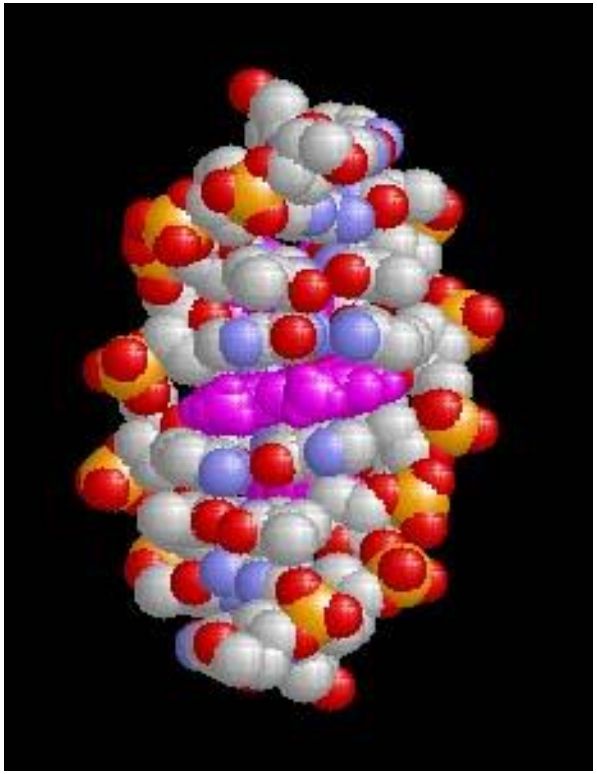
- **In the cancer clinic it finds use against special tumours, particularly Wilm's tumour which is a cancer of the kidney in children (in combination with vincristine).**

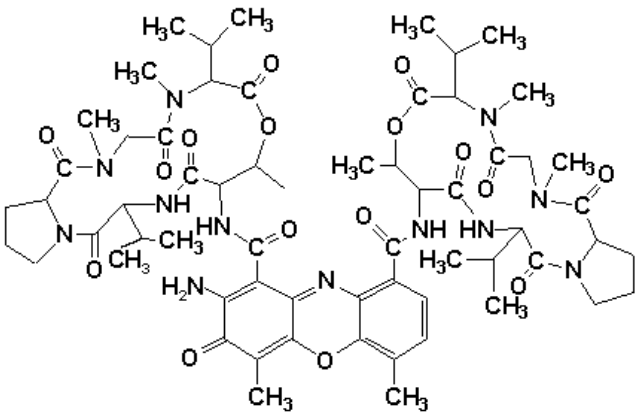
- **It is also combine with methotreaxate in the treatment of gestational choriocarcinoma.**

- **Its toxicities are bone marrow and gut suppression.**

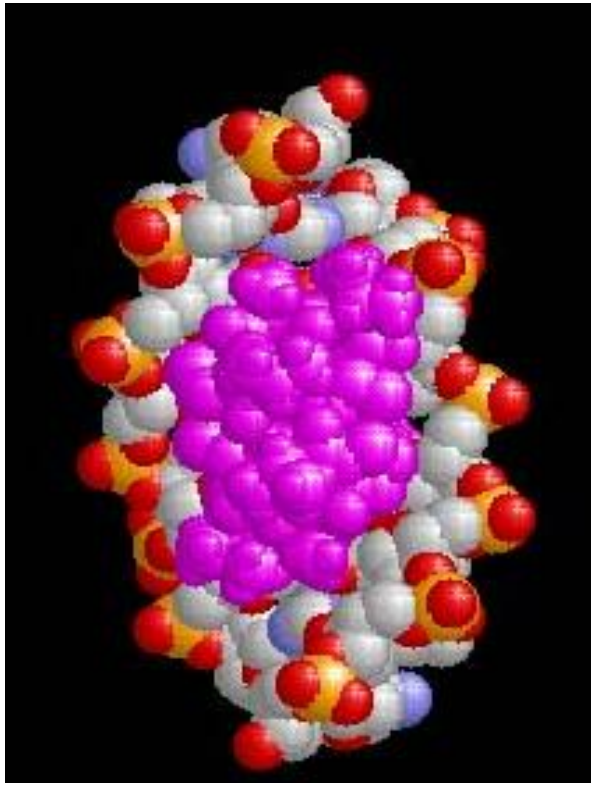
  Oral ulcers, Skin eruptions is less freqient.

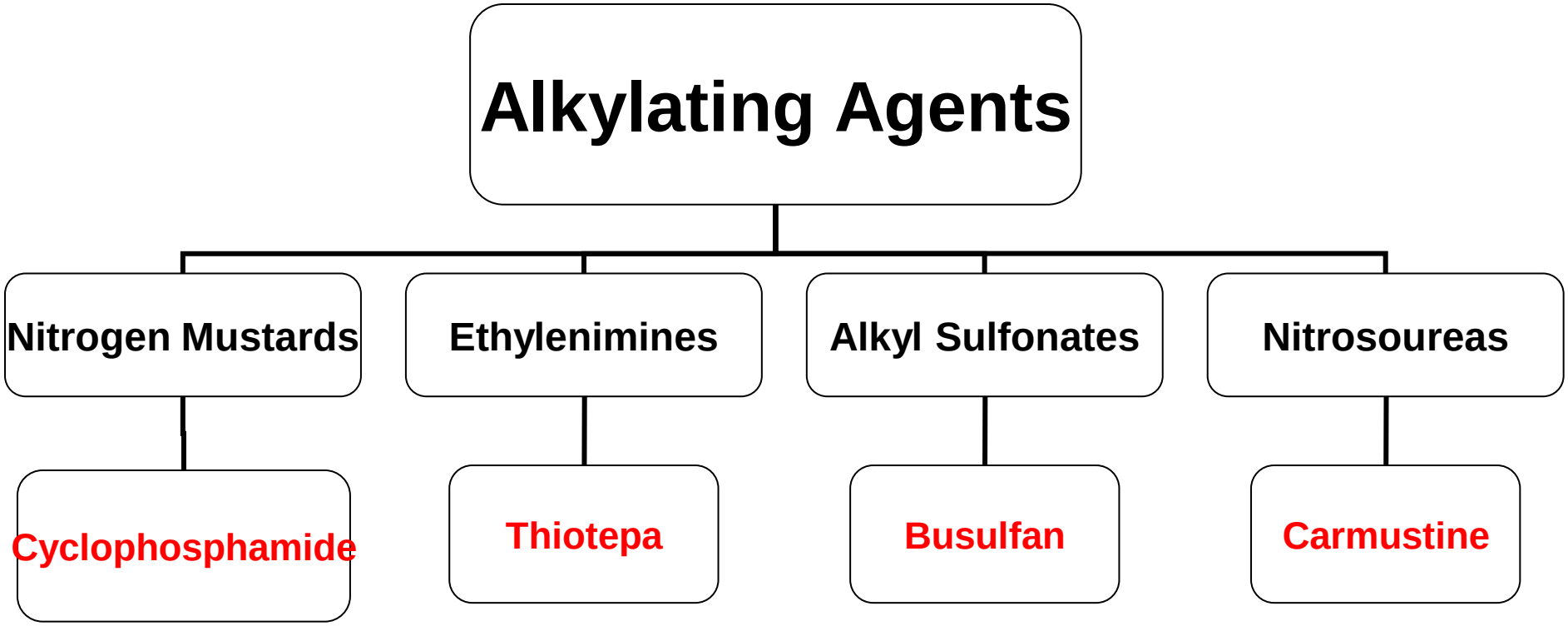
Actinomycin-DNA Complex





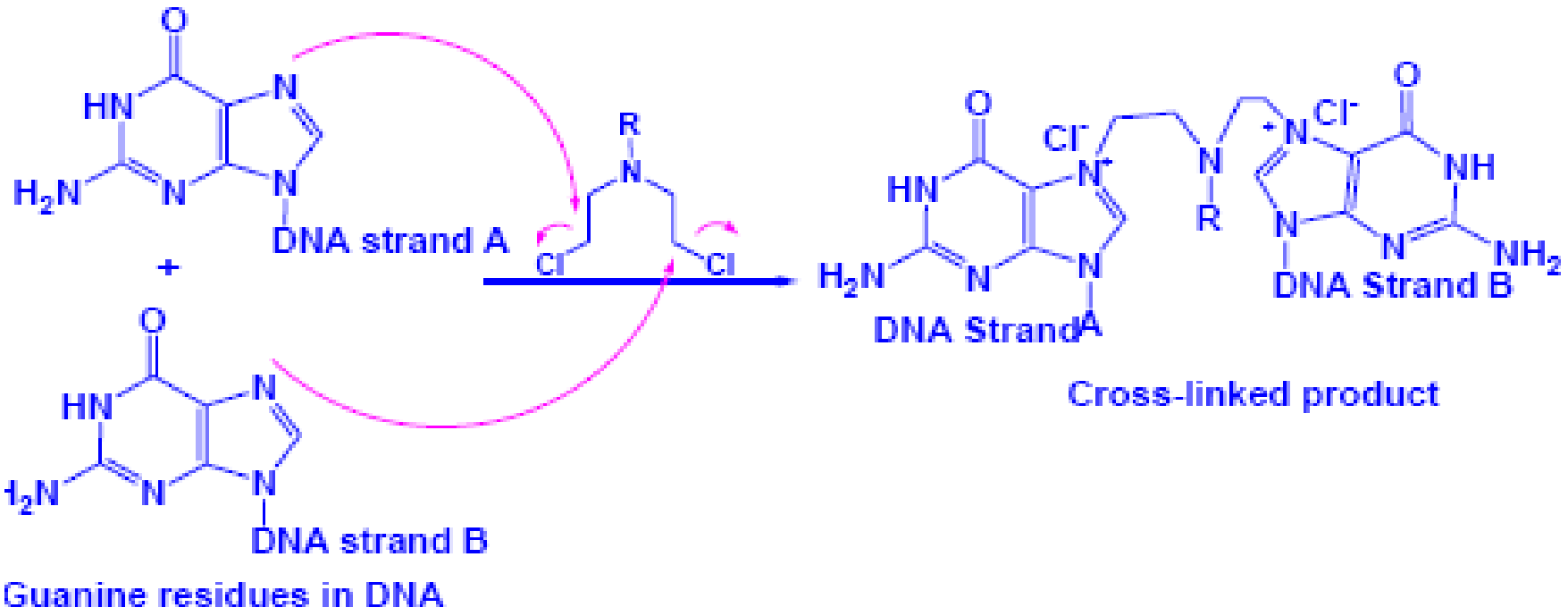
Actinomycin D




Alkylating Agents
Nitrogen Mustards
Ethylenimines
Alkyl Sulfonates
Nitrosoureas
Cyclophosphamide
Thiotepa
Busulfan
Carmustine

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**
- **Ifosfamide**
- **Mechlorethamine**
- **Melphalan**
- **Chlorambucil**

cyclophosphamide (most commonly used alkylating agent) has a special place in the maintenance therapy for breast cancer.

It is also a potent immunosuppressant, it is used in the management of rheumatoid disorders and autoimmune nephritis.

Their main toxicities are bone marrow and gut suppression.

- **Clinical use of nitrogen mustardtoday is mostly limited to the treatment of lymphomas, especially Hodgkin's disease.**

- **Melphalan It can be taken orally as hydrochloride.**

- **Chlorambucil acts most slowly and is the least toxic of any nitrogen mustard derivative in use. It is used in chronic lymphocytic leukemia and usually taken orally.**

- **Cyclophpsphamide It can be administered orally or parenterally. It is used in lymphomas, leukemias, sarcomas, carcinomas of breast or ovary, as well as childhood malignancies. Acrolein is believed to be responsible for the cystitis produced bycyclophosphamide. Therefore, cyclophosphamide is co-administered**
- **with N-acetylcystein or 2-mercaptoethanesulfonate (mesna). Both are thiols that neutralized acrolein by giving non-toxicconjugate addition to its double bond**

Nitrosoureas

- **The best known clinical agents are CARMUSTINE and LOMUSTINE.**

- **The nitrosoureas pass the blood-brain barrier and are active against brain tumours.**

- **These drugs appear to be non-cross-resistant with other alkylating agents.**

- **Another important member is streptozocin that has activity in the treatment of** insulin-secreting islet cell carcinoma of the pancreas, **intrestingly this agents has minimal bone marrow toxicity.**

ALKYLATING AGENTS

- **In the clinic, cisplatin behaves very similarly to the organic alkylating agents and finds widespread use.**

- **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.**

- **Its main toxicities are to the kidney and to the ear in addition to the usual dose limiting myelosuppression. ?//////**

- **Carboplatin is a second generation platinum analog that has less renal toxicity and gastrointestinal toxicity.**

- **Though Carboplatin has widely replace cisplatin in chemotherapeutic regimen.**

Cisplatin:

Indications:

- **Cisplatin has efficacy against a wide range of neoplasms. It is given intravenously as a first-line drug for testicular, ovarian, and bladder cancer, and it is also useful in the treatment of melanoma and a number of other soild tumors.**

Adverse Effect:

- **Cisplatin produces relatively little myelosuppression but can cause severe nausea, vomiting, and**

Alkylating Agents
Toxicity

- Bone marrow depression, with leukopenia and thrombocytopenia

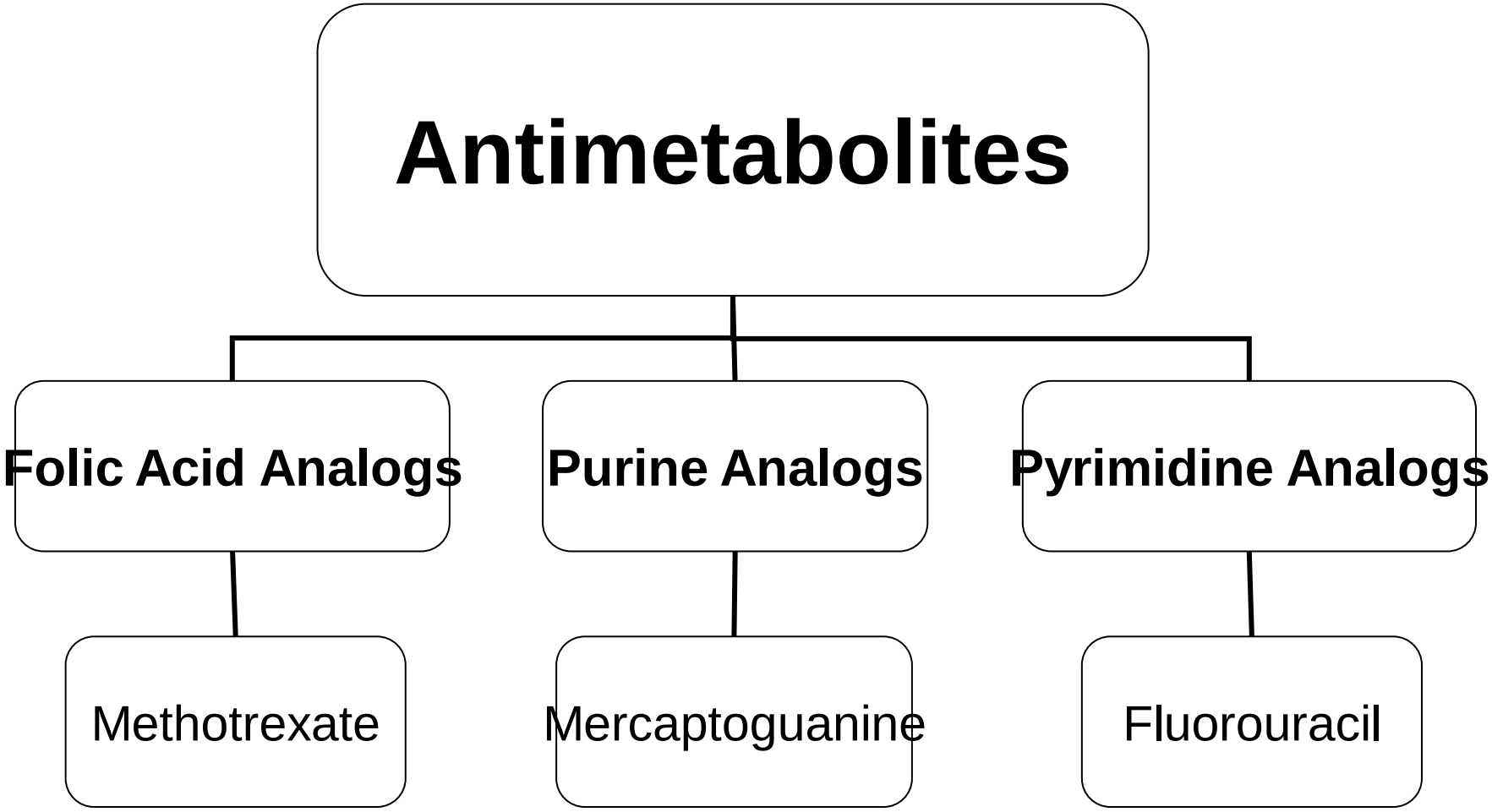
- *Cyclophosphamide/Ifosfamide* - hemorrhagic cystitis
  - Reduced by coadministration with MESNA
- *Cisplatin/Carboplatin* - ototoxic and nephrotoxic
  - Nephrotoxicity reduced by chloride diuresis and hydration

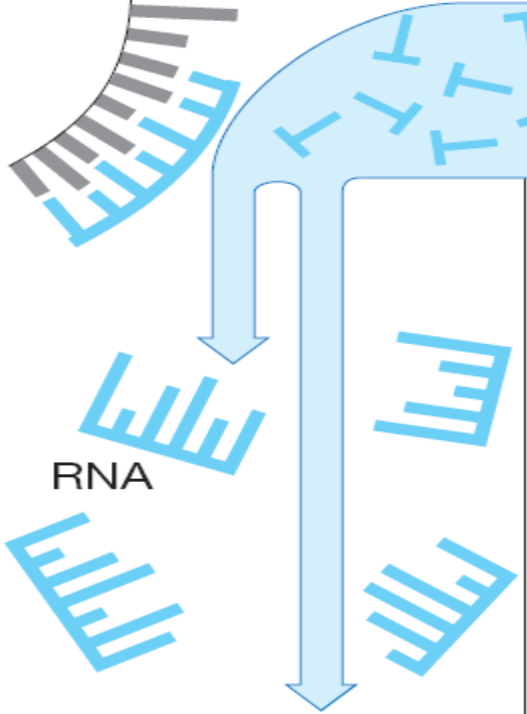
Alkylating Agents
Therapeutic Uses

- Used to treat a wide variety of hematologic and solid tumors
- *Thiotepa –* ovarian cancer
- *Busulfan* – chronic myeloid leukemia
- *Nitrosoureas* - brain tumors
- *Streptozocin* – insulin-secreting islet cell carcinoma of the pancreas

ALKYLATING AGENTS

- **Cells become resistant to alkylating agents by directly repairing the DNA lesion by a variety of mechanisms, and by up-regulating thiol-containing compounds such as glutathione and the metallothionines.**


Antimetabolites
Folic Acid Analogs
Purine Analogs
Pyrimidine Analogs
Methotrexate
Mercaptoguanine
Fluorouracil



Inhibition of nucleotide synthesi

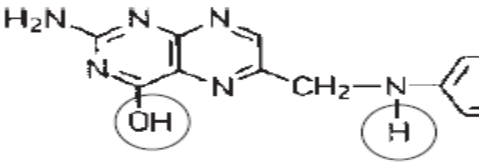
Purines

Thymine Nucleotide

Tetrahydro-folate

Dihydrofolate Reductase

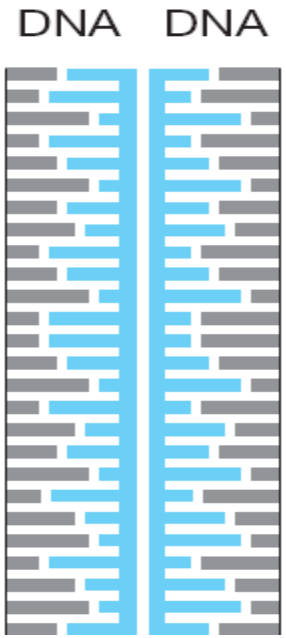
Folic acid



Inhibition by

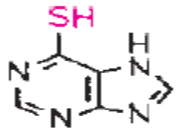
Aminopterin
Methotrexate

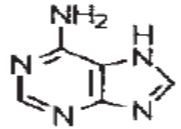
2



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**

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 where 20% of patients have partial responses.**

- **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 toxicites are myelosuppression and gut epithelial damage.**

Pyrimidine antagonists

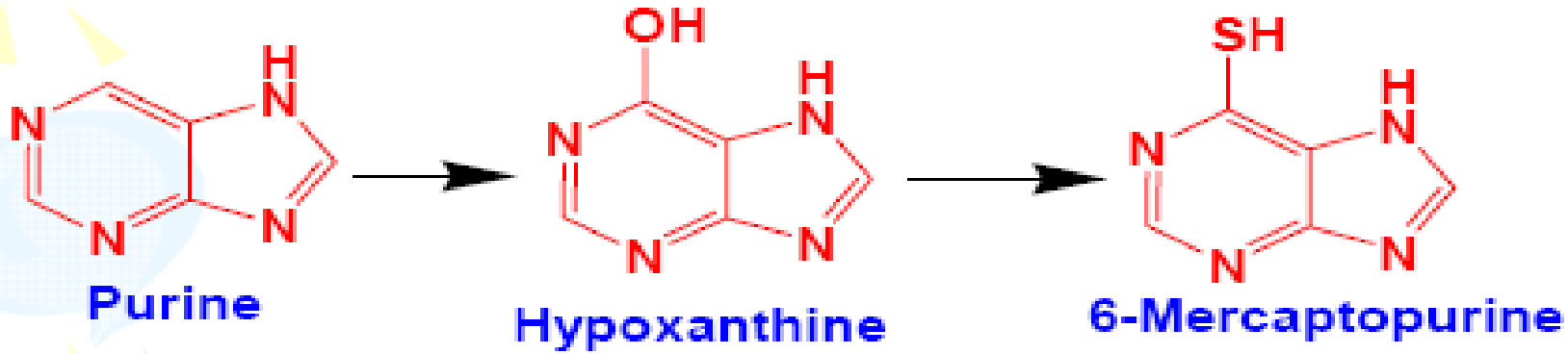
- **Cytosine arabinoside, Cytarabine, is a naturally-occuring analogue of cytidine.**

- **Their mode of action is due to its rapid conversion into *cytosine arabinoside triphosphosphate*, which damages DNA when the cell cycle holds in the S phase.**

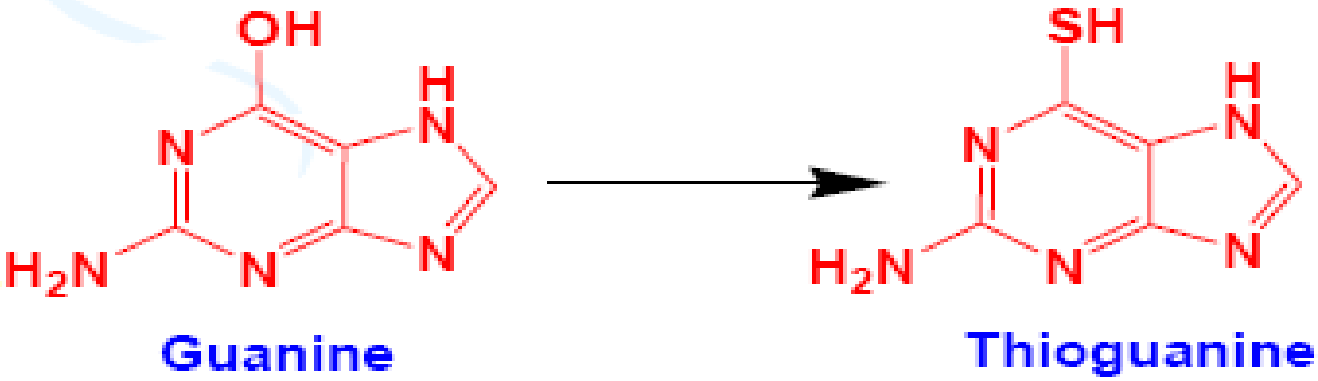
- **Main use is in leukaemias and lymphomas. Main toxicity is to bone marrow and gut damage.**

Purine antagonists

- **1) 6-Mercaptopurine (6-MP)**



2) 6-Thioguanine (6-TG)



Purine antagonist

- **they inhibit various steps in *de novo* purine synthesis and antagonise the enzyme Ribonucleotide Reductase.**
- **Ribonucleotide reductase is a key enzyme in DNA synthesis.**
- **Both 6-MP and 6-TG are administered orally and used for treating acute leukemia.**
- **their main toxicity is to the bone marrow and gut.**

MITOTIC SPINDLE INHIBITORS

Inhibition of formation

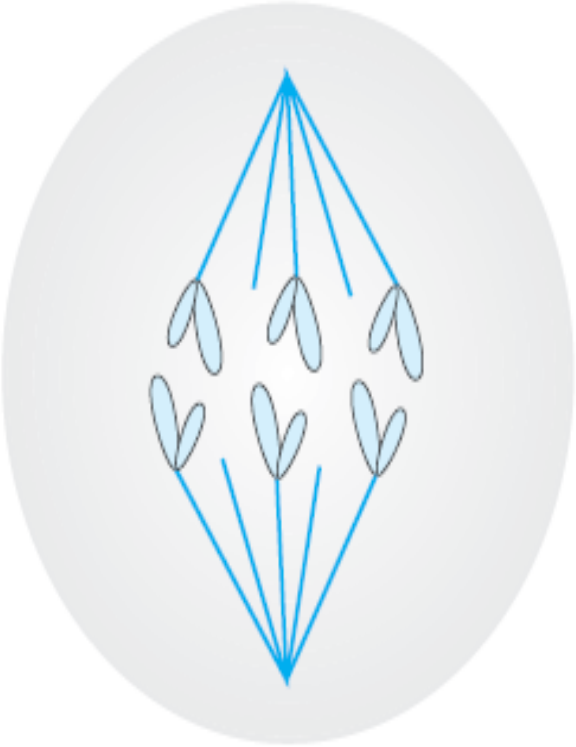
Vinca alkaloids

Microtubules of mitotic spindle

Inhibition of degradation

Paclitaxel

Vinca rosea



Western yew tree

INHIBITORS OF TUBULIN POLYMERISATION

- **The vinca alkaloids Vincristin and Vinblastin are natural products isolated from the periwinkle plant.**

- **They act by binding to tubulin and inhibit its polymerisation into microtubules, thereby preventing spindle formation during mitosis. This causes dividing cells to arrest at metaphase.**

- **The Vinca alkaloids are relatively non-toxic, generally having mild myelosuppressive activity but they cause sensory changes and neuromuscular abnormalities fairly frequently.**

INHIBITORS OF TUBULIN POLYMERISATION

- They are widely used in the treatment of solid carcinomas and leukaemias and lymphomas.
- Vinblastine therapeutic Uses include Systemic Hodgkin's disease Lymphomas
- Vincristine used With prednisone for remission of Acute Leukemia

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.**

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

- **Taxol has proven beneficial in late-stage drug-resistant ovarian and breast cancers, prolonging life by about 6 months.**