

# 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

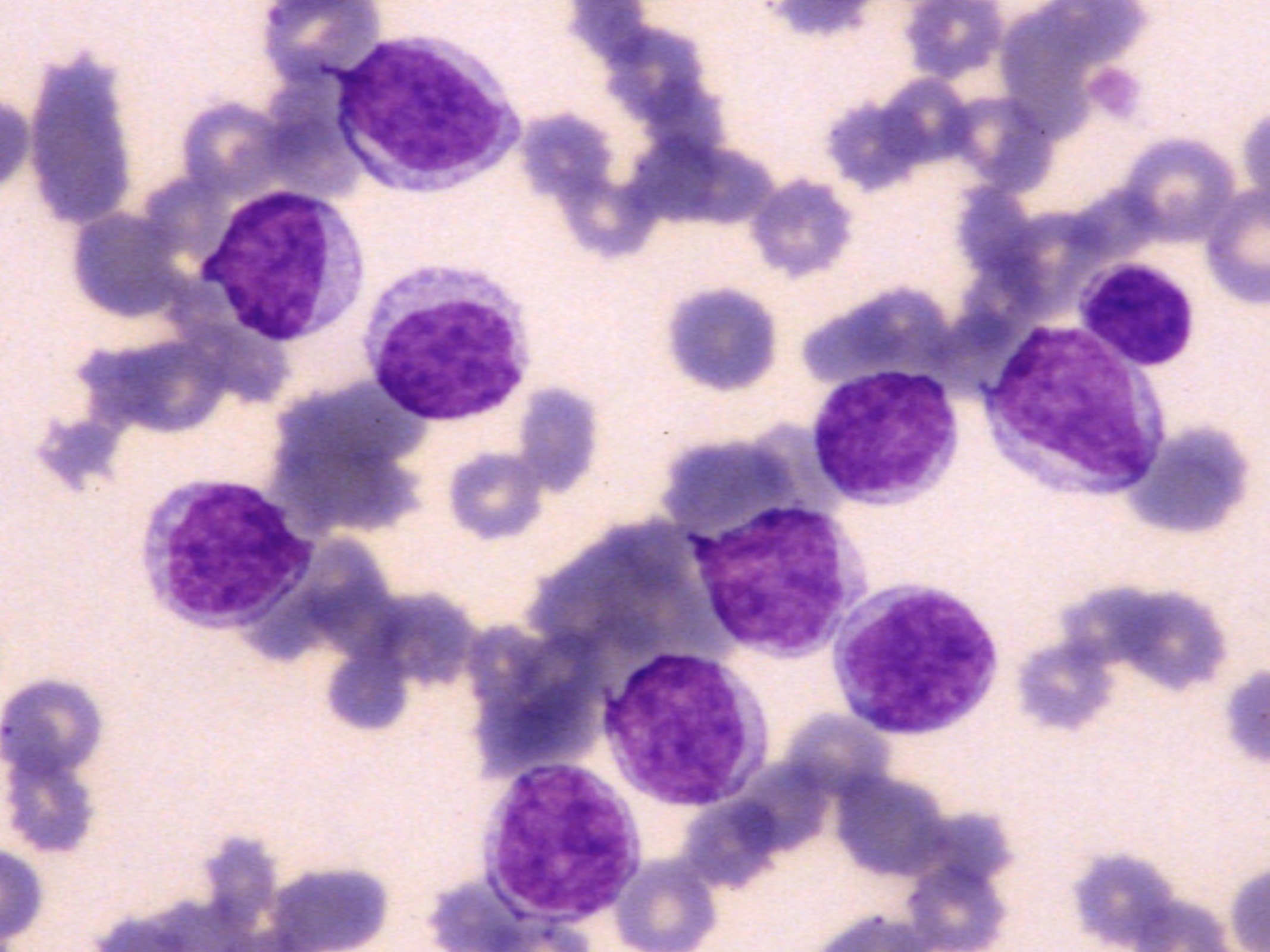




# further tests

- **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

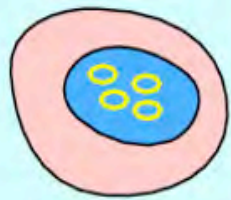
- cyclophosphamide 50mg/m<sup>2</sup> 4d
- vincristine 0.7mg/m<sup>2</sup> iv once
- prednisolone 1mg/kg twice daily
- repeat for 8 weeks



# maintenance

- cyclophosphamide  $50\text{mg}/\text{m}^2$  every other day
- vincristine  $0.5\text{mg}/\text{m}^2$  iv every other week
- prednisolone  $1\text{mg}/\text{kg}$  every other day of every other week





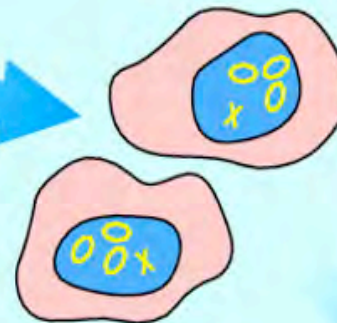
Normal cell

Initiation (DNA damaging agents)



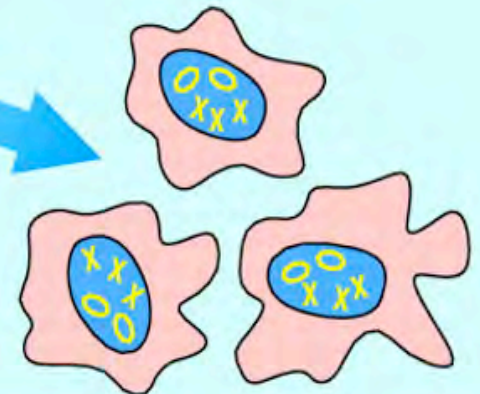
Initiated cell

Promotion (increased cell proliferation)



Preneoplastic cells

Progression (additional genetic alterations)



Neoplastic cells

### Anti-initiation strategies

- Alter carcinogen metabolism
- Enhance carcinogen detoxification
- Scavenge electrophiles and reactive oxygen species
- Enhance DNA repair

### Anti-promotion and progression strategies

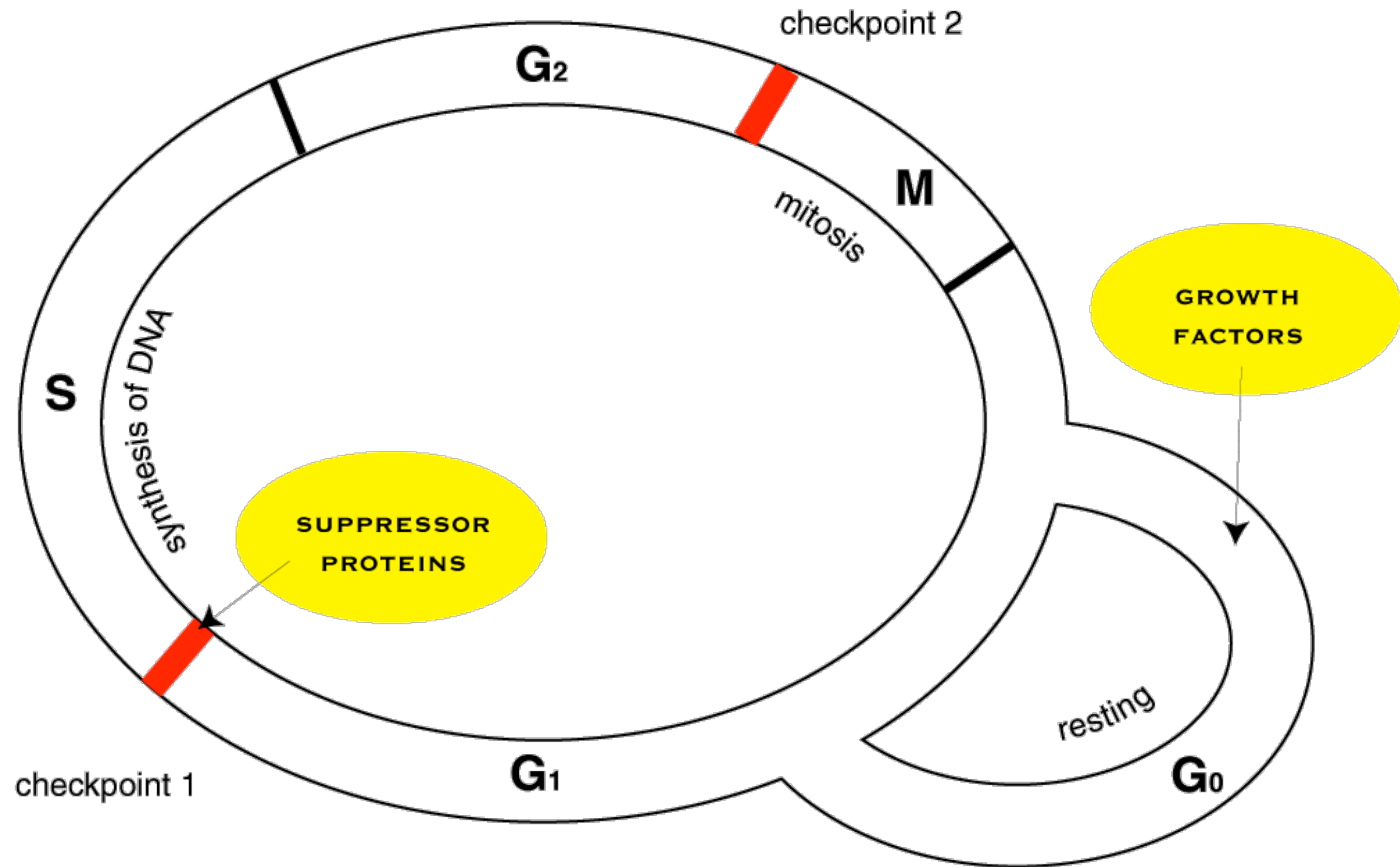
- Scavenge reactive oxygen species
- Alter gene expression
- Decrease inflammation
- Suppress proliferation
- Induce differentiation
- Encourage apoptosis
- Enhance immunity
- Discourage angiogenesis



# cancer cells

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





# 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



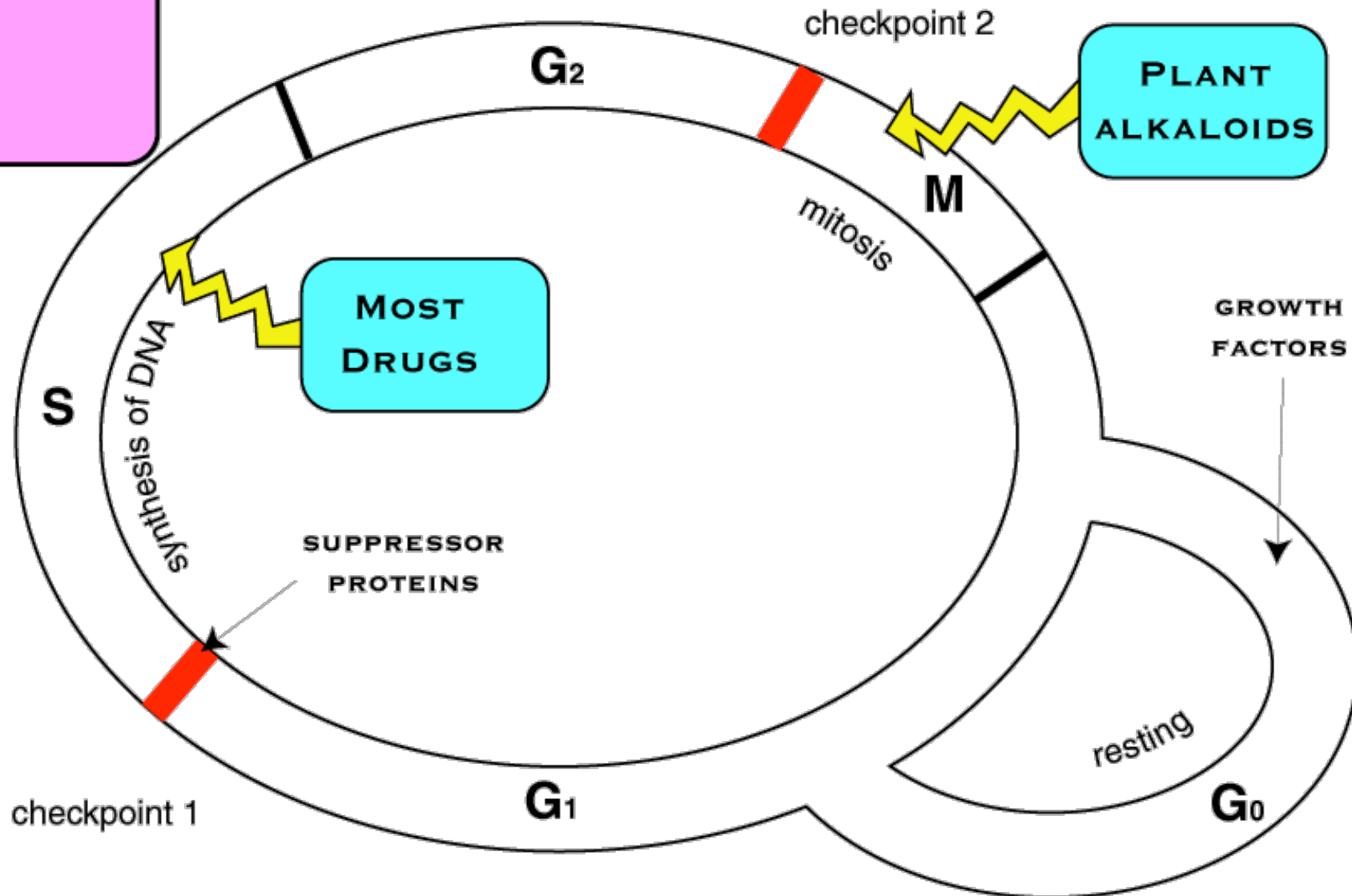
kill all phases

ALKYLATING AGENTS

ANTIBIOTICS

CISPLATIN

NITROSUREAS





# 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

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



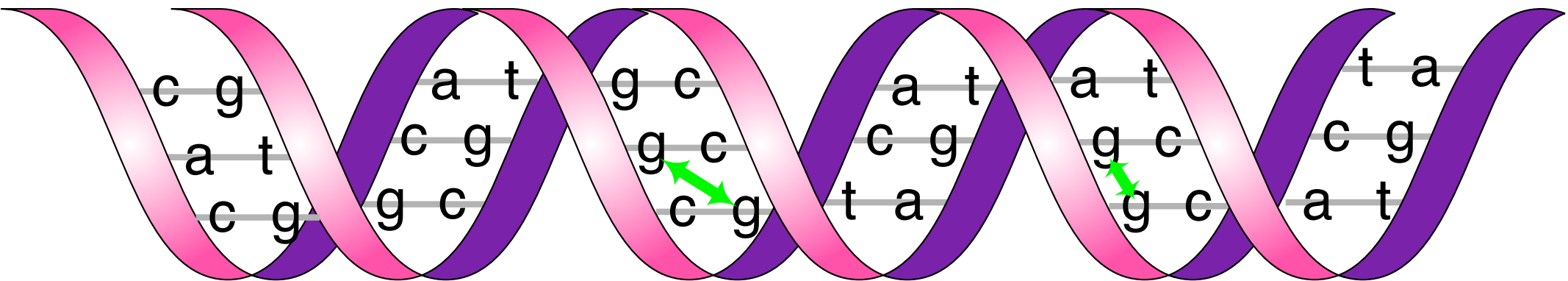


# drugs

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



# alkylating agents



# alkylating agents

- **nitrogen mustards**

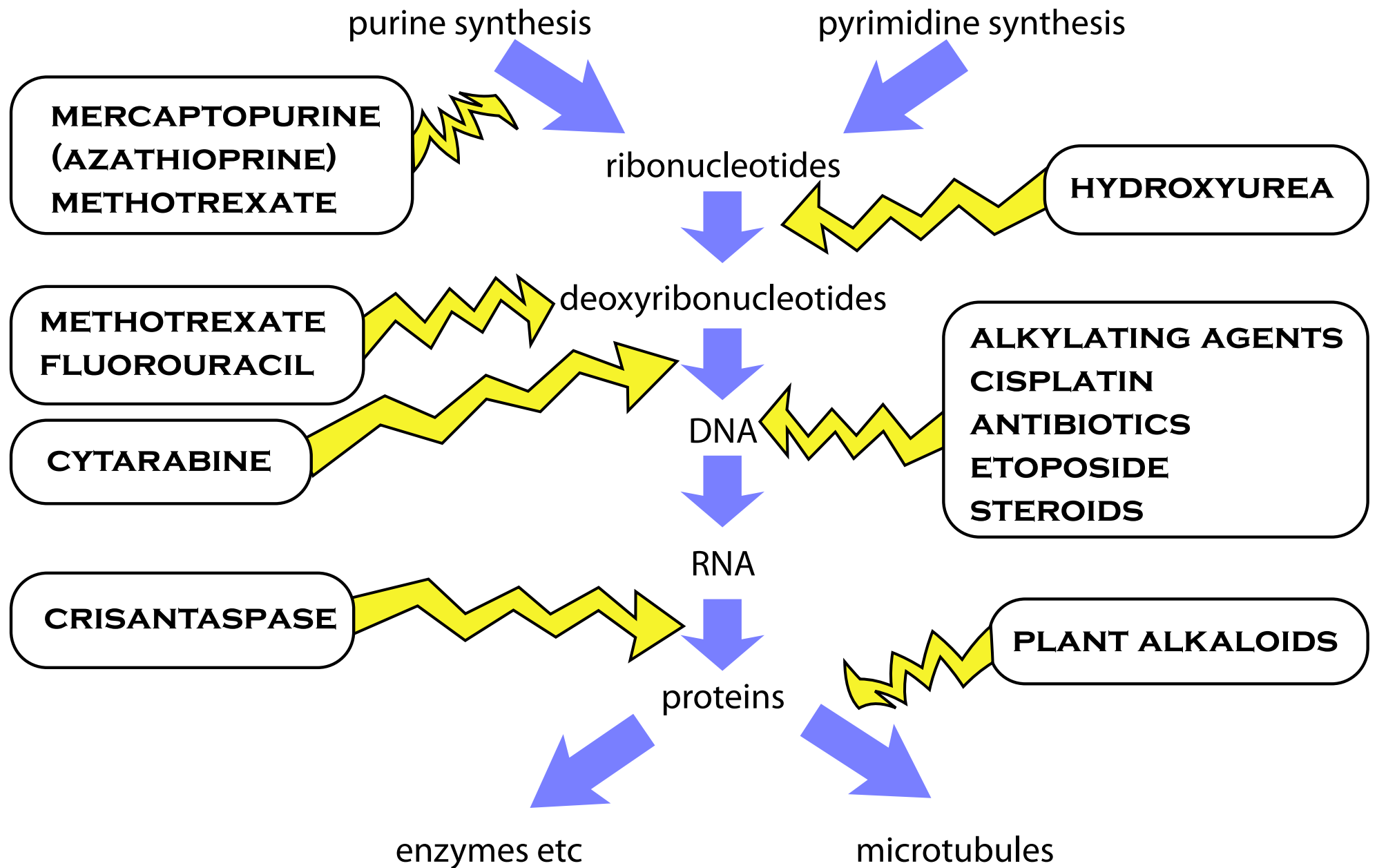
- cyclophosphamide
- chlorambucil
- melphalan

- **similar to alkylating agents**

- cisplatin
- carboplatin
- nitrosureas







# 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 targeting – 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

