Anti-cancer Drugs

principles

- **objective**
  - to prolong **useful** life – not cure
- **treatment**
  - surgery
  - radiotherapy
  - chemotherapy
  - (euthanasia)

indications

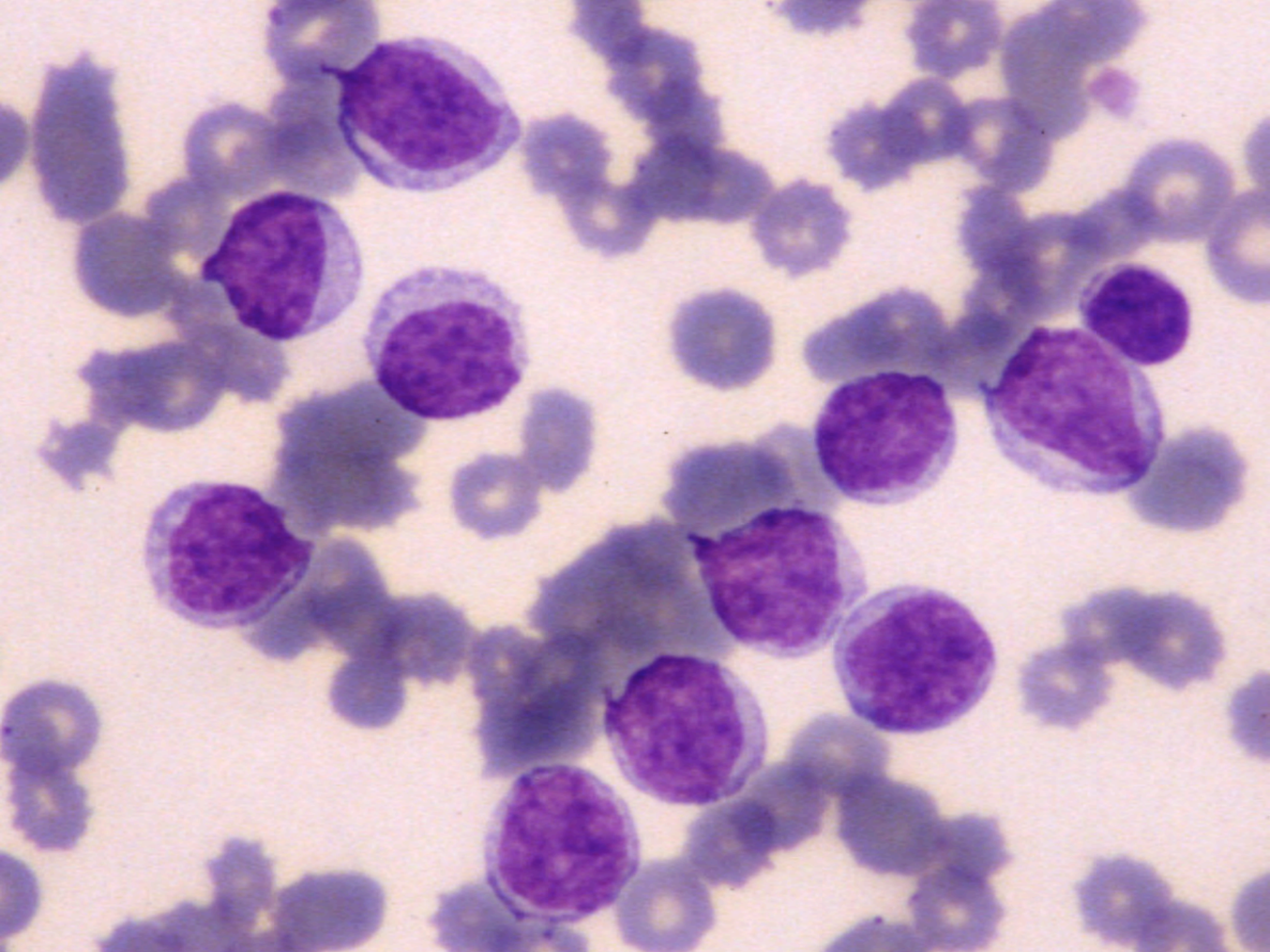
- **non resectable tumours**
  - generalised
  - metastatised
- **delay metastasis**
- **adjunct to surgery**
- **treating relapses**

7 yr old Boxer

- swollen submandibular lymph nodes
- anorexia
- weight loss
- lethargy

further tests

- **bloods**
  - haematology
  - biochemistry
- **lymph node biopsy**



lymphoma treatment

- 38 protocols for dogs published
- all empirical
- no comparative trials
- combinations
  - increase effectiveness
  - reduce side effects

COP protocol

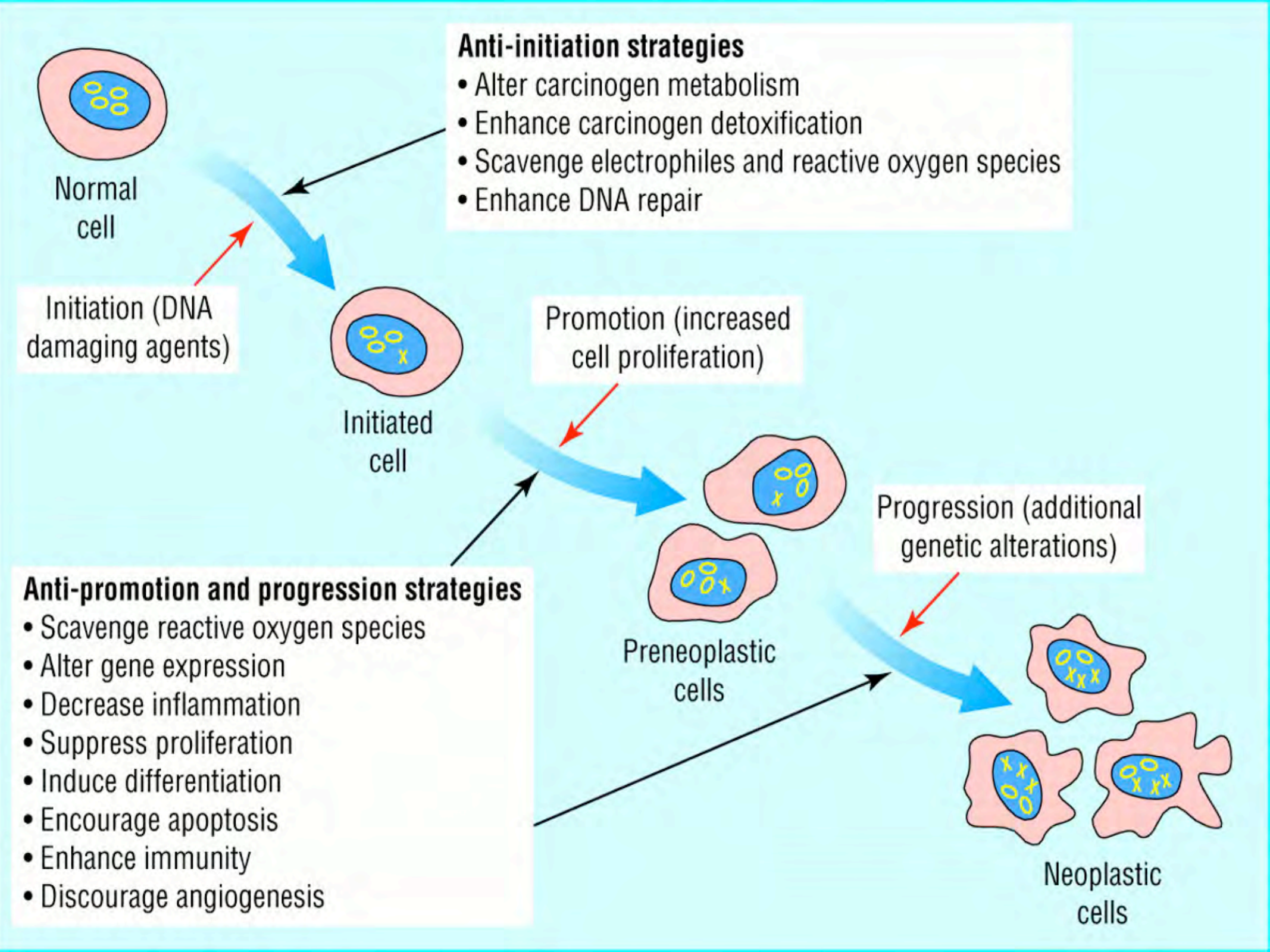
- cyclophosphamide
- vincristine (Oncovin)
- prednisolone

induction

- cyclophosphamide 50mg/m² 4d
- vincristine 0.7mg/m² iv once
- prednisolone 1mg/kg twice daily
- repeat for 8 weeks

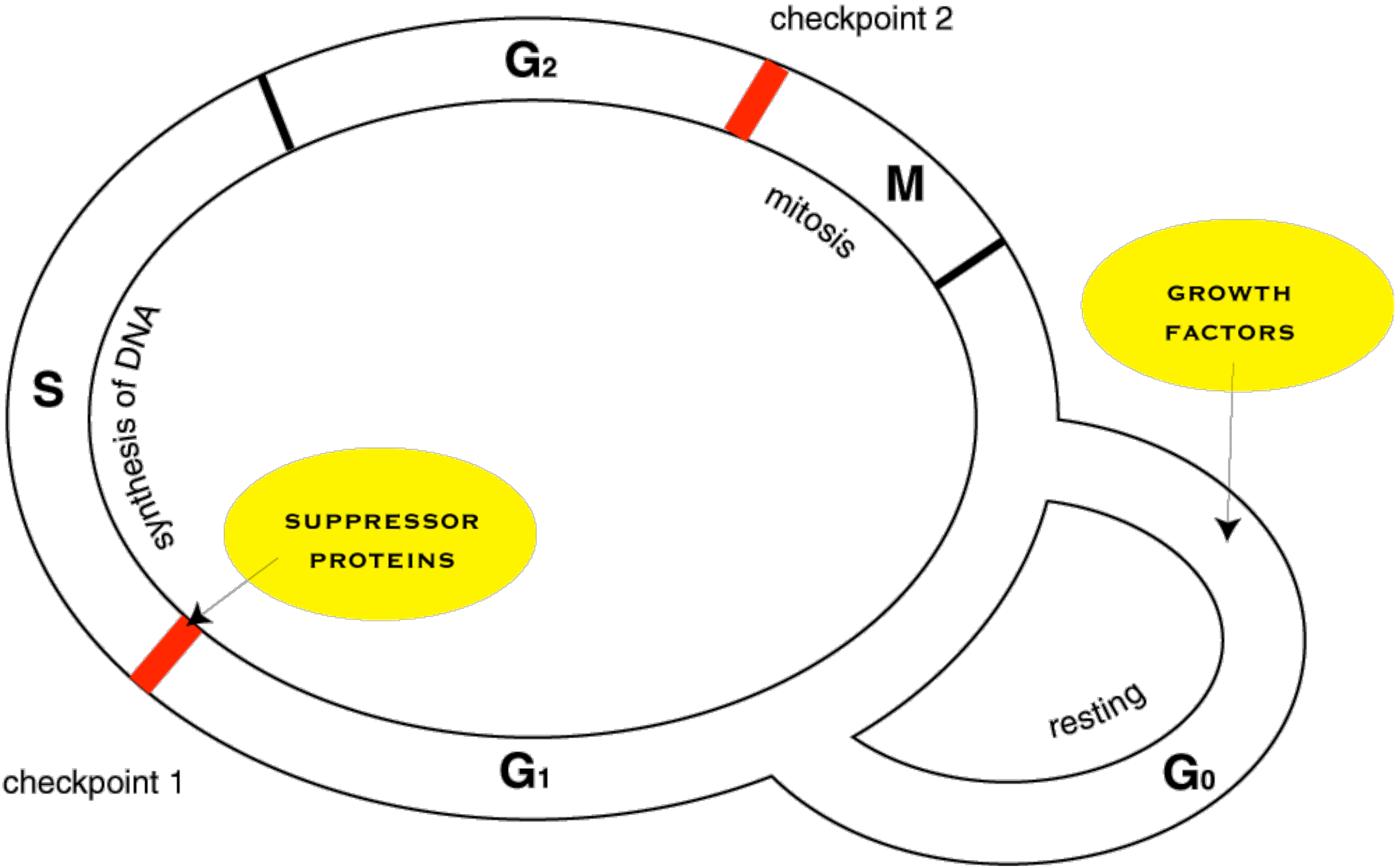
maintenance

- cyclophosphamide 50mg/m² every other day
- vincristine 0.5mg/m² iv every other week
- prednisolone 1mg/kg every other day of every other week


Anti-initiation strategies
• Alter carcinogen metabolism
• Enhance carcinogen detoxification
• Scavenge electrophiles and reactive oxygen species
• Enhance DNA repair
Normal cell
Initiation (DNA damaging agents)
Initiated cell
Promotion (increased cell proliferation)
Preneoplastic cells
Progression (additional genetic alterations)
Neoplastic cells
Anti-promotion and progression strategies
• Scavenge reactive oxygen species
• Alter gene expression
• Decrease inflammation
• Suppress proliferation
• Induce differentiation
• Encourage apoptosis
• Enhance immunity
• Discourage angiogenesis

cancer cells

- **inactivation of tumour suppressor genes**
  - mutation?
- **activation of oncogenes**
  - viruses
  - mutation
  - translocation
  - inflammation???


checkpoint 2
G2
M
mitosis
S
synthesis of DNA
GROWTH
FACTORS
SUPPRESSOR
PROTEINS
resting
checkpoint 1
G1
G0

cancer cells

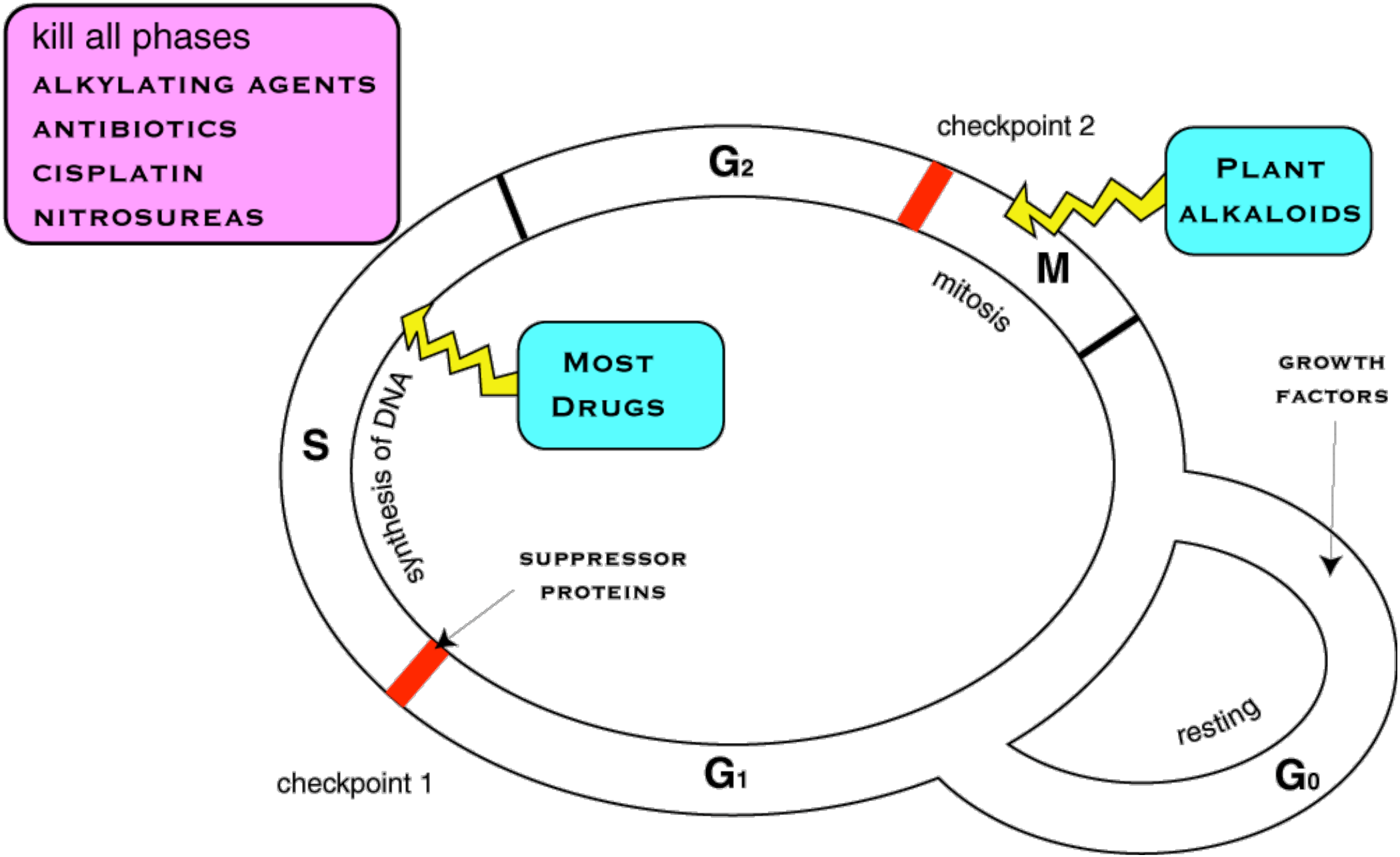
- **uncontrolled proliferation**
- **loss of function**
  - lack of differentiation
- **invasiveness**
  - new blood supply
- **metastases**

cancer cells

- **very similar / the same as normal cells**
  - interference with apoptosis
  - telomerase

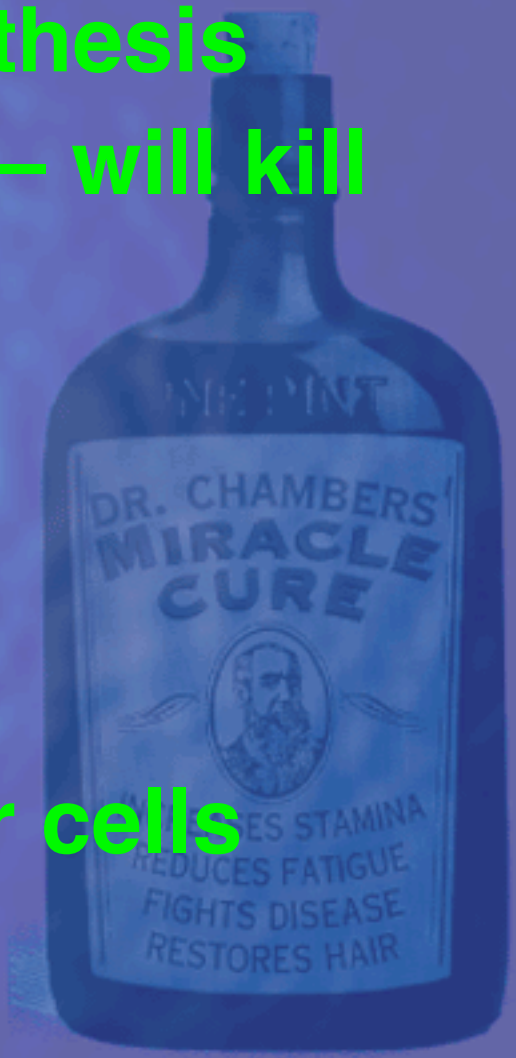
drug strategies

- **interfere with DNA**
  - apoptosis
- **interfere with mitosis**
- **interfere with blood supply**
  - angiogenesis inhibitors
    - MMP inhibitors
    - FGF inhibitors


kill all phases
ALKYLATING AGENTS
ANTIBIOTICS
CISPLATIN
NITROSUREAS
checkpoint 2
G2
PLANT ALKALOIDS
M
mitosis
MOST DRUGS
S
synthesis of DNA
GROWTH FACTORS
SUPPRESSOR PROTEINS
resting
checkpoint 1
G1
G0

general actions of drugs

- most interfere with DNA synthesis
- not specific for cancer cells – will kill any rapidly dividing cells
  - bone marrow
  - gut mucosa
  - germ cells
  - hair follicles
- not possible to kill all cancer cells
- normal cells recover faster



general side effects

- vomiting and diarrhoea
- bone marrow suppression
- alopecia
- impaired wound healing
- sterility
- teratogenesis
- plus specific side effects

dosage

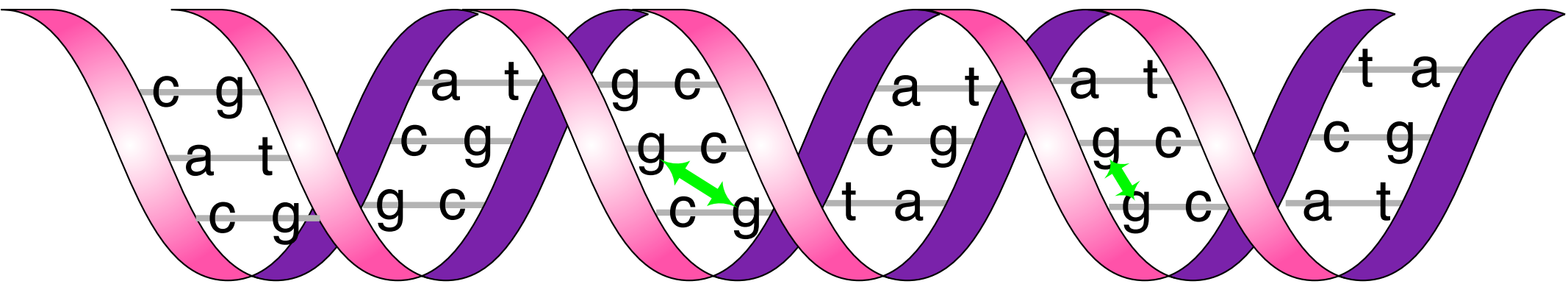
- body surface area

$$= \frac{W^{0.67}}{10} \; m^2$$

drugs

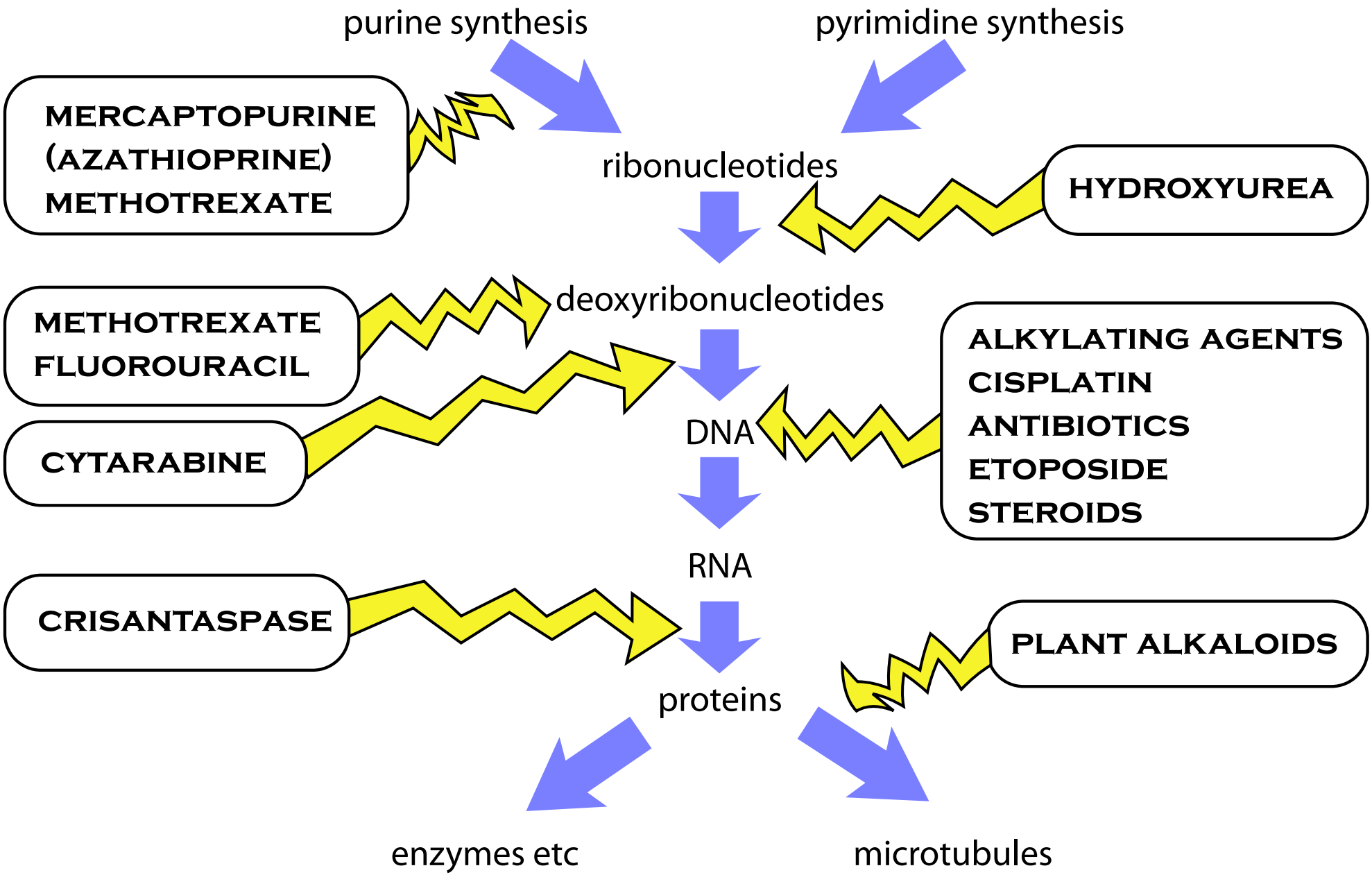
- alkylating agents
- antimetabolites
- cytotoxic antibiotics
- plant alkaloids
- sex hormones / antagonists
- odds & ends

alkylating agents



alkylating agents

- **nitrogen mustards**
  - cyclophosphamide
  - chlorambucil
  - melphalan
- **similar to alkylating agents**
  - cisplatin
  - carboplatin
  - nitrosureas


purine synthesis
pyrimidine synthesis
MERCAPTOPURINE
(AZATHIOPRINE)
METHOTREXATE
ribonucleotides
HYDROXYUREA
METHOTREXATE
FLUOROURACIL
deoxyribonucleotides
ALKYLATING AGENTS
CISPLATIN
ANTIBIOTICS
ETOPOSIDE
STEROIDS
CYTARABINE
DNA
RNA
CRISANTASPASE
PLANT ALKALOIDS
proteins
enzymes etc
microtubules

antimetabolites

- **folate antagonists**
  - methotrexate
- **pyrimidine analogues**
  - fluorouracil
  - cytarabine (cytosine arabinoside)
- **purine analogues**
  - mercaptopurine (azathioprine)
  - thioguanine

antibiotics

- doxorubicin
- bleomycin
- dactinomycin

plant alkaloids

- vincristine
- vinblastine
- taxol (paclitaxel)
- etoposide

sex hormones

- **oestrogens**
  - ethinyloestradiol
- **anti-androgens**
  - delmadinone
  - (GnRH analogues)
- **anti-oestrogens**
  - tamoxifen

others

- crisantaspase (asparaginase)
- mitotane
- radioactive iodine

drug resistance

- **many mechanisms**
  - P glycoprotein
- **use combinations**
- **not usually treated in veterinary medicine**

protocols

- usually combinations
- large doses with intervals?
- supportive therapy
- monitor side effects

supportive therapy

- **analgesics**
  - NSAIDs
- **anti-emetics**
  - ondansetron
  - metaclopramide
- **appetite stimulants**
  - diazepam
- **anabolic steroids**

the future???

- angiogenesis inhibitors
- specific cell targetting – MCA
- oncogene antisense oligonucleotides
- oncogene transduction blockers
- suppressor gene therapy
- telomerase inhibitors
- exogenously sensitised lymphocytes

handling drugs

- wear protective clothing – gloves & mask
- use fume cupboard for mixing drugs
- avoid spillage or leaks
- avoid breaking tablets up
- dispose of faeces and urine by burning
- pregnant women should not handle drugs / animals being treated
- keep animals away from children

handling drugs

- OSH guidelines cover vet use
- buy injections already made up
- hospitalise animals

anti-cancer drugs

- seek advice before using and check latest protocol
- remember the aim is to prolong **useful** life
- handle drugs with great care