

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

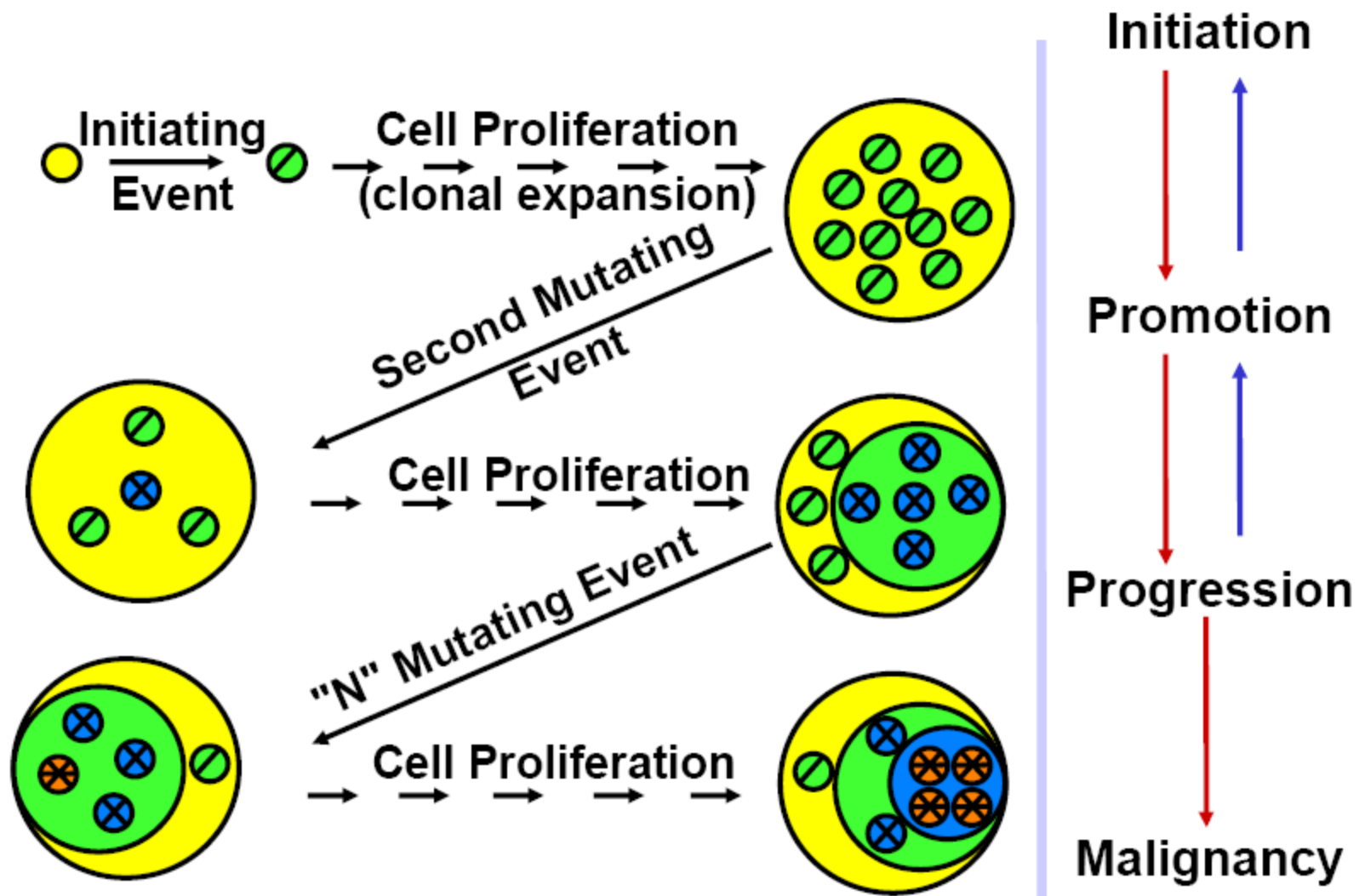
(3) Damage is also done to DNA repair genes so that, over time, giving rise to hypermutability and tumour heterogeneity.

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

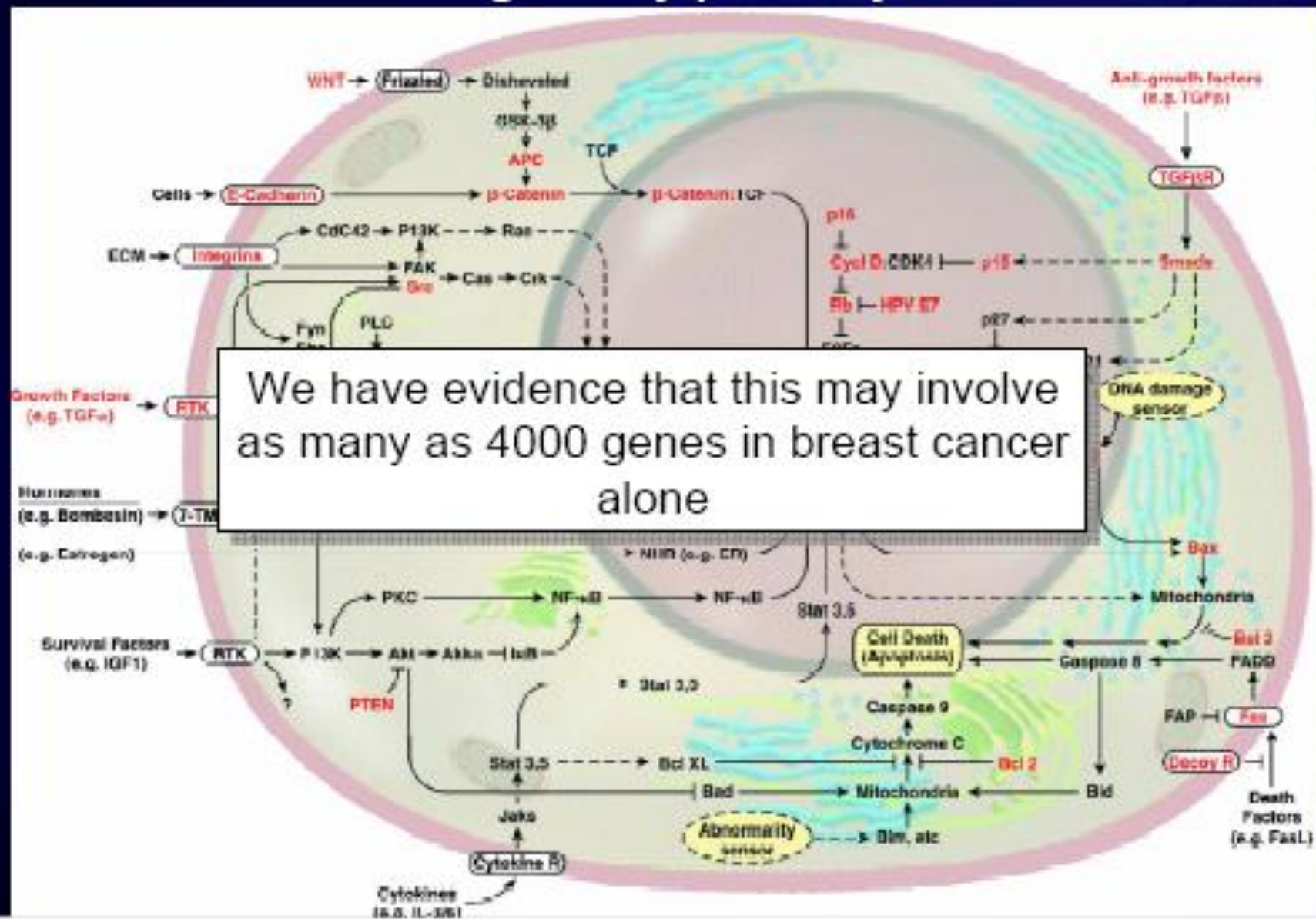
(4) To become MALIGNANT

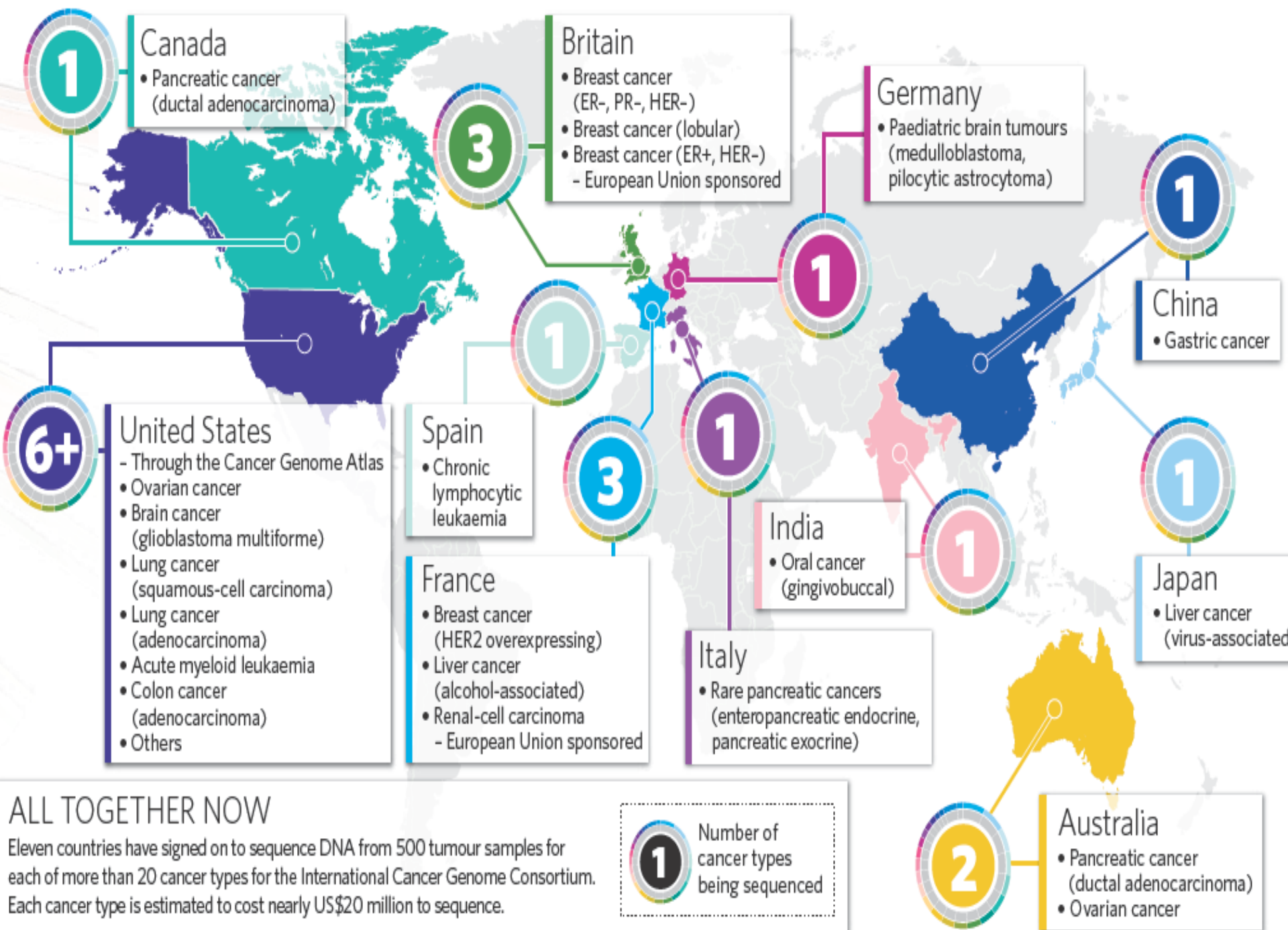
- a. The mutated cells have to acquire the capacity to avoid immune detection to metastasise and**
- b. to be able to induce angiogenesis in order to provide themselves with a blood supply.**

Stages of Carcinogenesis



This happens through deregulation of complex regulatory pathways





Self-sufficiency in growth signals

Evading apoptosis

Insensitivity to anti-growth signals



Sustained angiogenesis

Tissue invasion & metastasis

Limitless replicative potential

Cancer treatment

- There 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.

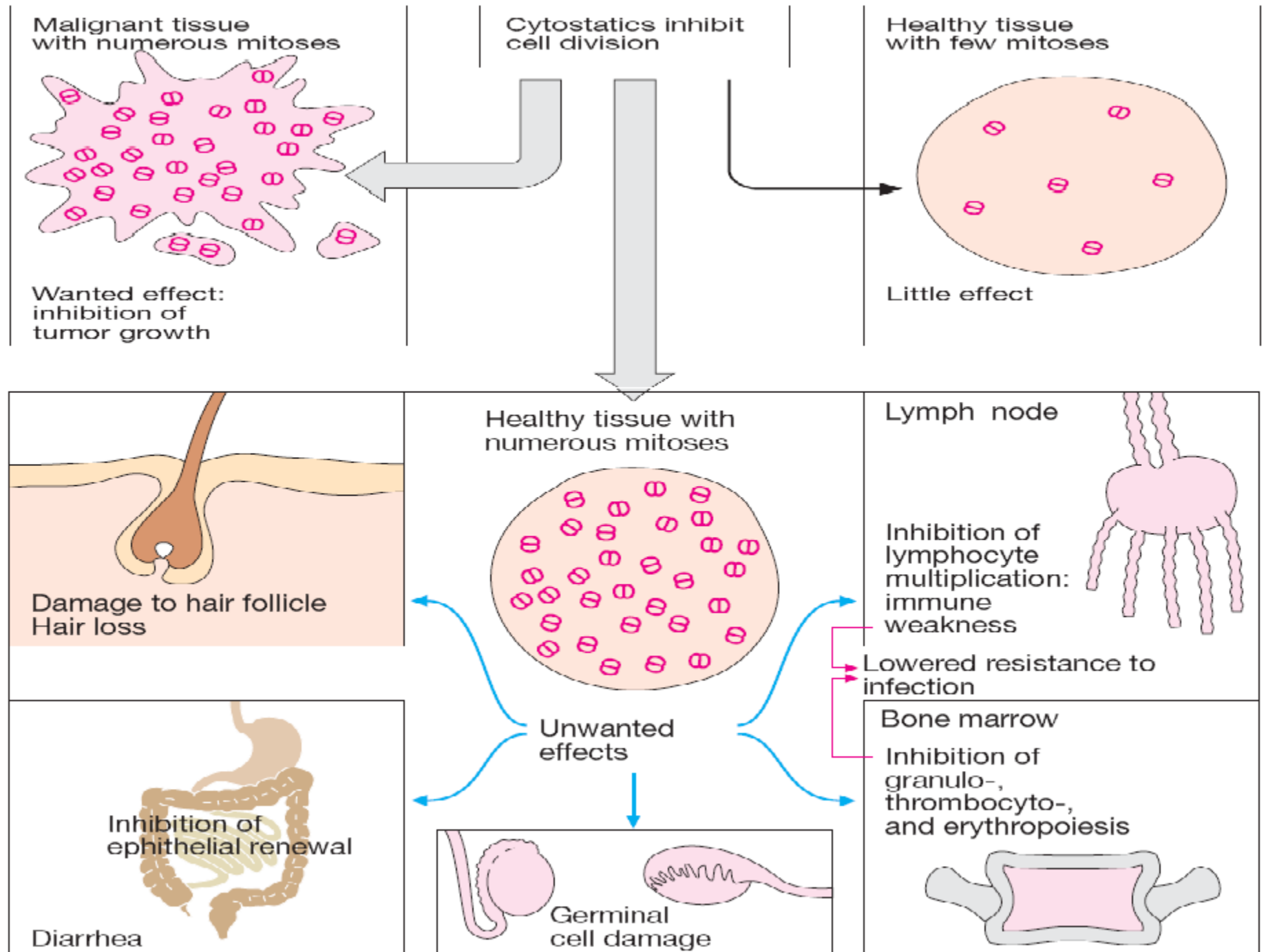
- X-rays kill tumour cells (and healthy normal cells in division) by free radical damage to DNA that results in double strand breaks which are lethal to cells at mitosis.
- Tumours that are not resectable may be treated by radiotherapy alone, in which case treatment is largely palliative.
- Most of the 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 eradication 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



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 heterogeneity 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

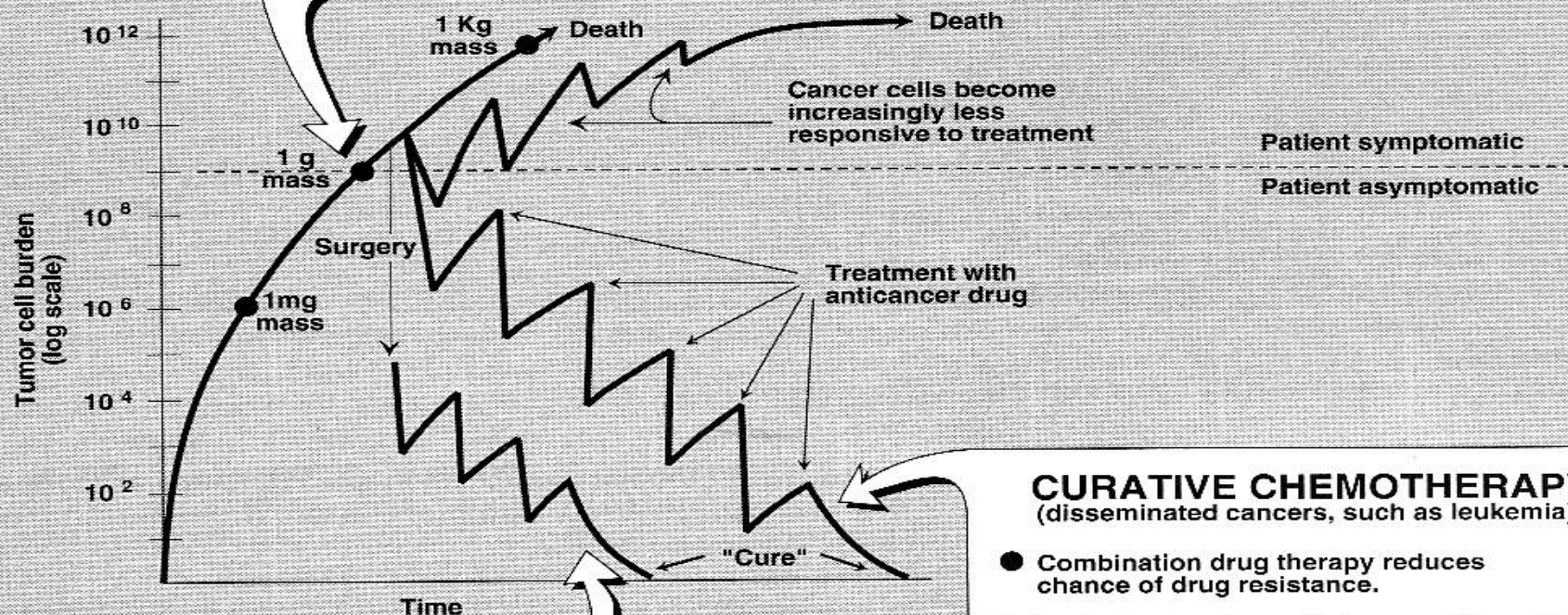
- **1×10^8 tumour cells are visible on an X-ray.**
- **1×10^9 cells is a palpable lump weighing a gram.**
- **1×10^{12} cells weighs a kilogram and the patient is dead.**
- **Cancer is hard to detect in its early stages and may already have grown to 10^{10} - 10^{11} cells at presentation.**
- **You've 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 1×10^7 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 (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.

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.

(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.



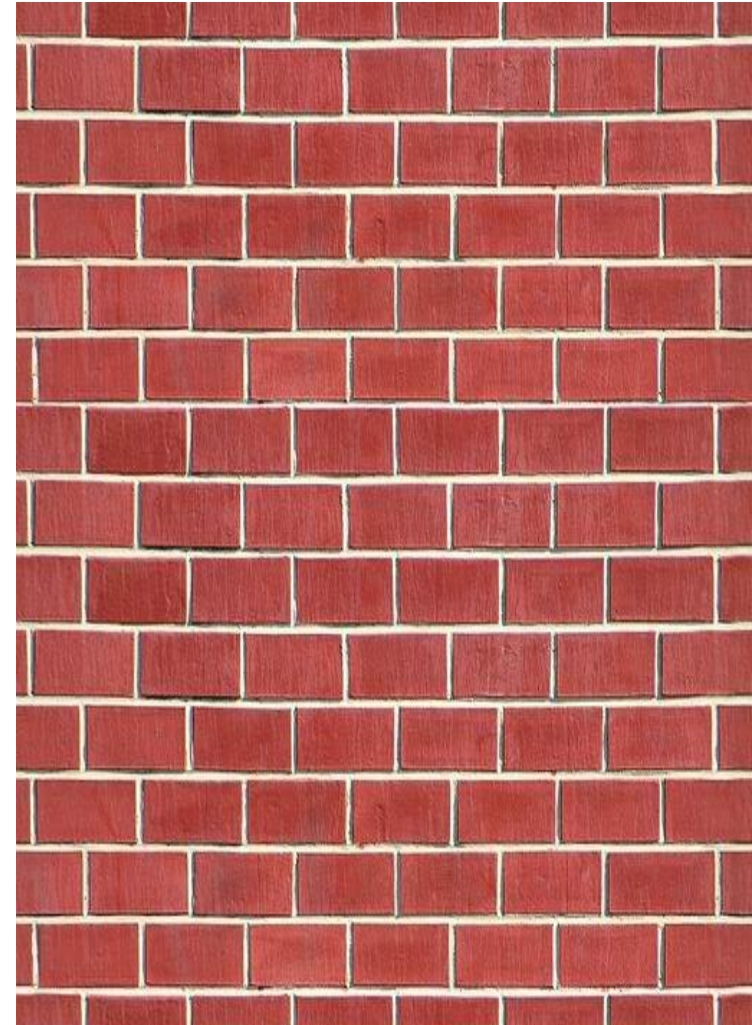
(5) Deregulation of apoptosis

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. DNA Binding Agents (intercalating and alkylating agents)**
 - 2. Mitotic Spindle Inhibitors (modulators of tubulin polymerisation)**
 - 3. Antimetabolites (anti-folates, pyrimidine and purine analogues)**
 - 4. Hormones and Hormone Antagonists**
 - 5. Miscellaneous anticancer drugs**

Anti-cancer drugs

Subclass	Prototype	Major Variants	Other Significant Agents
Alkylating agents			
Nitrogen mustards	Mechlorethamine		Cyclophosphamide, chlorambucil
Nitrosoureas	Carmustine	Lomustine	
Alkylsulfonates	Busulfan		
Platinum complex	Cisplatin	Carboplatin	
Triazenes	Dacarbazine		
Hydrazines	Procarbazine		
Antimetabolites			
Folate analogs	Methotrexate		
Purine analogs	Mercaptopurine		Thioguanine
Pyrimidine analogs	Fluorouracil		Cytarabine
Plant alkaloids			
Vinca alkaloids	Vinblastine	Vincristine	
Podophyllotoxins	Etoposide	Teniposide	
Other	Paclitaxel		Docetaxel
Antibiotics			
Anthracyclines	Doxorubicin	Daunorubicin	
Bleomycins	Bleomycin		
Actinomycins	Dactinomycin		
Mitomycins	Mitomycin		
Hormones			
Adrenocorticoids	Prednisone	Hydrocortisone	
Androgens	Testosterone	Fluoxymesterone	
Estrogens	Diethylstilbestrol	Ethinyl estradiol	
Progestins	Hydroxyprogesterone	Medroxyprogesterone	
Antiestrogens			
Receptor blockers	Tamoxifen	Toremifene	
Aromatase inhibitors	Anastrozole	Letrozole	
Antiandrogens	Flutamide		
Gonadotropin-releasing hormone agonists	Leuprolide	Goserelin, naferelin	
Monoclonal antibodies	Rituximab trastuzumab		

Malignant tissue
with numerous mitoses

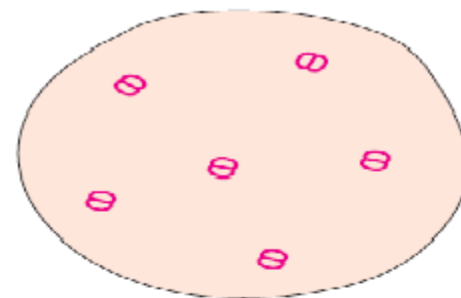


Wanted effect:
inhibition of
tumor growth

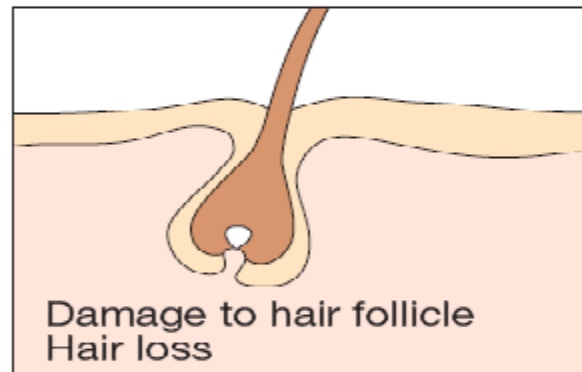
Cytostatics inhibit
cell division



Healthy tissue
with few mitoses

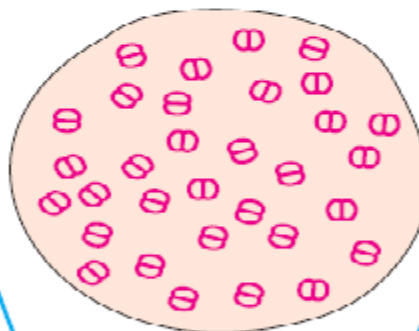


Little effect

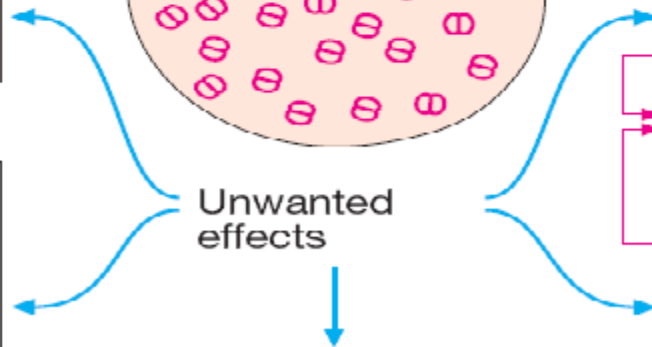


Damage to hair follicle
Hair loss

Healthy tissue with
numerous mitoses



Unwanted
effects



Lymph node

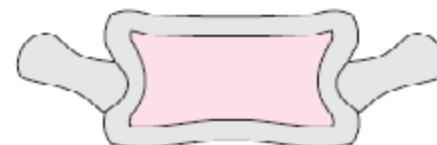


Inhibition of
lymphocyte
multiplication:
immune
weakness

Lowered resistance to
infection

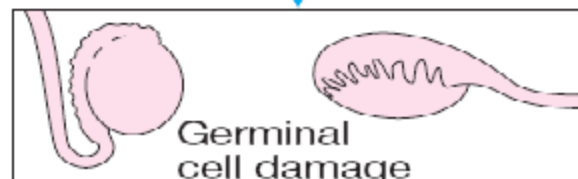
Bone marrow

Inhibition of
granulo-,
thrombocyto-,
and erythropoiesis



Inhibition of
ephithelial renewal

Diarrhea



Germinal
cell damage

Classes of Adjuvant Therapy	Classical Agent/Regimen	Present Agent/Regimen	Future Agent/Regimen
Hormonal therapy (only considered for ER-positive patients, not for ER-negative patients)	Premenopausal: tamoxifen or oophorectomy Postmenopausal: tamoxifen	Premenopausal: classical options or gonadotrophin-releasing hormone analogues or combinations of these Postmenopausal: tamoxifen or AIs	--
Chemotherapy (regardless of ER status)	Cyclophosphamide, methotrexate, 5-fluorouracil (CMF)	Most effective regimens are considered to include an anthracycline and/or a taxane	--
HER2-targeting therapy (only considered for HER2-positive patients)	Trastuzumab	Trastuzumab	Lapatinib being evaluated in clinical trials
Angiogenesis as a target	Not available	None proven	Bevacizumab currently in clinical trials

Drugs approved in Metastatic Breast Cancer

Preferred first-line chemotherapy

- Anthracycline-based.
- Taxanes.
- Cyclophosphamide, methotrexate and 5-fluorouracil (CMF).

Preferred second-line chemotherapy

- If first-line was anthracycline-based or CMF, then a taxane.
- If first-line was a taxane, then anthracycline-based or CMF.

DNA binding agents

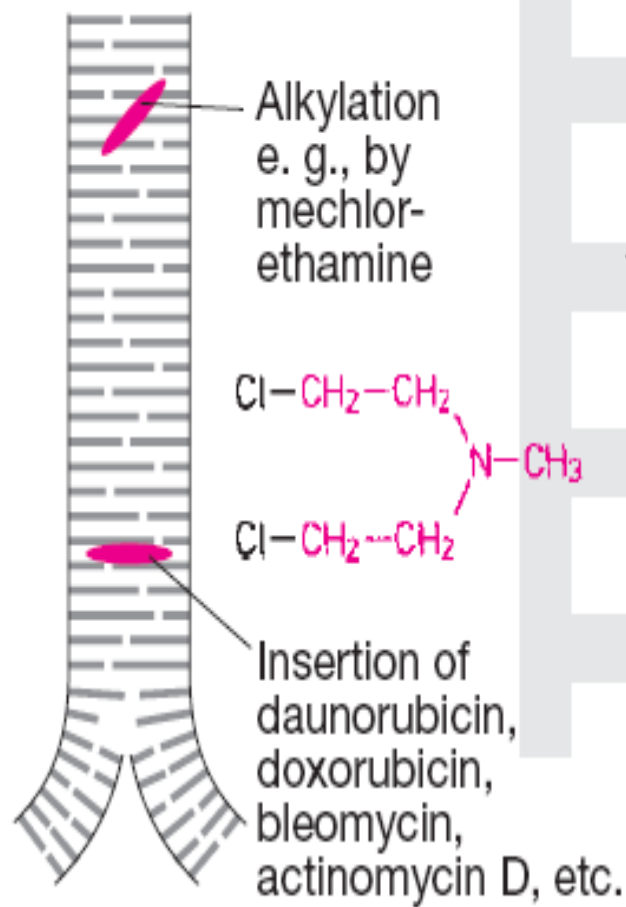
Intercalating agents

- 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, ACTINOMYCIN D and Bleomycin**

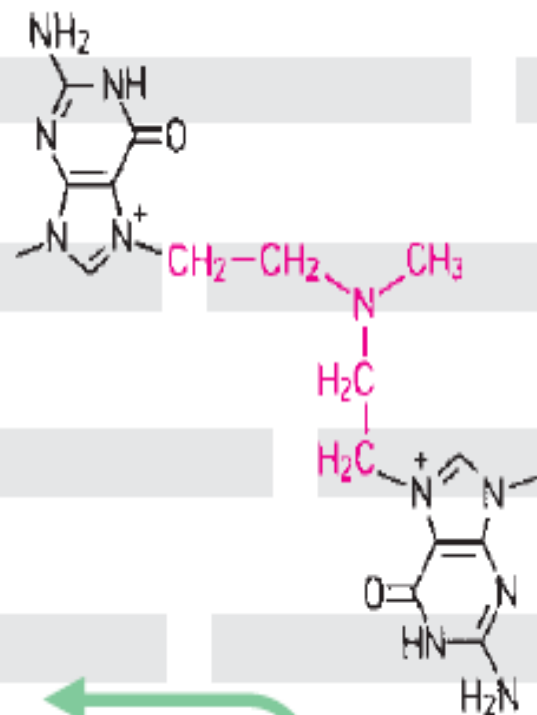
DNA



Damage to template



1



Streptomyces bacteria

Anthracyclines

- are the most commonly used anticancer drug,
- Doxorubicin (adriamycin) having activity against a wide range of solid tumours. (Most common drug)
- Daunorubicin (daunomycin) being used against acute myeloid leukemia (AML)
- Idarubicin is a semisynthetic anthracycline that took Daunorubicin place in AML therapy.
- Epirubicin is a doxorubicin analogue used in metastatic breast cancer and gastric cancer

Anthracyclines

- **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.

HOW TO REDUCE THIS Dexrazoxane

Distinctive Toxicities of Some Anticancer Drugs

Toxicity	Drug(s)
Renal	Cisplatin,* methotrexate
Hepatic	6-MP, busulfan, cyclophosphamide
Pulmonary	Bleomycin,* busulfan, procarbazine
Cardiac	Doxorubicin, daunorubicin
Neurologic	Vincristine,* cisplatin, paclitaxel
Immunosuppressive	Cyclophosphamide, cytarabine, dactinomycin, methotrexate
Other	Cyclophosphamide (hemorrhagic cystitis); procarbazine (leukemia); asparaginase* (pancreatitis)

***Less Bone marrow suppression – “marrow sparing”**

Alkylating Agents

```
graph TD; A[Alkylating Agents] --> B[Nitrogen Mustards]; A --> C[Ethylenimines]; A --> D[Alkyl Sulfonates]; A --> E[Nitrosoureas]; B --> F[Cyclophosphamide]; C --> G[Thiotepa]; D --> H[Busulfan]; E --> I[Carmustine];
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Nitrogen Mustards

Cyclophosphamide

Ethylenimines

Thiotepa

Alkyl Sulfonates

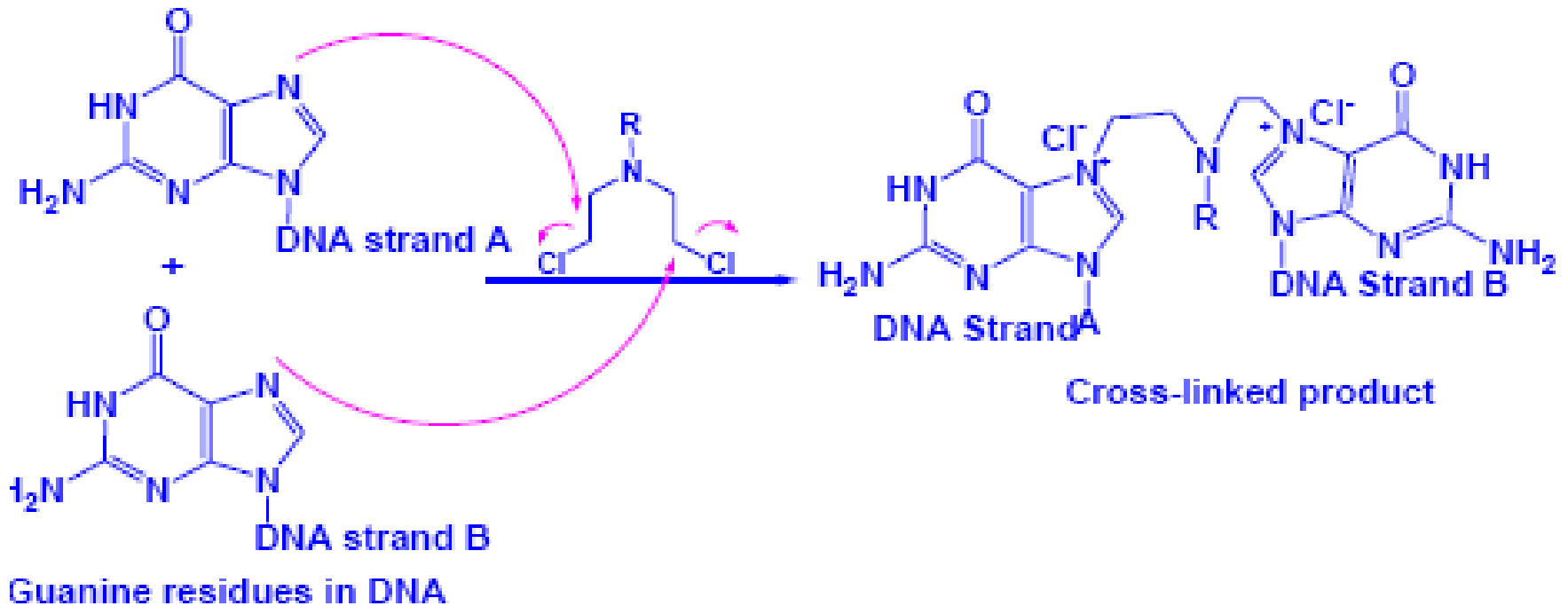
Busulfan

Nitrosoureas

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

- 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.**
- 3. It is also a potent immunosuppressant,
it is used in the management of rheumatoid disorders
and autoimmune nephritis.**
- 4. Cystitis (inflammation of the urinary bladder) may result.
co-administered with N-acetylcystein or 2-
mercaptoethanesulfonate (mesna). Both are thiols that
neutralized acrolein**

Nitrosoureas

- **The best known clinical agents are CARMUSTINE and LOMUSTINE (oral).**
- **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.**
- **Streptozocin (minimal bone marrow toxicity)
used to treat insulin-secreting islet cell carcinoma of the
pancreas**

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.

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.

Antimetabolites

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graph TD; A[Antimetabolites] --> B[Folic Acid Analogs]; A --> C[Purine Analogs]; A --> D[Pyrimidine Analogs]; B --> E[Methotrexate]; C --> F[Mercaptopurine]; D --> G[Fluorouracil];
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Folic Acid Analogs

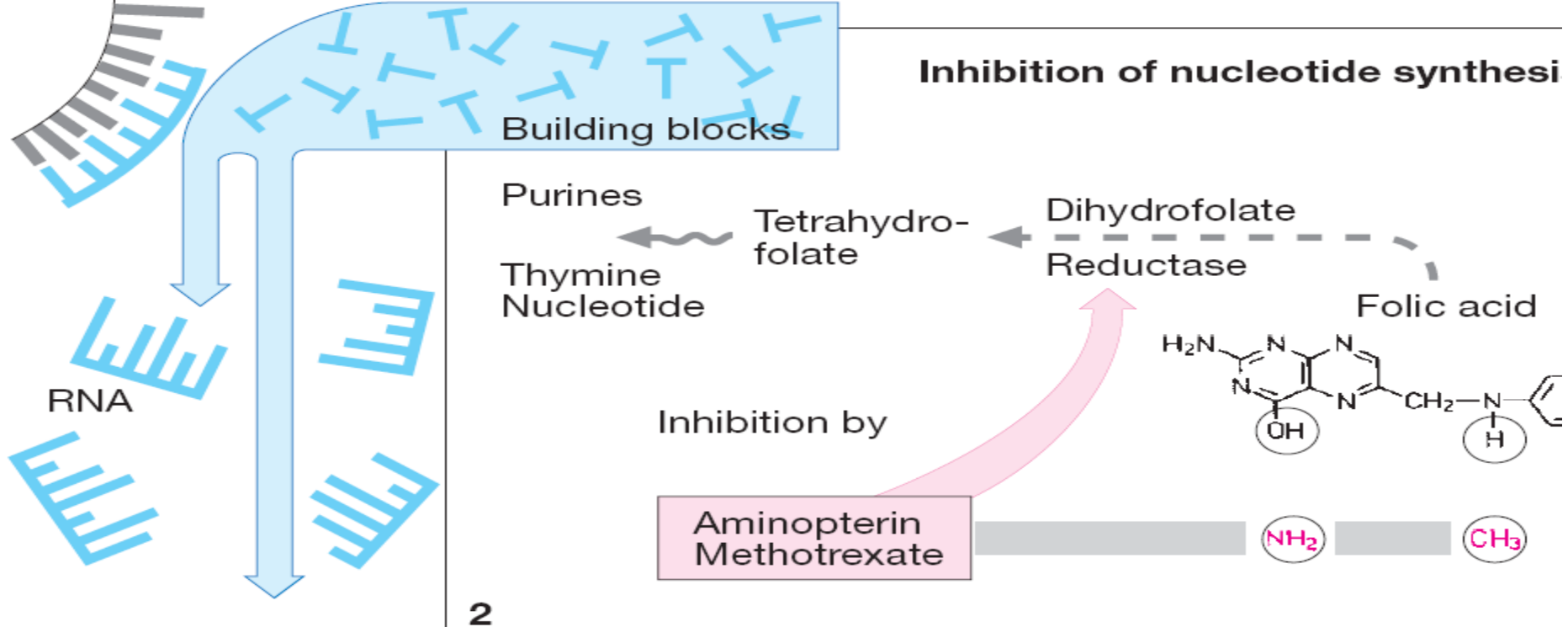
Methotrexate

Purine Analogs

Mercaptopurine

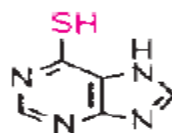
Pyrimidine Analogs

Fluorouracil



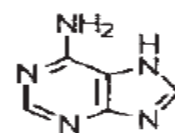
Insertion of incorrect building block

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.

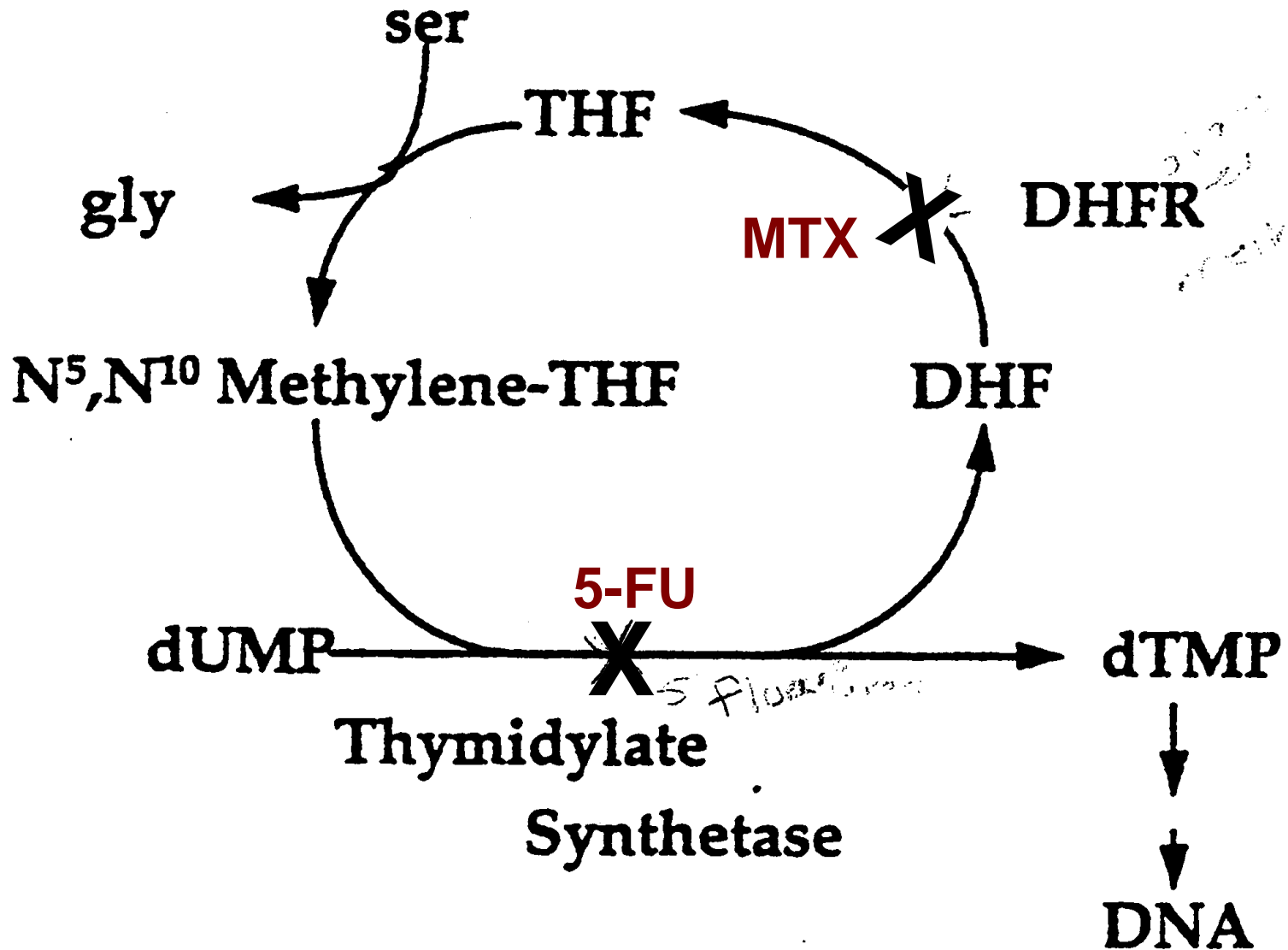


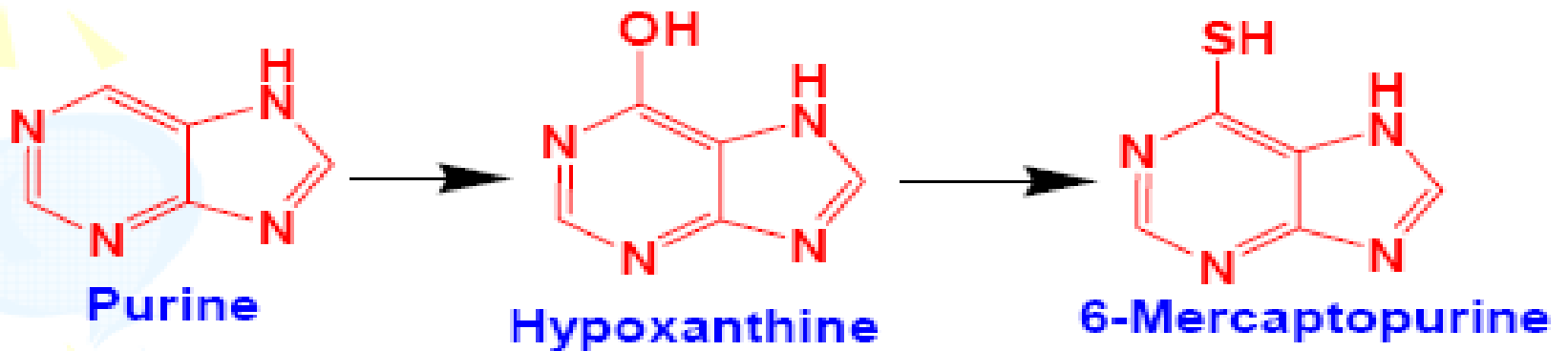
Figure 2. This figure illustrates the effects of MTX and 5-FU on the biochemical pathway for reduced folates.

Pyrimidine antagonists

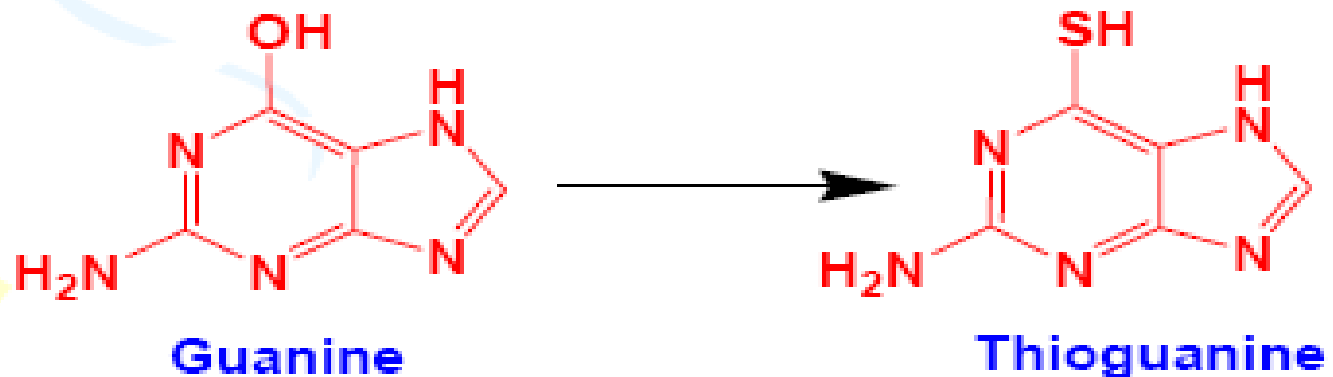
- Cytosine arabinoside, Cytarabine, is a naturally-occurring analogue of cytidine.
- Their mode of action is due to its rapid conversion into *cytosine arabinoside triphosphosphate*, which damages DNA when the cell cycle holds in the S phase.
- Main use is in leukaemias and lymphomas.
- Main toxicity 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.
- allpuranoL

MITOTIC SPINDLE INHIBITORS

Inhibition of
formation

Vinca
alkaloids

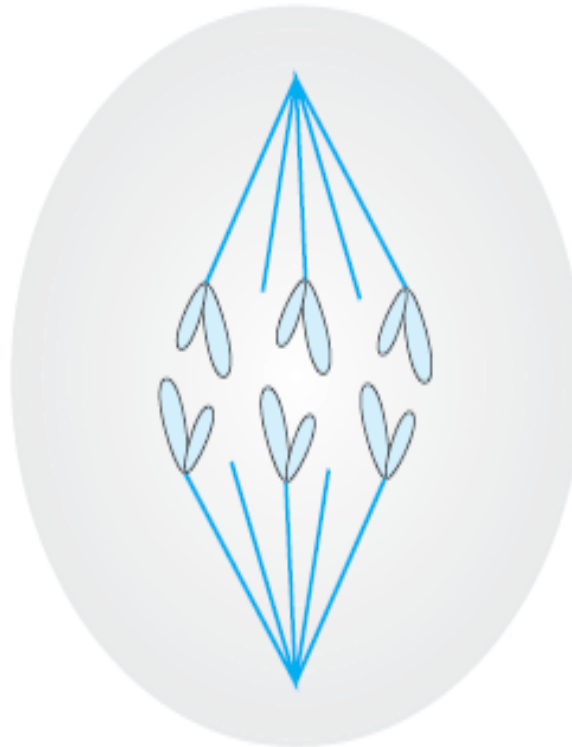
Microtubules
of mitotic spindle

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.**
- **They are widely used in the treatment of solid carcinomas and leukaemias and lymphomas.**

INHIBITORS OF TUBULIN POLYMERISATION

- **Vinblastine therapeutic Uses include Systemic Hodgkin's disease Lymphomas**
- **Vincristine is used against lymphomas, breast cancer, sarcomas, and the various childhood neoplasms.**
- **Vincristine used With prednisone for remission of Acute Leukemia**

Toxicity of the Vinca alkaloids

- **Vinblastine main toxicity is Nausea & Vomiting, Bone Marrow depression, and Alopecia**
- **While Vincristine is relatively non-toxic, generally having mild myelosuppressive activity but cause they cause sensory changes and neuromuscular abnormalities fairly frequently.**

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 depolymerisation. (mitotic spindle poison)
- The taxanes are generally more toxic than the Vinca alkaloids and side-effects include myelosuppression and Peripheral neuropathy.
- Taxol has proven beneficial in late-stage drug-resistant ovarian and breast cancers, prolonging life by about 6 months.
- Dec pica ad more

Asparaginase

- **Asparaginase (L-asparagine amidohydrolase) is an enzyme that is isolated from various bacteria for clinical use.**
- **The drug is used to treat childhood acute lymphocytic leukemia.**
- **It hydrolyze circulating L-asparagine to aspartic acid and ammonia. Because tumor cells lack asparagine synthetase, they require an exogenous source of L-asparagine.**
- **Thus, depletion of L-asparagine results in effective inhibition of protein synthesis. (normal cells can synthesize L-Asparagine)**
- **The main side effect of this agent is a hypersensitivity reaction manifested by fever, chills, nausea and vomiting, skin rash, and urticaria.**

Treatment results in ALL

- **Adults**
 - Complete remission (CR) 80-85%
 - Leukemia-free survival (LFS) 30-40%
- **Children**
 - Complete remission (CR) 95-99%
 - Leukemia-free survival (LFS) 70-80%

Chemotherapy for acute leukemias

- Phases of ALL treatment
 - induction
 - intensification
 - CNS prophylaxis
 - maintenance
- } post-remission therapy

Induction

four to six weeks:

- Vincristine
- Glucocorticoid (prednisone, prednisolone or dexamethasone)
- L-asparaginase
- Anthracycline?????

In children with standard-risk ALL, such intensive induction therapy may actually increase morbidity and mortality and they standardly receive triple therapy with either anthracycline or asparaginase.

Consolidation

- Once normal haematopoiesis is achieved, patients undergo **Consolidation** therapy.
- Common regimens in childhood ALL include:
 1. **Methotrexate with mercaptopurine**
 2. High-dose asparaginase over an extended period
 3. Reinduction treatment (a repetition of the initial induction therapy in the first few months of remission).

Maintenance

- Maintenance usually consists
 1. weekly methotrexate and
 2. daily mercaptopurine.
- 2-3 years

CNS prophylaxis

- Patients with ALL frequently have meningeal leukaemia at the time of relapse (50-75% at one year in the absence of CNS prophylaxis) and a few have meningeal disease at diagnosis (<10%).
- Intrathecal (methotrexate, cytarabine, steroids)
- **and for adult high-dose systemic chemotherapy (methotrexate, cytarabine, L-asparaginase)**

Hormonal Agents

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graph TD; HA[Hormonal Agents] --> EAI[Estrogen & Androgen Inhibitors]; HA --> GRHAG[Gonadotropin-Releasing Hormone Agonists]; HA --> AI[Aromatase Inhibitors]; EAI --> T[Tamoxifen]; GRHAG --> L[Leuprolide]; AI --> A[aminogluthethimide];
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**Estrogen & Androgen
Inhibitors**

Tamoxifen

**Gonadotropin-Releasing
Hormone Agonists**

Leuprolide

Aromatase Inhibitors

Aminogluthethimide

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
- Patients with estrogen-receptor (ER) positive tumors are more likely to respond to tamoxifen therapy, while the use of tamoxifen in women with ER negative tumors is still investigational
- When used prophylactically, tamoxifen has been shown to decrease the incidence of breast cancer in women who are at high risk for developing the disease
- **It is active orally and is therefore particularly useful in maintenance therapy.**
- Hot flashes, Fluid retention, nausea.

HORMONE ANTAGONISTS

- **ANTIANDROGENS** such as Flutamide bind to androgen receptors and are effective in the treatment of prostate cancer.
- **Aromatase inhibitors** decrease the production of estrogens.

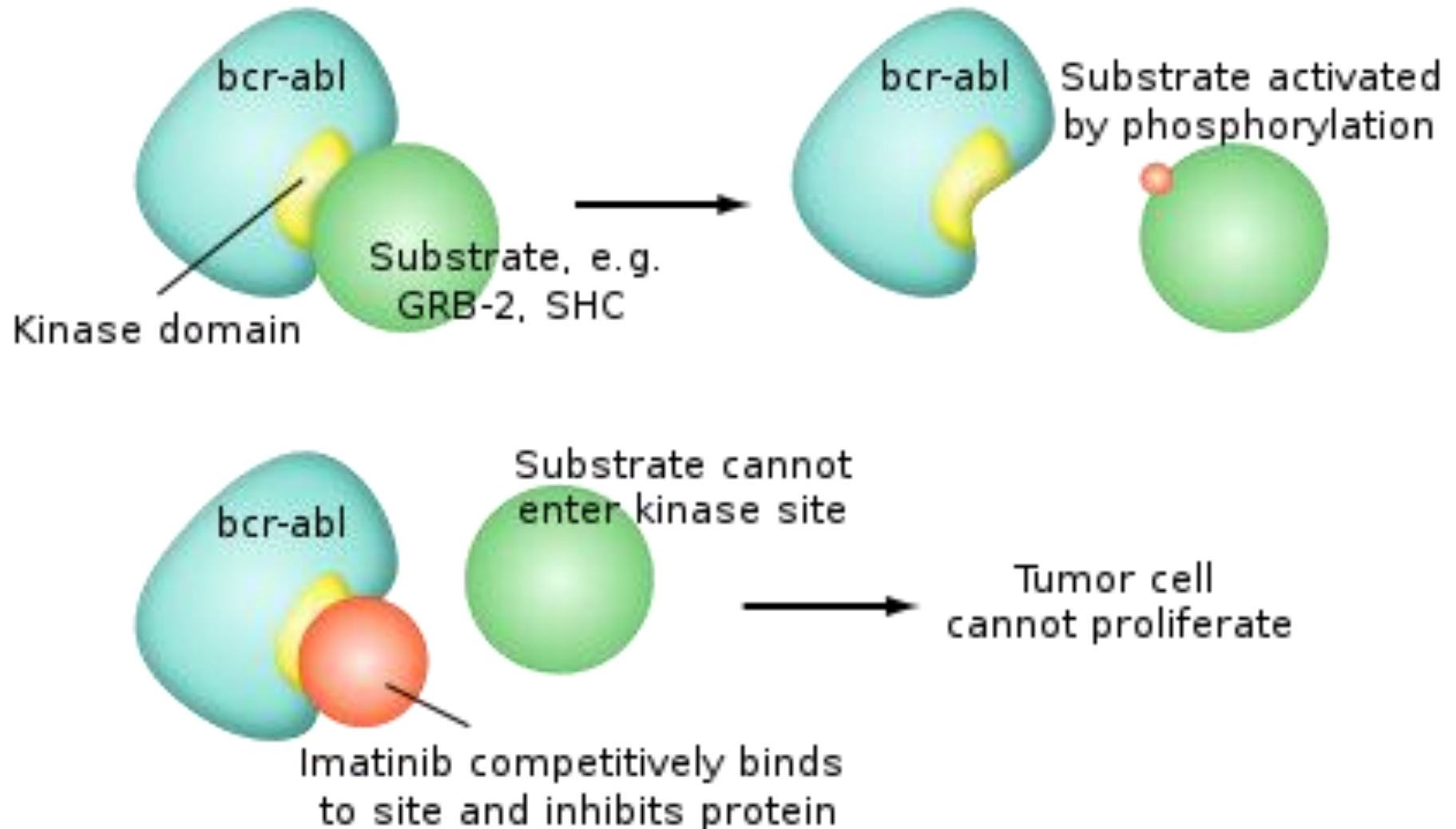
aminoglutethimide is an example that inhibit hydrocortisone synthesis.

Anastrozole is the newer agent that have less problem

- 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.

Imatinib

- **Philadelphia chromosome** or **Philadelphia translocation** is a specific chromosomal abnormality that is associated with chronic myelogenous leukemia (CML).
- This translocation results in the Bcr-Abl fusion protein, the causative agent in CML, and is present in up to 95% of patients with this disease.
- Imatinib is an inhibitor of the tyrosine kinase domain of the Bcr-Abl oncoprotein and prevents the phosphorylation of the kinase substrate by ATP.



Gleevec is one of the most effective modern medications for cancer treatment,.

Types	Name	Trade Name	Target	Indication
Small Molecules	Imatinib (STI-571)	Gleevec	Tyrosine Kinase bcr-abl	CML GIST DFP
	Gefitinib (ZD1839)	Iressa	TK Her1 (ErbB-1)	NSCLC
	Erlotinib	Tarceva	TK	NSCLC
	Bortezomib	Velcade	Proteasome	MM
Monoclonal Antibodies	Rituximab (antiCD20)	MabThera	CD20, antibody-dependent cellular cytotoxicity & complement-mediated cytotoxicity	NHL
	Trastuzumab (anti-HER2)		TK Her2(ErbB-2)	CA Breast
	Cetuximab	Erbitux	EGFR, antibody-dependent cellular cytotoxicity	CA Colon H&N Cancer
	Bevacizumab	Avastin	VEGF	CA Colon CA Breast NSCLC

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

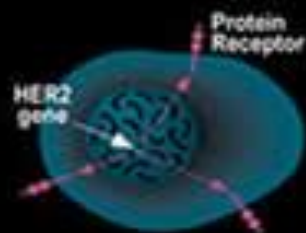
More common side effects of Are:

high blood pressure

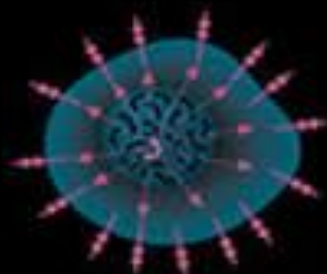
- tiredness/weakness
- clots in veins
- diarrhea

Trastuzumab

- **HER2 (epidermal growth factor receptor family) is overexpressed in 25% to 30% of breast cancers**
- **Trastuzumab is an anti-HER2 monoclonal antibody for HER2-positive metastatic breast cancer treatment**
- **Approved for adjuvant treatment of HER2-positive breast cancer (in combination with doxorubicin, cyclophosphamide, and paclitaxel) in 2006**



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.