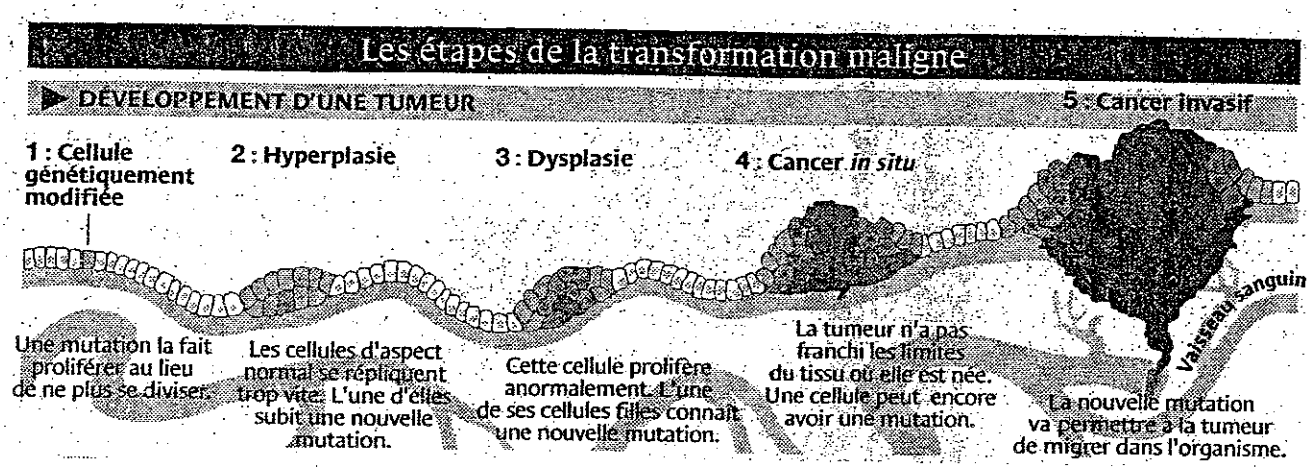
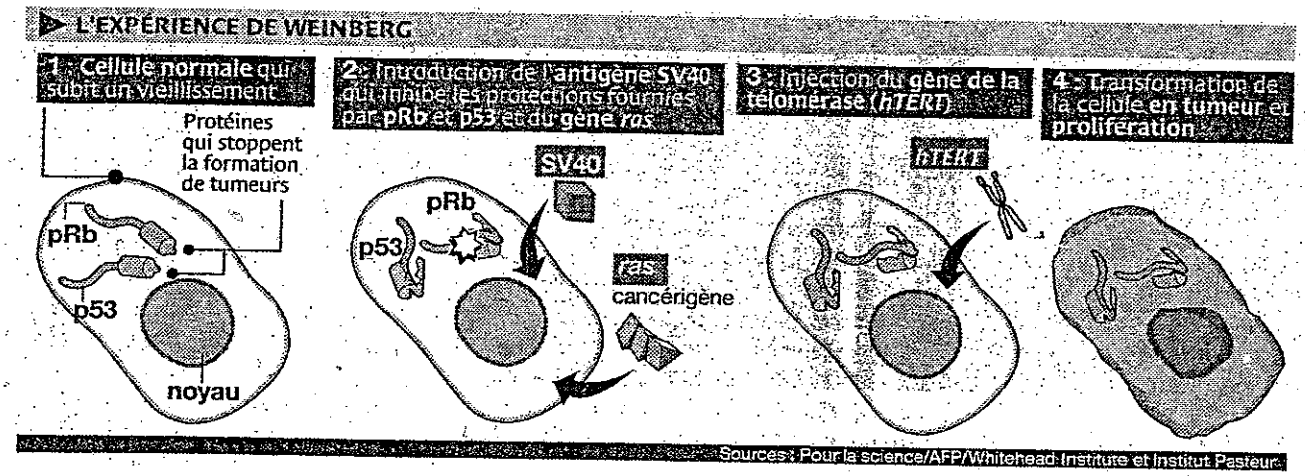
(Rang.)

Cancer cell biology and cancer chemotherapy: general principles

- The term 'cancer' refers to a malignant neoplasm (new growth).
- Cancer cells can manifest:
  - —uncontrolled proliferation
  - —loss of function due to lack of the capacity to differentiate
  - —invasiveness
  - —the ability to metastasise.
- Cancer arises as a result of a series of genetic changes in the cell, the main genetic lesions being:
  - —inactivation of tumour suppressor genes
  - —the activation of oncogenes.
- Most anticancer drugs are antiproliferative and will also affect rapidly dividing normal cells; they are thus likely to depress bone marrow, impair healing, depress growth, cause sterility and hair loss, and be teratogenic. Most cause nausea and vomiting.





(Article original : Nature 400 : 464-468, 1999)

1: *Semin Cancer Biol* 2000 Dec;10(6):399-406 Related Articles, Books, LinkOut

Telomerase and human tumorigenesis.

Stewart SA, Weinberg RA

Whitehead Institute for Biomedical Research, 9 Cambridge Center, Massachusetts Institute of Technology, Cambridge, MA 02142, USA

[Record supplied by publisher]

Human cancer cells, unlike their normal counterparts, have shed the molecular restraints to limited cell growth and are immortal. Exactly how cancer cells manage this at the molecular level is beginning to be understood. Human cells must overcome two barriers to cellular proliferation. The first barrier, referred to as senescence, minimally involves the p53 and Rb tumor-suppressor pathways. Inactivation of these pathways results in some extension of lifespan. However, inactivation of these pathways is insufficient for immortalization. As normal cells undergo repeated rounds of DNA replication, their telomeres shorten due to the inability of traditional DNA polymerases to completely replicate the end of the chromosomal DNA. This shortening continues until the cells reach a second proliferative block referred to as crisis, which is characterized by chromosomal instability, end-to-end fusions, and cell death. Stabilization of the telomeric DNA through either telomerase activation or the activation of the alternative mechanism of telomere maintenance (ALT) is essential if the cells are to survive and proliferate indefinitely. Conversely, loss of telomere stabilization by an already-immortalized cell results in loss of immortality and cell death. Together this indicates that telomere maintenance is a critical component of immortality. In this review we attempt to describe our current understanding of the role of telomere maintenance in senescence, crisis, and tumorigenesis. Copyright 2000 Academic Press.

PMID: 11170862

Display Abstract Save Text Order Add to Clipboard

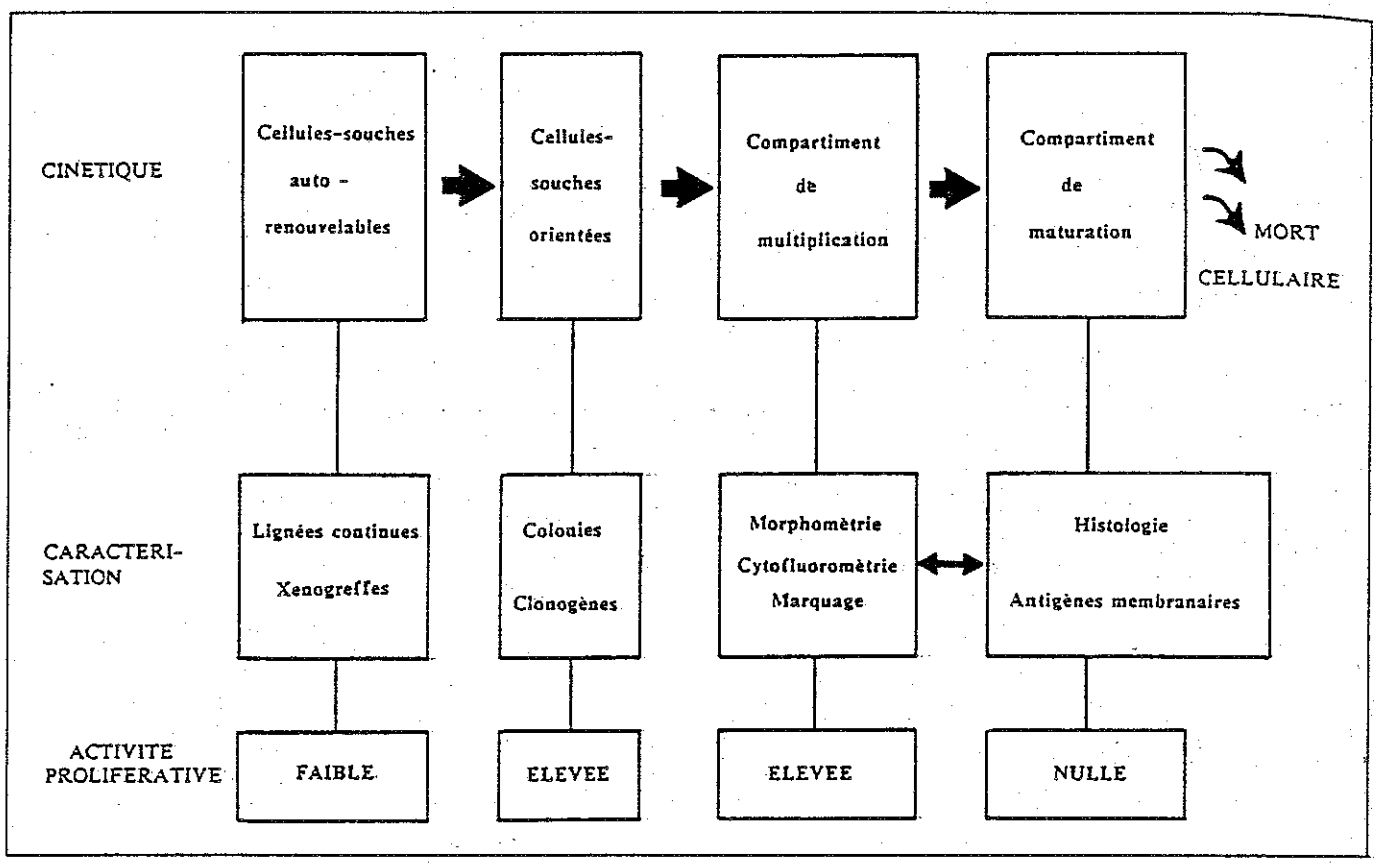


Figure 1. Cinétique, caractérisation et activité prolifération des cellules et tissus cancéreux.

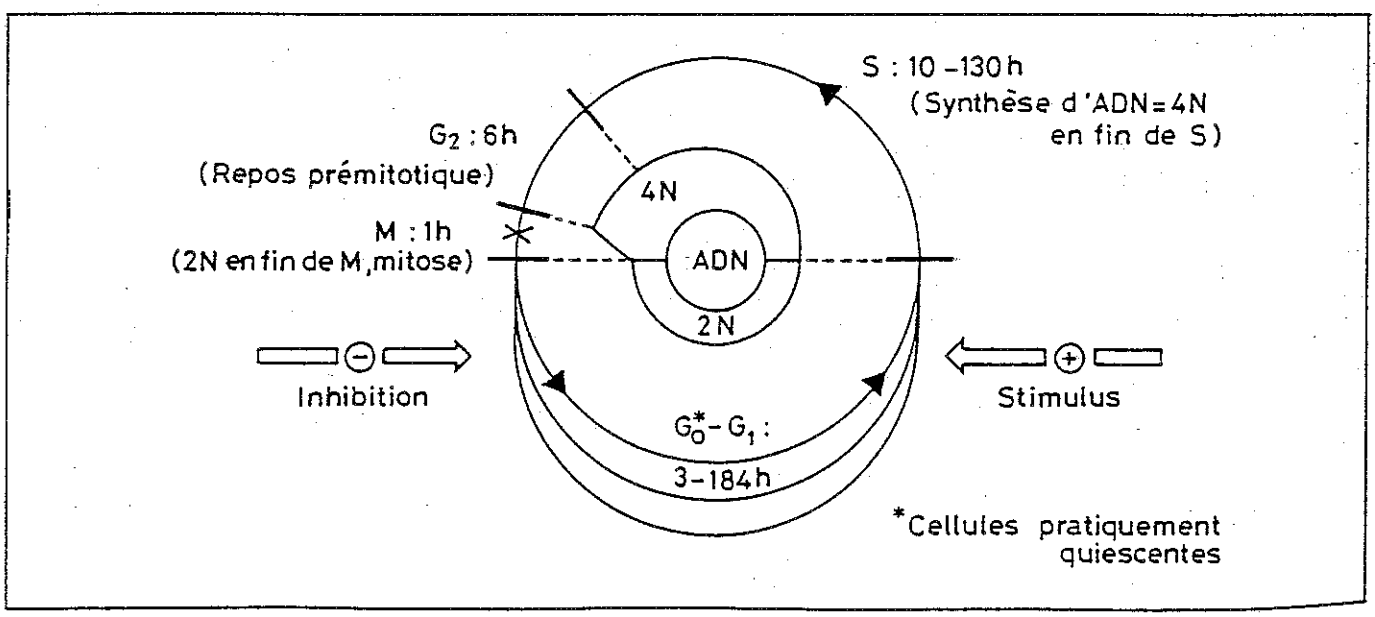


Figure 2. Schéma et phases du cycle cellulaire des cellules cancéreuses.

(Rang)

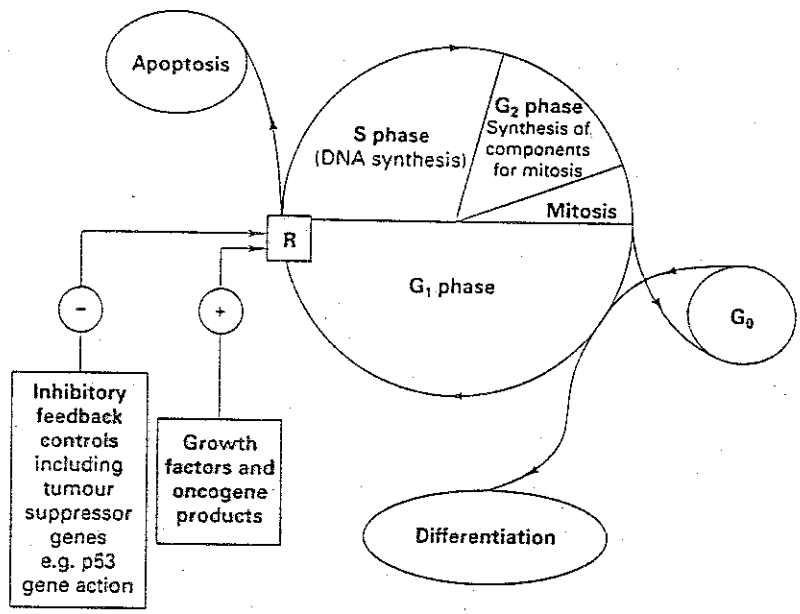


Fig. 36.1 The cell cycle. A dividing cell starts in G_1 phase, tooling up for DNA synthesis. R = a restriction point or check point. Progression signals, provided by growth factors, are necessary for the cycle to progress beyond the check point. Inhibitory feedback controls hold up DNA synthesis if there is DNA damage, allowing time for repair. If repair fails, apoptosis (cell suicide) may occur. In cancer cells there is (1) abnormally increased growth factor function and/or abnormal DNA synthesis as a result of oncogene activity and/or (2) abnormal decrease in feedback control due to functional disturbance of tumour suppressor genes. G_0 represents a phase in which cells are not dividing but can re-enter the cell cycle. As a cell differentiates, it leaves the cycle.

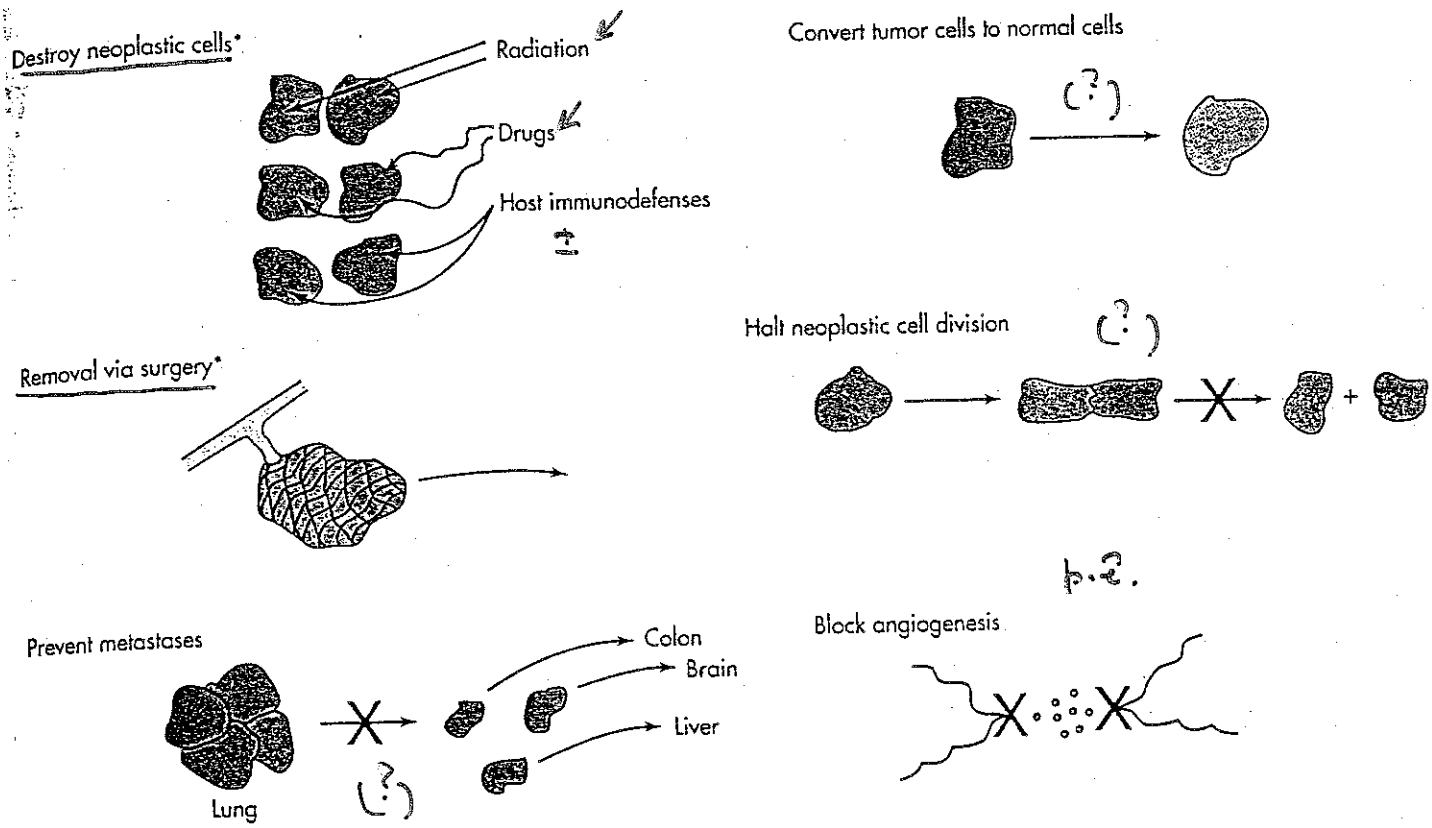


FIGURE VI-1 Major approaches to therapy of cancers. Tumor cells are shown in red and non-tumor cells in green. *In clinical use. Others are experimental.

gators attempt to utilize this information to design "rational" regimens for chemotherapy. A simplified overview of the sites of action of many of the drugs described in Chapter 55 is shown in Figure XIII-1.

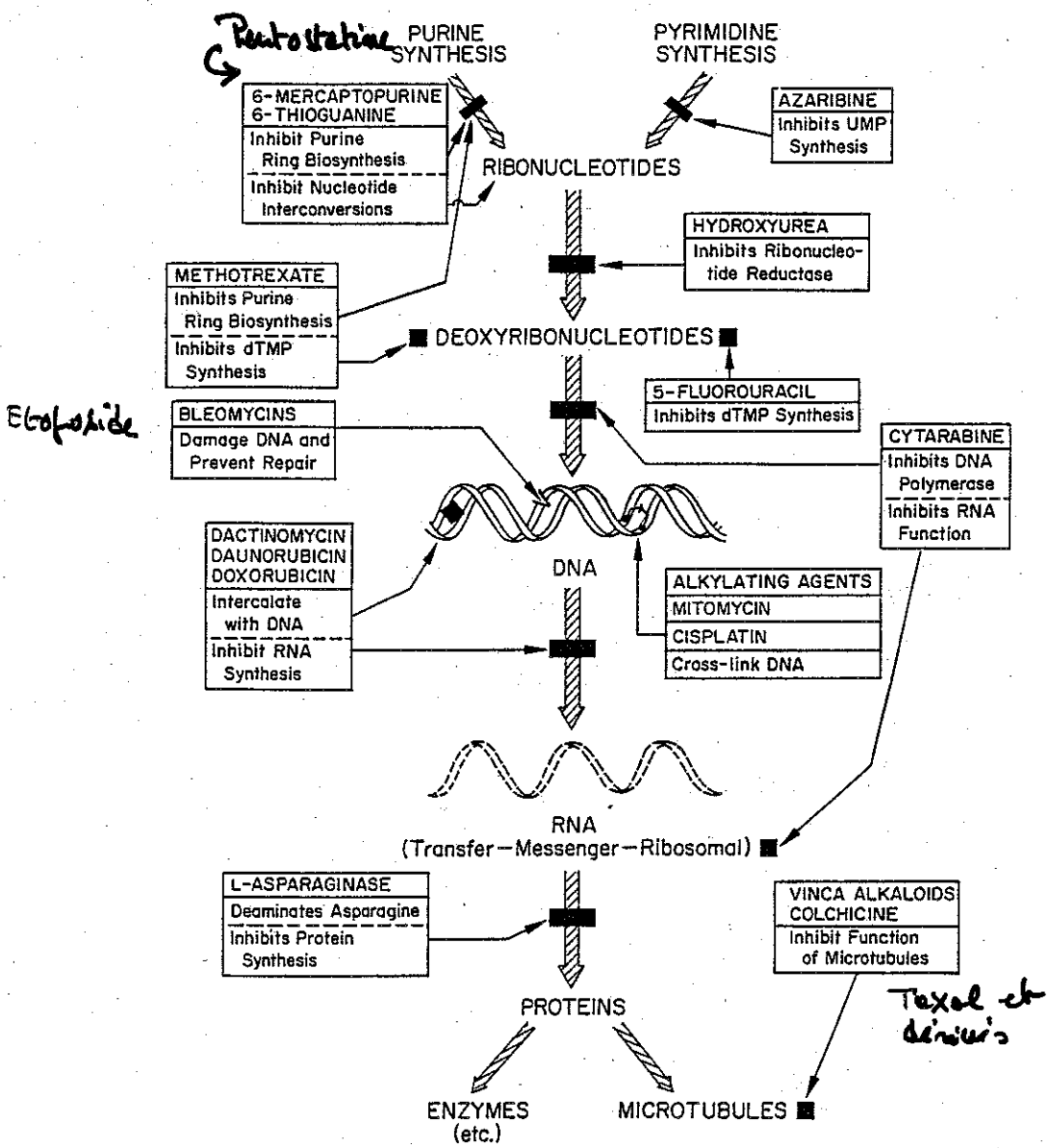


Figure XIII-1. *Summary of the mechanisms and sites of action of chemotherapeutic agents useful in neoplastic disease.*

(Brody)

Box 45-1 Primary Antineoplastic Drugs

ALKYLATING AGENTS

Nitrogen mustards
- Mechlorethamine HCl (nitrogen mustard, HN_2, HCl)
- Melphalan (L-phenylalanine [L-PAM])
- Chlorambucil
- Cyclophosphamide
- Ifosfamide

Nitrosoureas
- Carmustine (BCNU)
- Lomustine (CCNU)

Other
- Cisplatin (*cis*-diamminedichloroplatinum)
- Carboplatin (Paraplatin)
- Busulfan
- Dacarbazine (DTIC)
- Procarbazine
- Triethylenethiophosphoramide (thio-TEPA)

ANTIMETABOLITES

Methotrexate (MTX)
Mercaptopurine (6-MP)
Thioguanine (6-TG)
Fluorouracil (5-FU)
Gemcitabine (2^1, 2^1-difluorodeoxycytidine [dFd])

ANTIMETABOLITES—cont'd

Cytarabine (cytosine arabinoside [Ara-C])
Pentostatin (2-deoxycoformycin)

ANTIBIOTICS

Daunorubicin (daunomycin)
Doxorubicin (Adriamycin)
Bleomycin
Dactinomycin (actinomycin D)
Mitomycin
Plicamycin (mithramycin)

HORMONAL AGENTS

Prednisone
Tamoxifen
Flutamide
Leuprolide
Goserelin

OTHERS

Asparaginase
Hydroxyurea

PLANT ALKALOIDS

Vincristine
Vinblastine
Etoposide (VP-16)
Teniposide (VM-26)
Taxol (paclitaxel)
Topotecam (Hycamtin)

(Rouge)

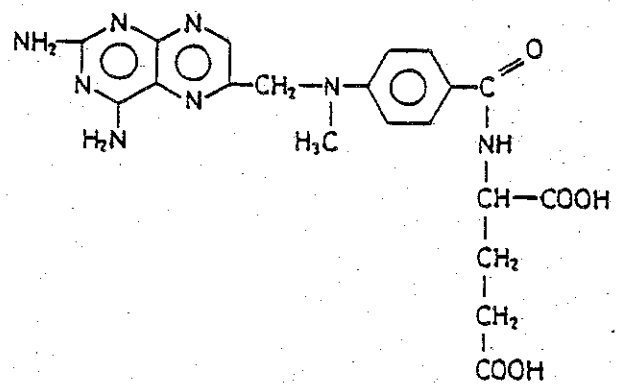
Résumé...

Anticancer drugs: antimetabolites

- These drugs block or subvert pathways in DNA synthesis.
- *Folate antagonists:* **Methotrexate** inhibits dihydrofolate reductase, preventing generation of tetrahydrofolate; the main result is interference with thymidylate synthesis. Methotrexate is taken up into cells by the folate carrier, and, like folate, converted to the polyglutamate form. Given orally. Normal cells affected by high doses can be 'rescued' by folinic acid.
  Unwanted effects: myelosuppression, possible nephrotoxicity.
- *Pyrimidine analogues:* **Fluorouracil**, given orally or intravenously, is converted to a fraudulent nucleotide and inhibits thymidylate synthesis. **Cytarabine**, given intravenously or subcutaneously; its triphosphate form inhibits DNA polymerase; potent myelosuppressive.
- *Purine analogues:* **Mercaptopurine**, given orally, is converted into a fraudulent nucleotide.

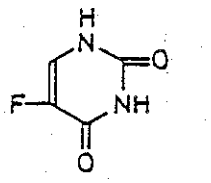
Figure 4. Structures chimiques des antimétaboliques (DCI)

3.1. **Antifolique**

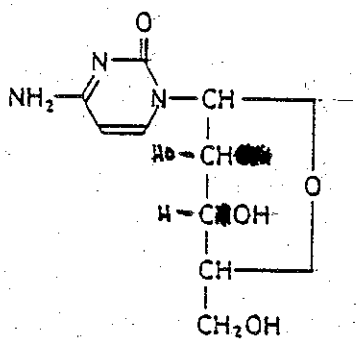


méthotrexate*

3.2. **Antipyrimidines**

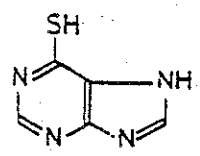


fluorouracil*

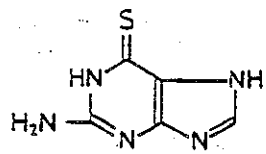


cytarabine*

3.3. **Antipurines**



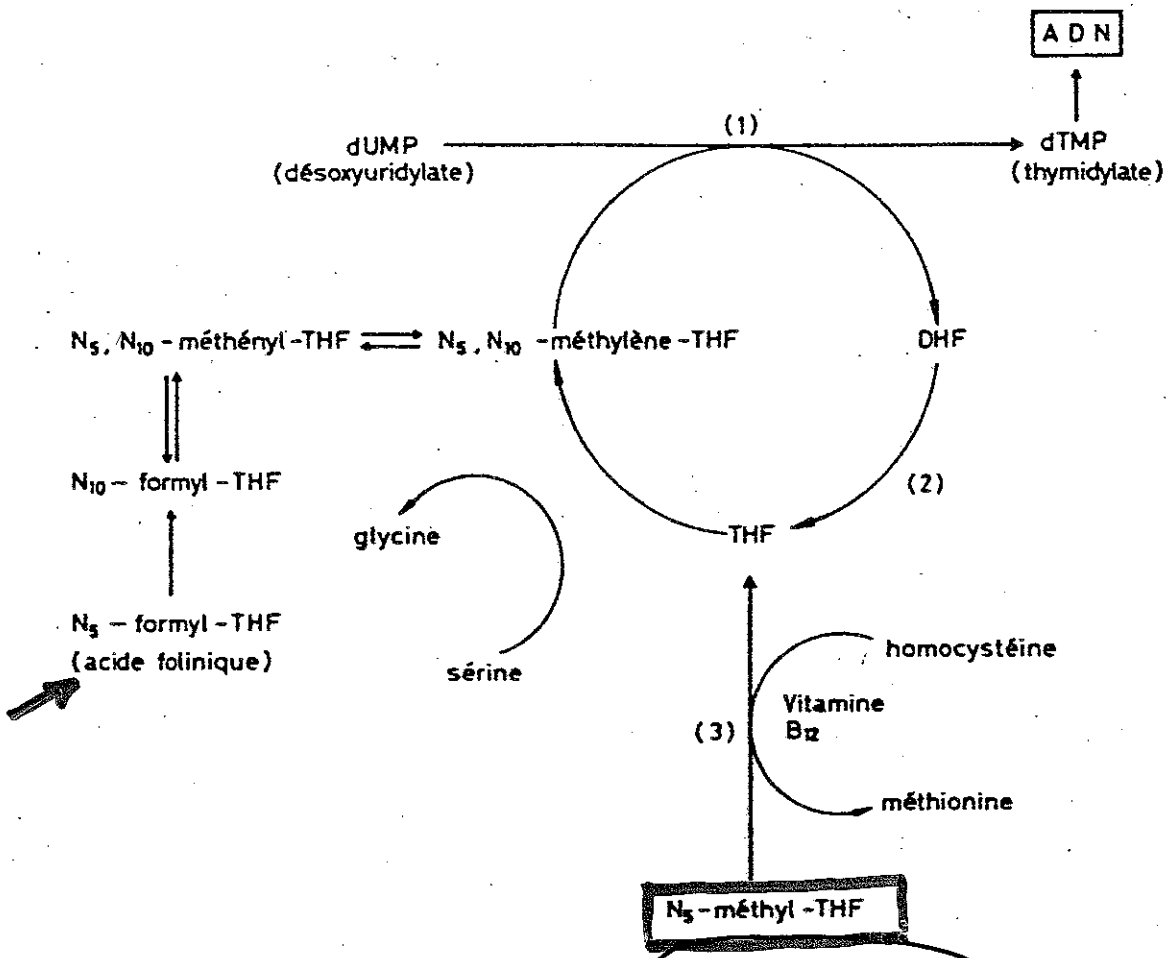
mercaptopurine*



tioguanine*

* Cf. Tableau 13 pour les noms de Spécialités (B, CH, F) et les présentations.

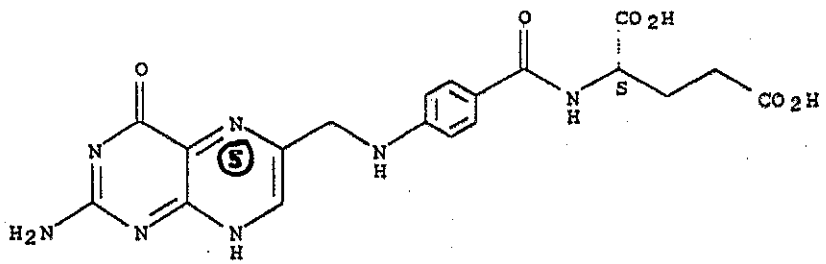
Figure 3. Rôles métaboliques et synthétiques (ADN) des folates en relation avec la vitamine B_{12}



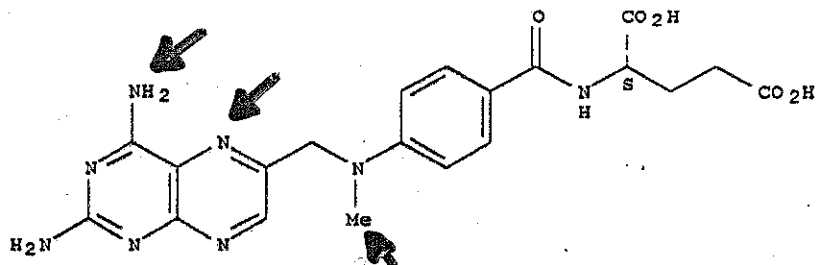
Enzymes: (1) thymidylate-synthétase
(2) dihydrofolate-réductase
(3) méthionine-synthétase

Folates:	**Actions:**
N_5-méthyl-THF	synthèse de la méthionine
N_5, N_{10}-méthylène-THF	synthèse de thymidylate
	conversion sérine-glycine
N_{10}-formyl-THF	synthèse des purines
N_5, N_{10}-méthényl-THF	synthèse des purines
N_5-formyl-THF (acide folinique)	conversion en formes actives

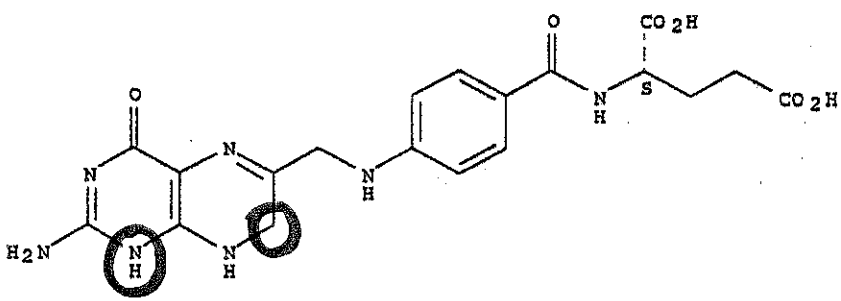
Acides foliques et agent antifolique



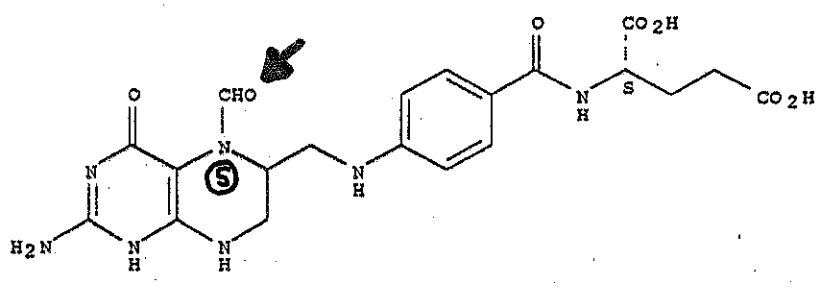
acide folique



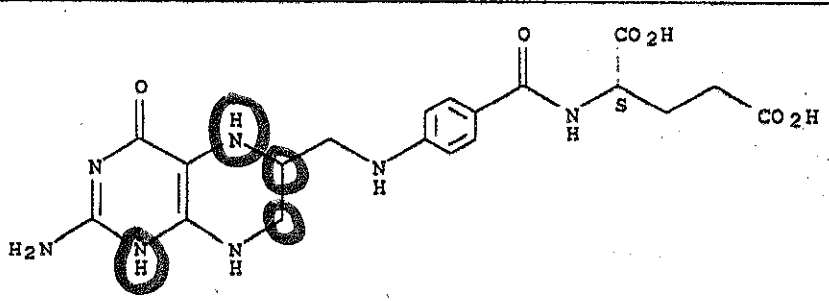
methotrexate



acide dihydofolique



acide folinique



acide tétrahydrofolique

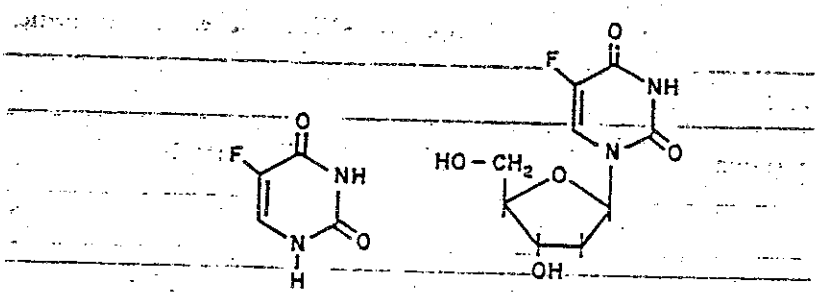


Fig. 18. Structure du fluoro-uracile et de son désoxynucléoside, la fluoxuridine.

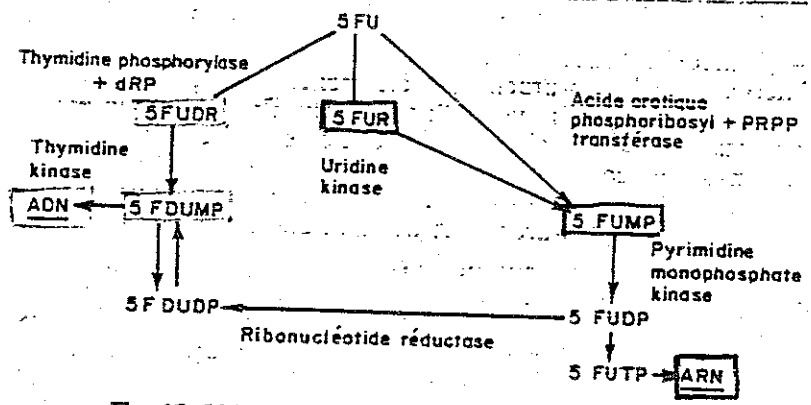
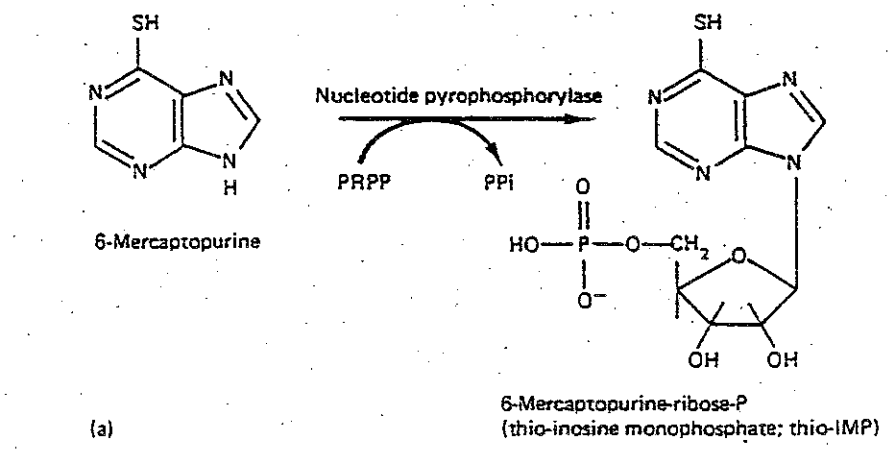


Fig. 19. Mécanisme d'action du fluoro-uracile (5 FU).



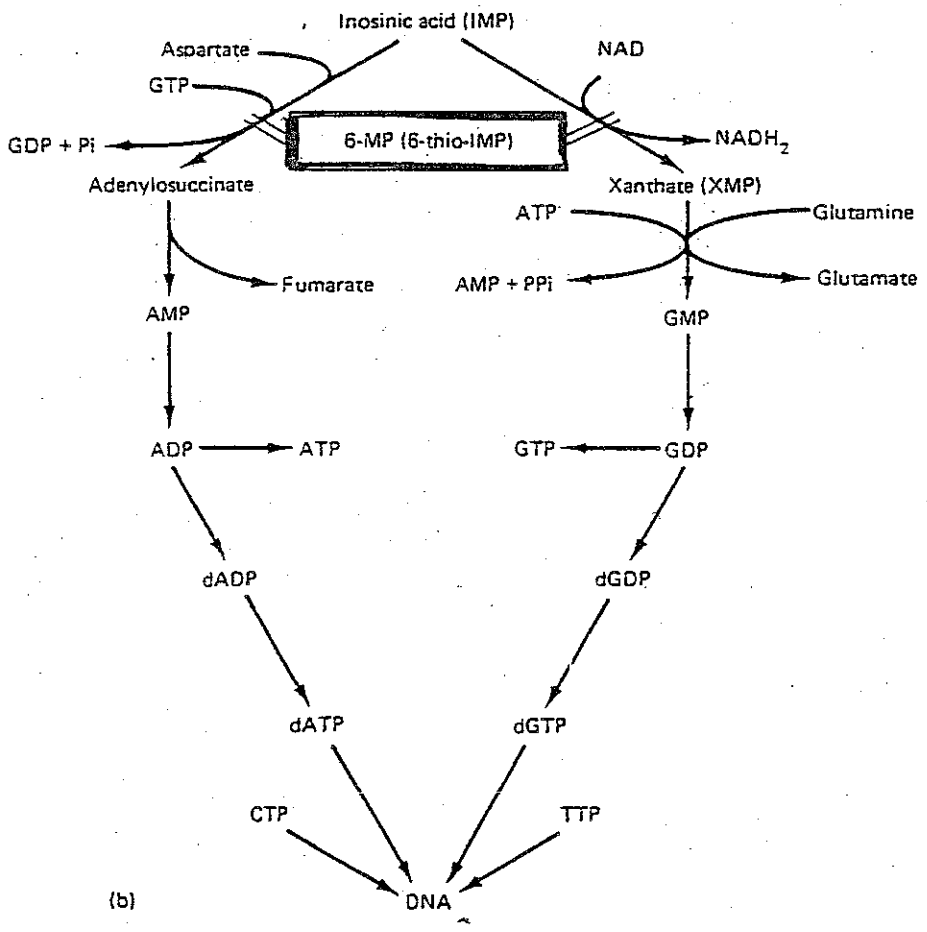
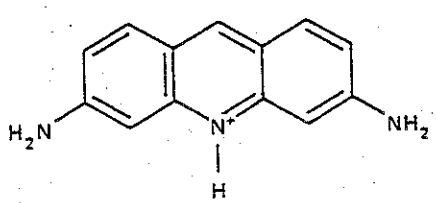


Figure 13.12 Action of 6-mercaptopurine as a purine biosynthesis inhibitor. (a) Conversion to thio-IMP; (b) inhibition of purine biosynthesis.

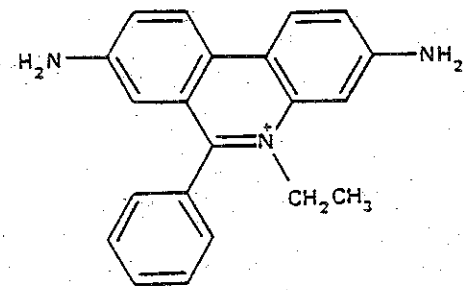
Anticancer drugs: cytotoxic antibiotics

- **Doxorubicin** inhibits DNA and RNA synthesis; the DNA effect is due to interference with topoisomerase II action. Given by intravenous infusion, it is excreted mainly in bile.
  Unwanted effects: nausea and vomiting, myelosuppression, hair loss; it is cardiotoxic in high doses.
- **Bleomycin** causes fragmentation of DNA chains. It can act on non-dividing cells. Given by injection.
  Unwanted effects: fever, allergies, mucocutaneous reactions, pulmonary fibrosis. Virtually no myelosuppression.
- **Dactinomycin** intercalates in DNA, interfering with RNA polymerase and inhibiting transcription. It also interferes with the action of topoisomerase II. Given by injection.
  Unwanted effects: nausea and vomiting, myelosuppression.
- **Mitomycin** is activated to give an alkylating metabolite. Given intravenously.

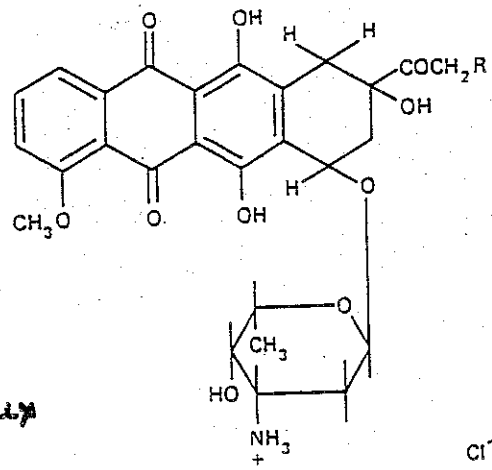
Les agents intercalants sont ⟨ anticancéreux ⊕ antibiotiques



Proflavine



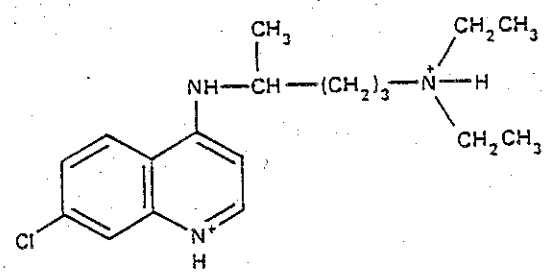
Ethidium



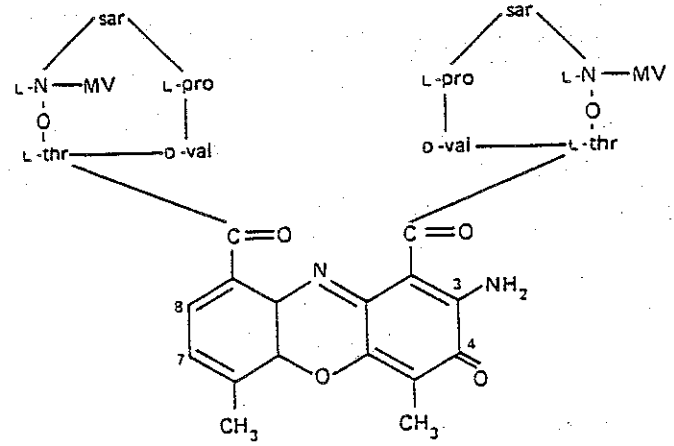
anticancéreux

→ R=H Daunomycin (rubidomycin)

→ R=OH Adriamycin



Chloroquine



Actinomycin D

Figure 8.1 Structures of intercalating drugs. Abbreviations: val = valine, pro = proline, sar = sarcosine, MV = *N*-methylvaline, thr = threonine.

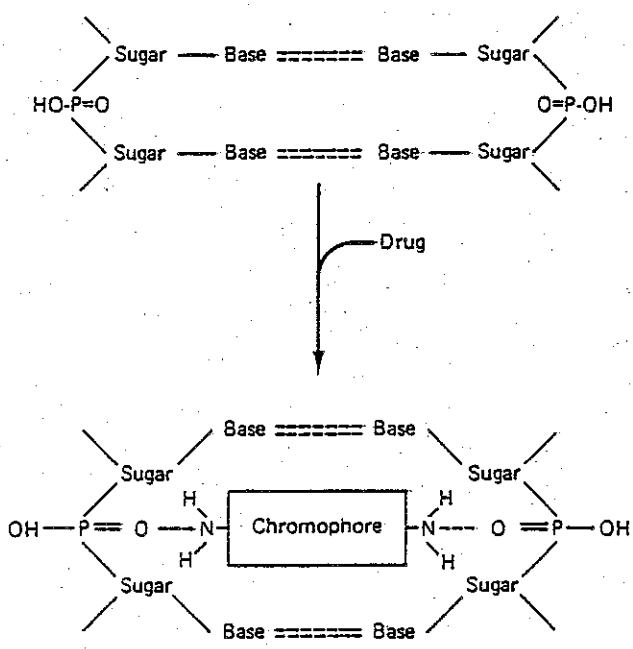


Figure 8.4 Binding of intercalators to DNA. Note that the intercalation of the drug is stabilised by hydrogen bonding between the amino groups of the drug and the phosphate groups of the backbone while the hydrophobic interaction of the drug chromophore and the bases increases as a result of the increased aromaticity of the drug. The distance between the NH_2 groups of acridines and ethidium is about 1 nm.

Tableau 6: Principales caractéristiques cinétiques des anthracyclines chez l'homme

Anthracyclines (DCI)	$T^1/_{t_\alpha}$ (min)	$T^1/_{t_\beta}$ (min)	$T^1/_{t_\omega}$ (h)	Clearance corporelle (L/h/m²)	Métabolites principaux
doxorubicine	5	60	30	20-24	doxorubicinol aglycones
daunorubicine	8-10	120-300	20	15-24	daunorubicinol aglycones
zorubicine	20	120-360	37	30-40	daunorubicine daunorubicinol
épirubicine	2-5	30-60	20-30	20-30	épirubicinol glucuroconjugués
aclarubicine	2-5	20	3	240	11 métabolites

Tableau 7: Principales toxicités aiguës des anthracyclines aux doses usuelles (doses utilisées dans le traitement des leucémies aiguës pour la daunorubicine, la zorubicine et l'aclarubicine)

Effets indésirables	doxorubicine	daunorubicine	zorubicine	épirubicine	aclarubicine
Myélosuppression	+ + +	+ + +	+ + +	+ +	+ + +
Vomissements	+ +	+ +	+	+	+
Alopécie	+ + +	+ + +	+ + +	+ +	—
Causticité	+ + +	+ + +	+ + +	+ + +	+
Cardiaques ✱					
Conduction	+/—	+/—	—	—	+ +
Rythme	—	—	—	—	+
Mucites	+ +	+ +	+	+	+ +
Hépatotoxicité	—	—	—	—	+

+ + + dénote un effet indésirable observé chez plus de 80% des malades traités;
+ + dénote un effet indésirable observé chez 50 à 80% des malades traités;
+ dénote un effet indésirable observé chez 25 à 50% des malades traités;
+/— dénote un effet indésirable observé chez moins de 25% des malades traités mais formellement imputable à la molécule indiquée.

Anticancer drugs: alkylating agents and related compounds

- **Alkylating agents** have alkyl groups which can form covalent bonds with cell substituents; a carbonium ion is the reactive intermediate.
- Most have two alkylating groups and can cross-link two nucleophilic sites such as the N7 of guanine in DNA. Cross-linking can cause:
  - —defective replication
  - —pairing of alkylguanine with thymine, and then substitution of AT for GC
  - —excision of guanine and chain breakage.
- Their principal effect occurs during DNA synthesis.
- *Unwanted effects* include myelosuppression, sterility and risk of non-lymphocytic leukaemia.
- The main alkylating agents are:
  - —*Nitrogen mustards:* e.g. **cyclophosphamide**, which is activated to give aldophosphamide, which is then converted to phosphoramide mustard (the cytotoxic molecule) and acrolein (which causes bladder damage that can be ameliorated by mesna). Cyclophosphamide myelosuppression affects particularly the lymphocytes. Given orally.
  - —*Nitrosoureas:* e.g. **lomustine** may act on non-dividing cells; can cross the blood–brain barrier; causes delayed, cumulative myelotoxicity. Given orally.
- **Cisplatin** causes intrastrand linking in DNA; it has low myelotoxicity but causes severe nausea and vomiting and can be nephrotoxic. Given intravenously, it has revolutionised the treatment of germ cell tumours.

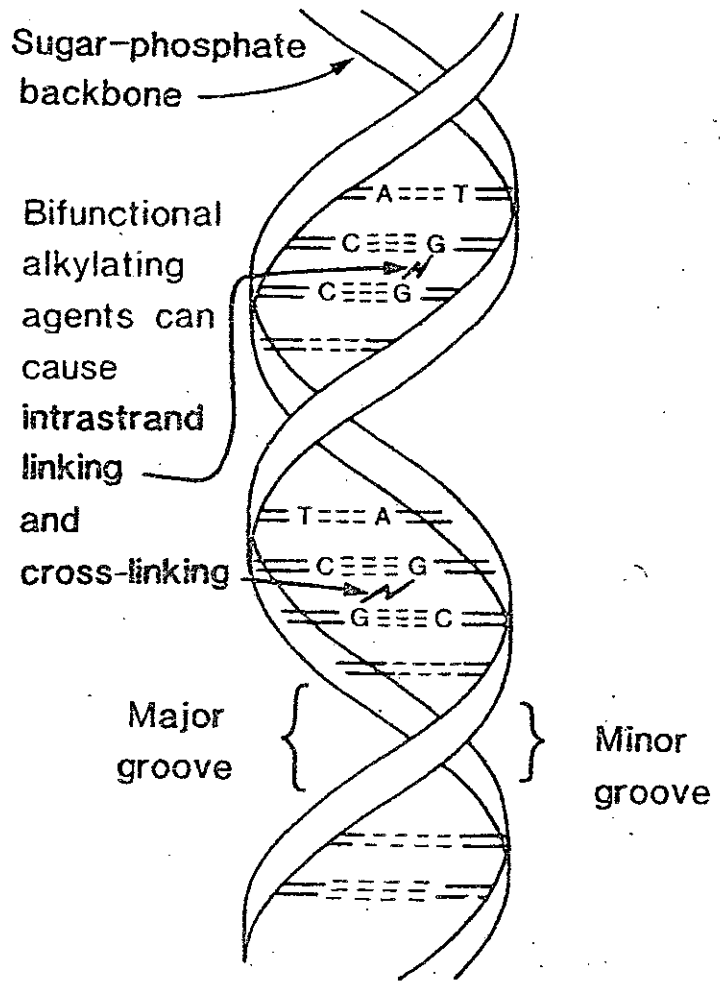


Fig. 36.3 The possible effects of bifunctional alkylating agents on DNA. (G = guanine; C = cytosine; A = adenine; T = thymine)

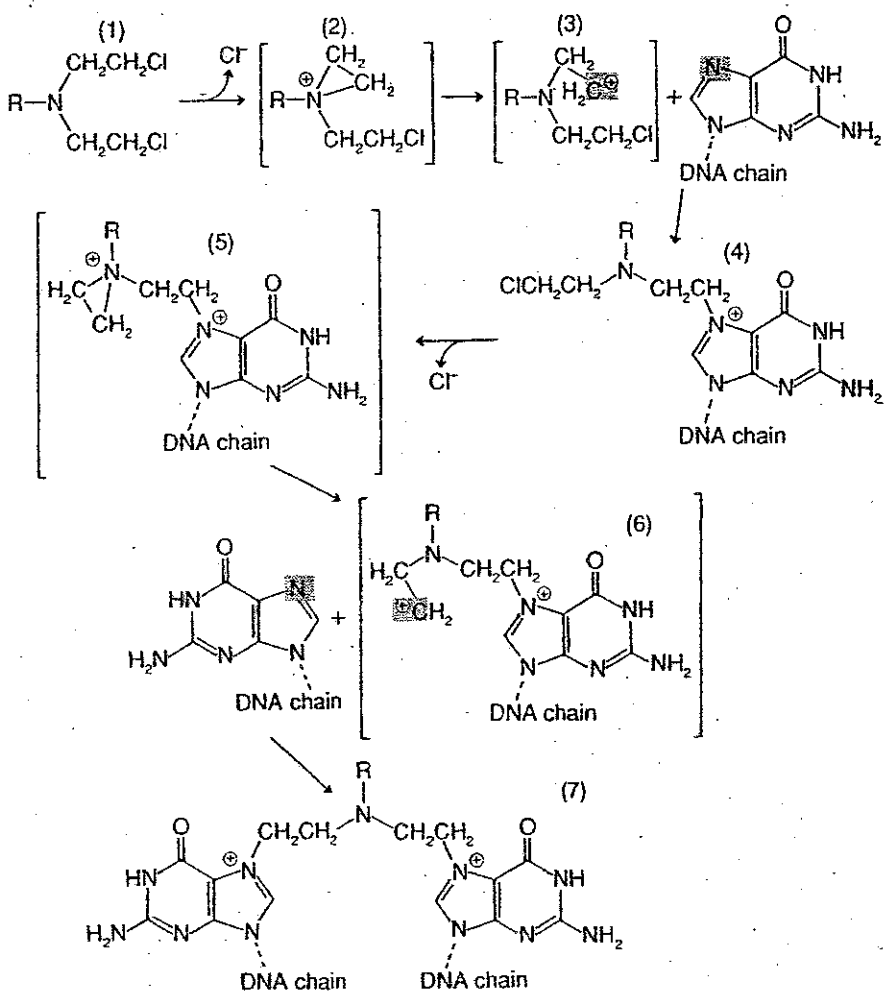


Fig. 36.4 An example of alkylation and cross-linking of DNA by a nitrogen mustard. A bis (chloroethyl) amine (1) undergoes intramolecular cyclisation forming an unstable ethylene immonium cation and releasing a chloride ion (2), the tertiary amine being transformed to a quaternary ammonium compound. The strained ring of the ethylene immonium intermediate opens to form a reactive carbonium ion (in light pink box) (3), which reacts immediately with N7 of guanine (in grey box) to give 7-alkylguanine (bond shown in red), the N7 being converted to a quaternary ammonium nitrogen (4). A bifunctional alkylating agent may undergo a second cyclisation (5), with carbonium ion formation—in light pink box (6), and interact with another guanine residue—in grey box—thus linking two bases as shown in Figure 36.3 (7).

philic (it has an available lone electron pair) and reacts with the carbonium ion to form a covalent bond lining the two. Only bifunctional alkylators, that is those which carry two chloroethyl side chains attached to the nitrogen, are capable of causing cross-linking in DNA.

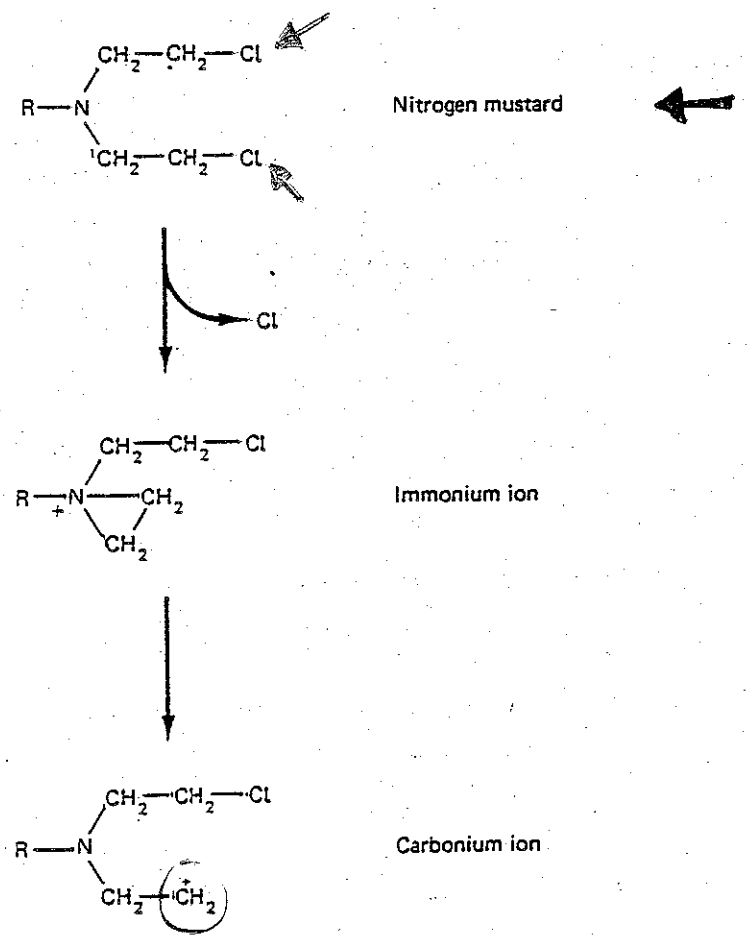


Figure 13.6 Formation of the active alkylation species. The reactive carbonium ion is formed for the second alkylation, which may result in cross-linking.

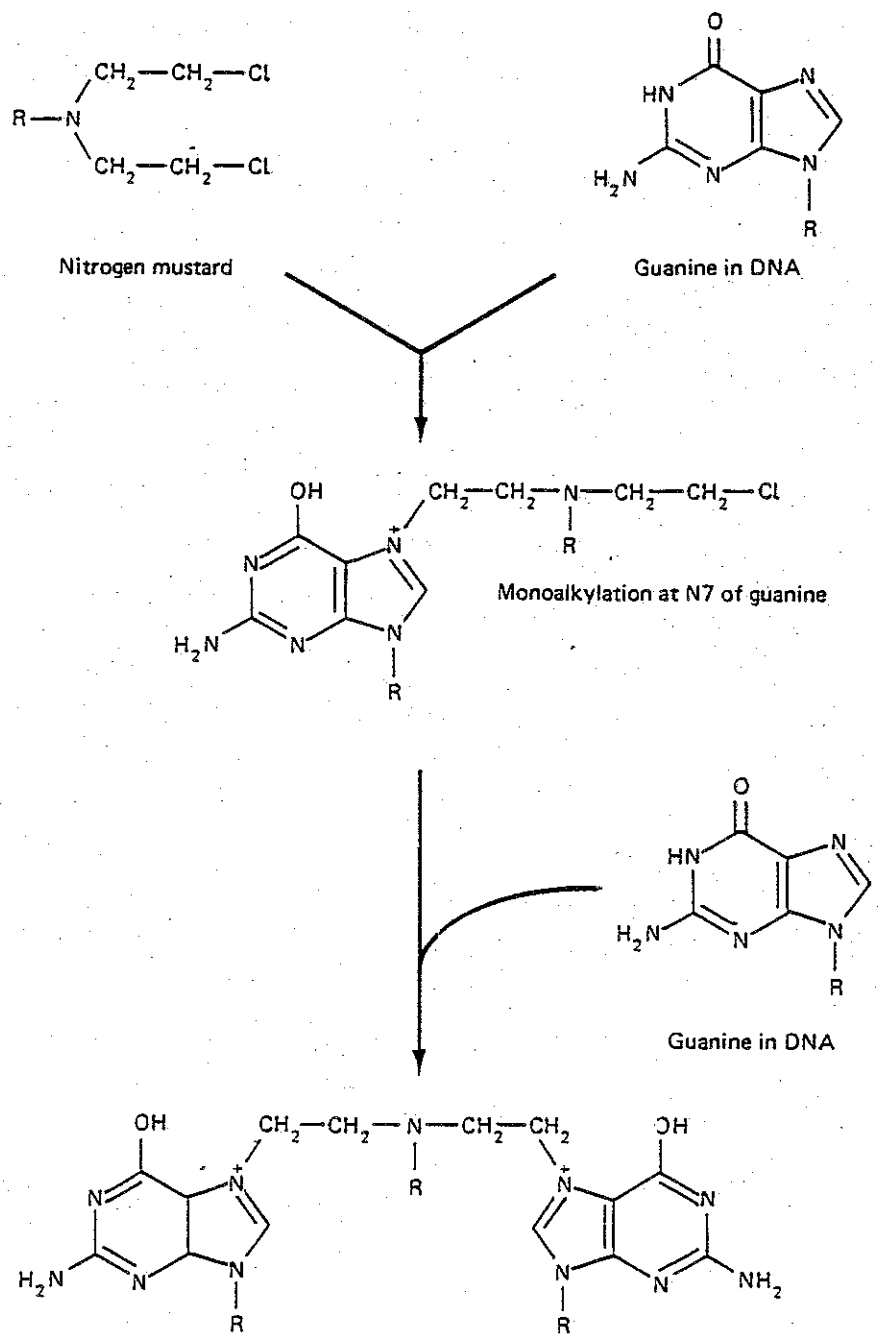


Figure 13.5 Action of alkylating agents on DNA.

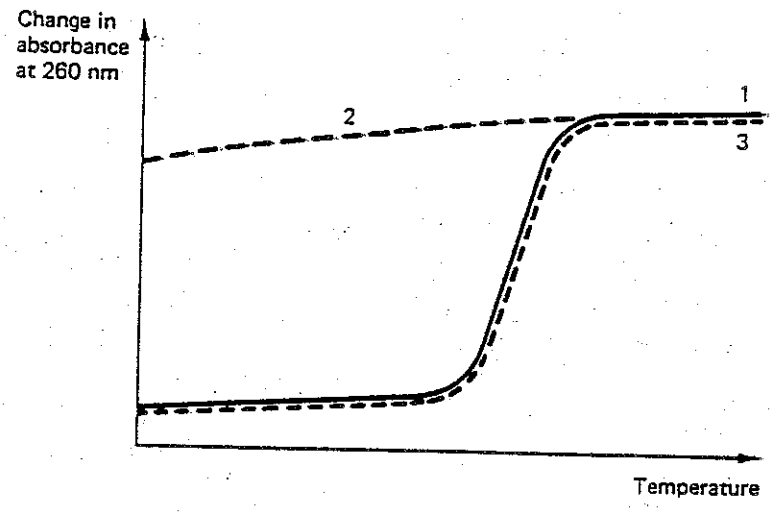


Figure 13.7 Melting profile of cross-linked DNA. Curve 1 is the heating profile of native double-stranded DNA in the presence or absence of a cross-linking agent; curve 2 is the cooling profile of DNA in the absence of drug; curve 3 is the cooling profile of DNA in the presence of drug. Note that these are idealised curves and would indicate 100 per cent cross-linking of the DNA molecule.

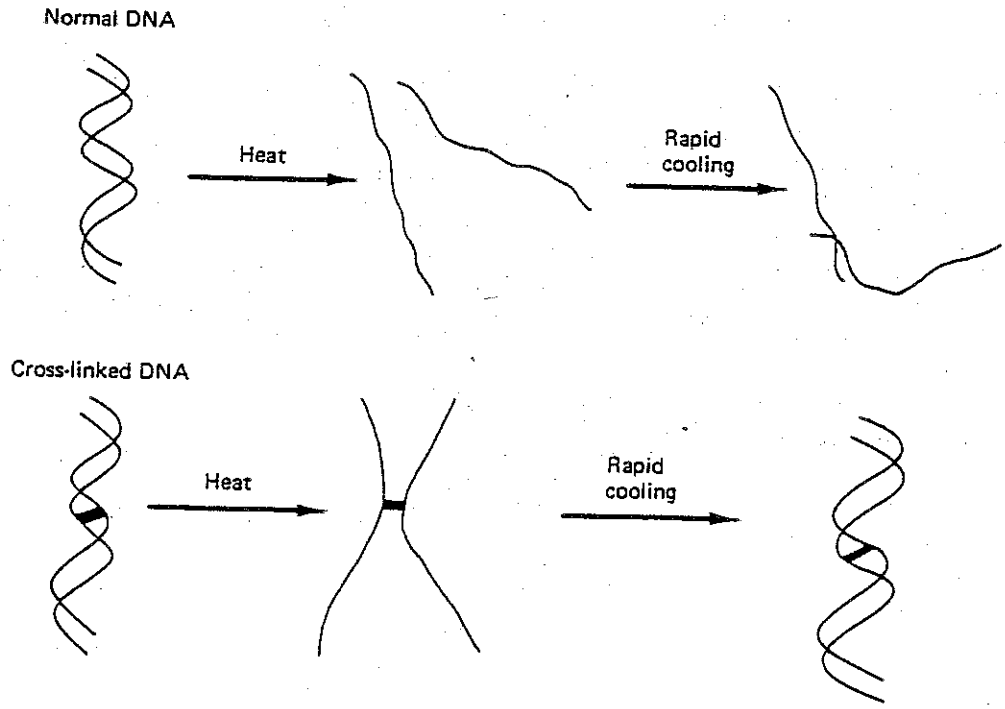


Figure 13.8

(Schindewolf)

Tableau 3: Principales toxicités aiguës des moutardes azotées aux doses usuelles

Effets indésirables	Moutardes azotées (DCI)		
	chlorméthine	melphalan	chlorambucil
Myélosuppression	+ + +	+ + +	+ + +
Vomissements	+ + +	+/—	+/—
Alopécie	+ + +	+/—	+/—
Causticité locale (i.v.)	+ + +	—	—
Cardiaques	—	—	—
Mucites	+ +	—	—
Fibrose pulmonaire*	—	+ +	—
Hépatotoxicité	—	—	—

+ + + dénote un effet indésirable observé chez plus de 80% des malades traités;

+ + dénote un effet indésirable observé chez 50 à 80% des malades traités;

+ dénote un effet indésirable observé chez 25 à 50% des malades traités;

+/— dénote un effet indésirable observé chez moins de 25% des malades traités mais formellement imputable à la molécule indiquée.

* Toxicité observée aux doses les plus élevées.

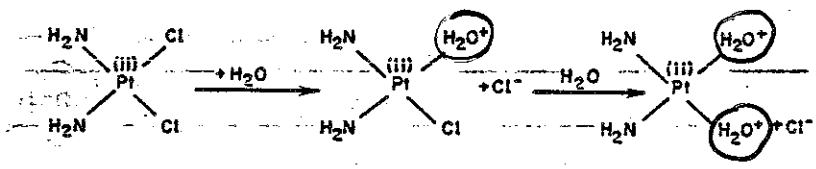


Fig. 14. Mode d'action du cisplatine.

Anticancer drugs: plant derivatives

- **Vincristine** inhibits mitosis at metaphase by binding to tubulin. Given by injection. Relatively non-toxic, but can cause unwanted neuromuscular effects.
- **Etoposide** inhibits DNA synthesis by an action on topoisomerase II, and also inhibits mitochondrial function. Given orally or intravenously. Common unwanted effects include vomiting, myelosuppression and alopecia.

Anticancer agents: hormones and radioactive isotopes

- Hormones or their antagonists are used in hormone-sensitive tumours:
  - —**Glucocorticoids** for leukaemias and lymphomas
  - —**Oestrogens** for prostate tumours
  - —**Tamoxifen** for breast tumours
  - —**GnRH analogues** for prostate and breast tumours
  - —**Antiandrogens** for prostate cancers
  - —**Inhibitors of sex hormone synthesis** for postmenopausal breast cancer.
- Radioactive isotopes can be targeted at specific tissues, e.g. ^{131}I for thyroid tumours.

Tableau 19: Principaux effets indésirables des alcaloïdes de la pervenche

Effets indésirables*	Alcaloïdes de la pervenche			
	vincristine	vinblastine	vindésine	vinorelbine
Myélosuppression	+/–	+ + +	+	+ +
Nausées/vomissements	+/–	+/–	+/–	+/–
Alopécie	+ +	+ +	+ +	+
Causticité	+ + +	+ + +	+ + +	+ + +
Neuropathie périphérique	+ + +	–	+ +	+
Neurotoxicité centrale	+	–	+/–	–

* Cf. Tableau 3 pour la signification précise des symboles utilisés.

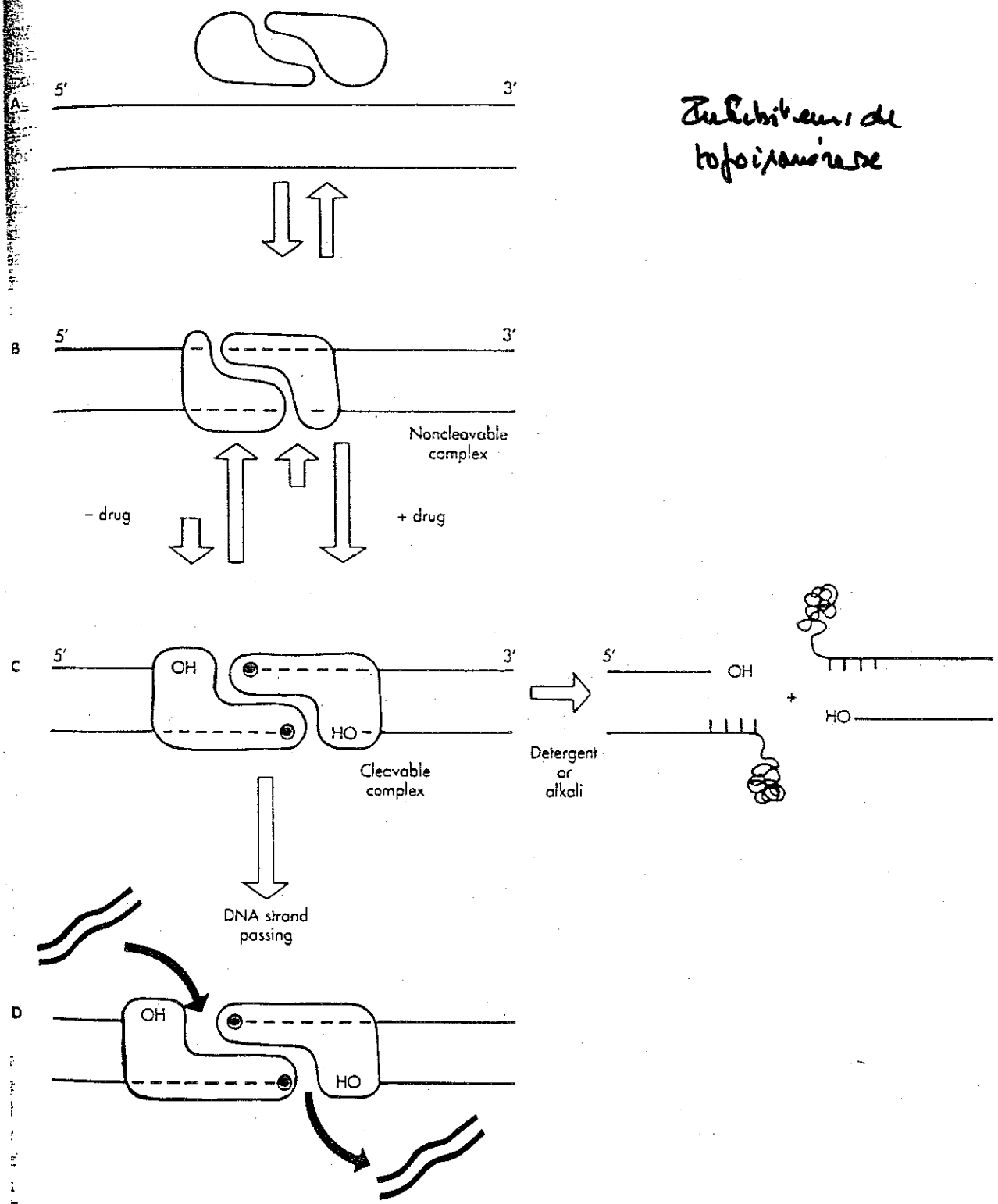


FIGURE 45-13 Mammalian DNA topoisomerase II mechanism and anticancer drug action. Mammalian DNA topoisomerase II forms two different types of protein-DNA complex that are in rapid equilibrium: the noncleavable complex *(B)* and the cleavable complex *(C)*. These complexes can be identified *in vitro* by the ability of detergent or alkali to separate DNA strands. The cleavable complex is transient but is stabilized by doxorubicin, daunorubicin, etoposide, and actinomycin D. In the absence of drug, DNA strand passage occurs, whereas drugs block DNA strand passage and DNA replication.

(Brody)

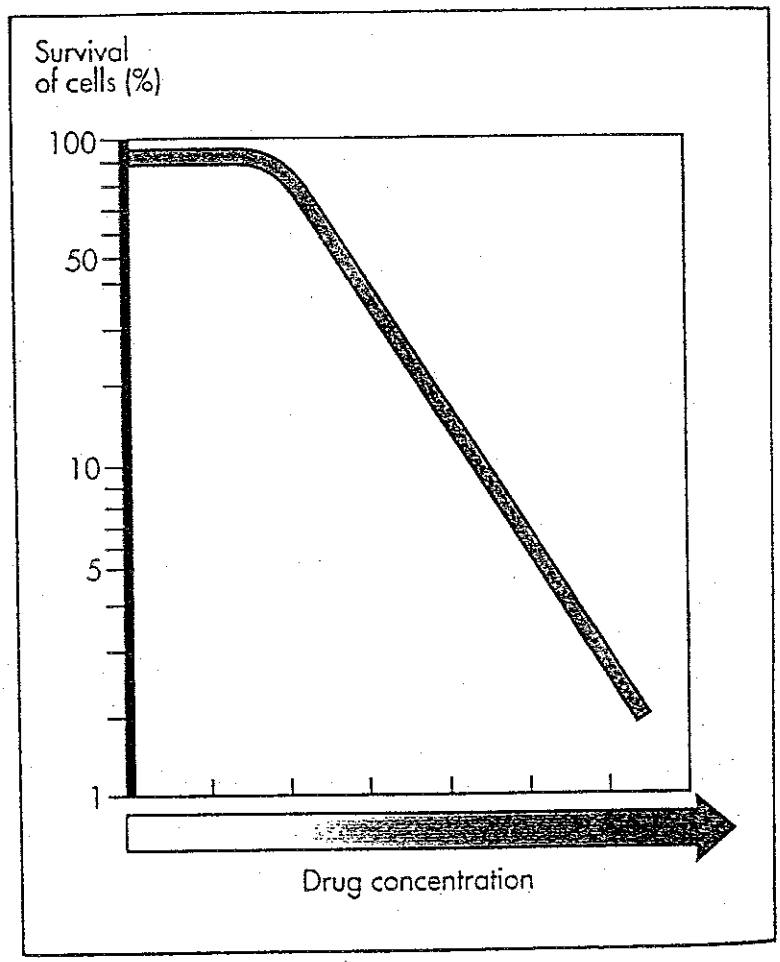


FIGURE 45-2 Decline in viable cells is first order with respect to drug concentration. Many antineoplastic agents and cultured tumor cells follow this relationship, thus establishing the principles of a fixed percentage of viable cells killed per concentration of drug. This same relationship appears to apply *in vivo*, although the actual situation may be more complex. A threshold concentration of drug is often required to cause a noticeable decrease in cell survival. This phenomenon, called *survival shoulder,* may reflect endogenous repair processes.

RESISTANCE

① decreased uptake

③ intracellular binding

④ change in target protein
- increase
- alteration / change

⑤ increased metabolism

⑦ enhanced repair of DNA

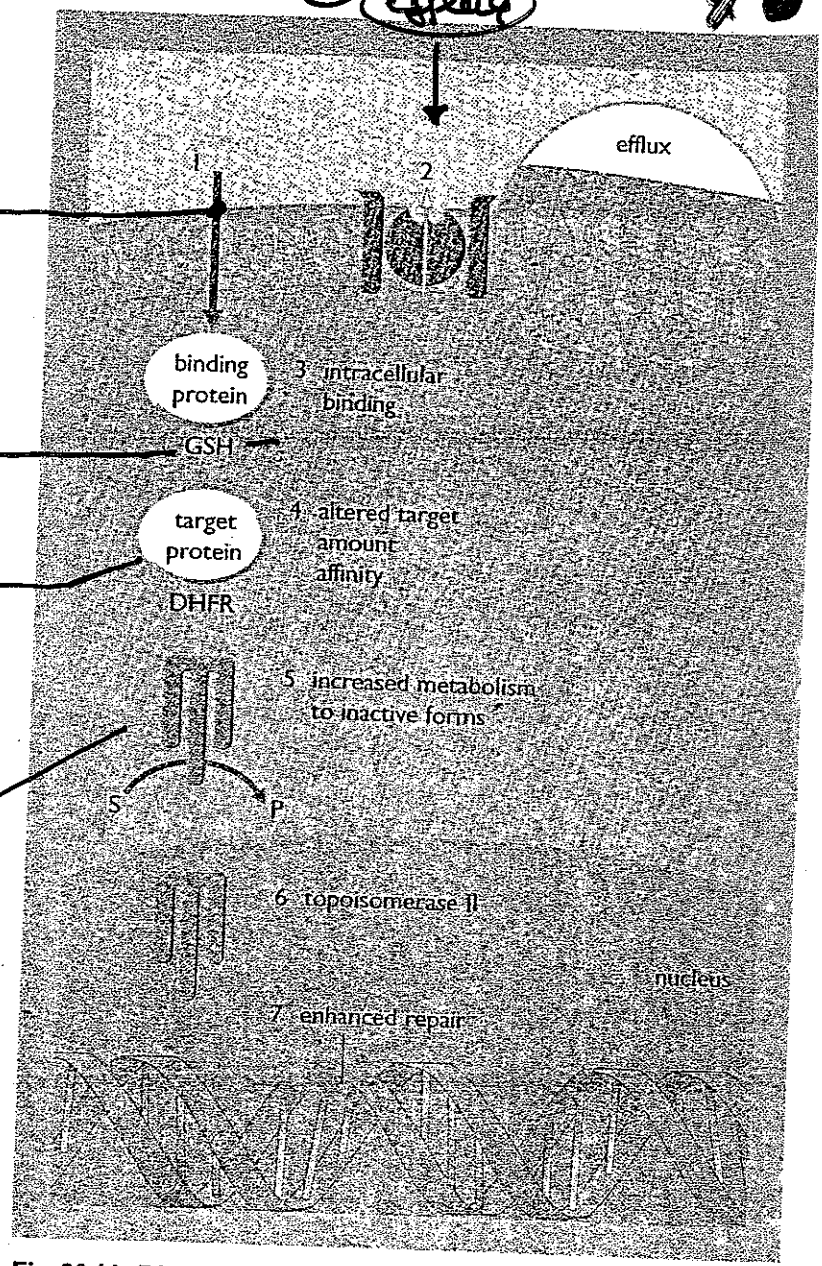
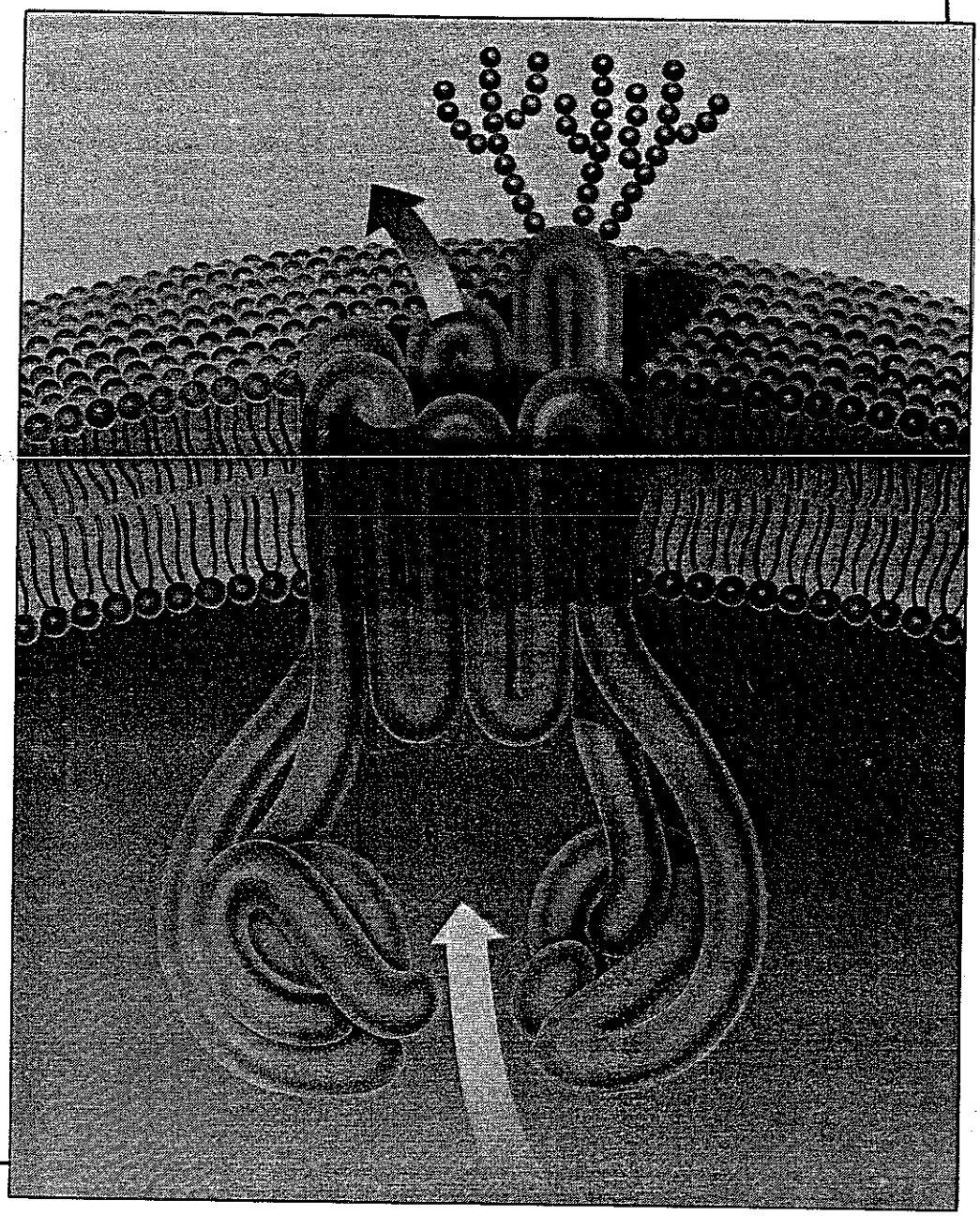


Fig. 28.11 Diagram showing several possible mechanisms of drug resistance. The classical biochemical view. Resistance can occur because of: (1) decreased uptake; (2) rapid efflux via membrane transport proteins; (3) increased intracellular binding to glutathione (GSH); (4) an altered target protein, either an increased amount or decreased binding affinity; (5) inactivation by intracellular detoxifying enzymes; (6) altered topoisomerase II, either a decreased amount or reduced affinity for a drug; and (7) enhanced repair of DNA damage. (DHFR, dihydrofolate reductase)

② ③ ④ ⑤ ⑦ } gene amplification

① ④ } gene mutation or deletion

Membrane plasmique avec p. glycoprotéine (document extrait de «Pour la science», n° 139, mai 1989).



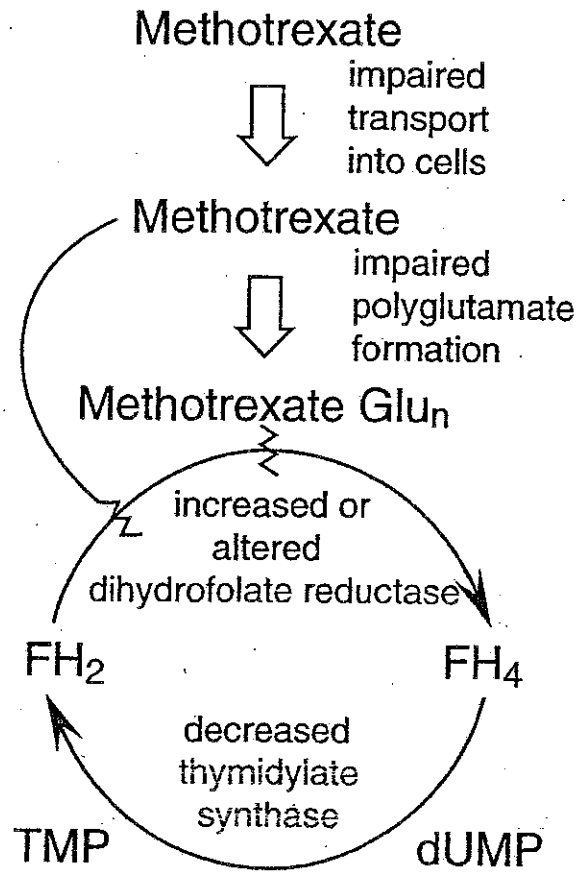


Figure 51–8. Mechanisms of tumor cell resistance to methotrexate.

TMP, thymidine monophosphate; dUMP, deoxyuridine monophosphate; FH_2, dihydrofolate; FH_4, tetrahydrofolate; Glu_n, polyglutamate.

Example of resistance mechanisms to methotrexate

Tableau I: Cotation de l'OMS relative aux effets toxiques aigus et subaigus des agents anticancéreux

	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Hématologique (adulte)						
Hémoglobine	> 11.0 g/100 ml > 110 g/L > 6.8 mmol/L	9.5-10.9 g/100 ml 95-109 g/L 5.6-6.7 mmol/L	8.0-9.4 g/100 ml 80-94 g/L 4.95-5.8 mmol/L	6.5-7.9 g/100 ml 65-79 g/L 4.0-4.9 mmol/L	< 6.5 g/100 ml < 65 g/L < 4.0 mmol/L	Toxicité létale
Leucocytes (1.000/mm³)	> 4.0	3.0-3.9	2.0-2.9	1.0-1.9	< 1.0	↓
Poly. Neutrophiles (1.000/mm³)	> 2.0	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5	
Plaquettes (1.000/mm³)	> 100	75-99	50-74	25-49	< 25	
Hémorragie	Absence	Pétéchies	Modérée	Moyenne	Importante	
Gastro-intestinal						
Bilirubine	> 1.25×N	1.26-2.5×N	2.6-5×N	5.1-10×N	< 10×N	
Transaminases	> 1.25×N	1.26-2.5×N	2.6-5×N	5.1-10×N	< 10×N	
Phosphatase alcaline	> 1.25×N	1.26-2.5×N	2.6-5×N	5.1-10×N	< 10×N	
Muq. buccale	Sans changement	Douleur	Erythème	Ulcération alimentation liquide seulement	Alimentation impossible	
Nausée Vomissement	Absence	Nausée	Vomissement transitoire	Vomissements nécessitant traitement anti-émétique	Vomissements incoercibles	
Diarrhée	Absence	Transitoire < 2 jours	Tolérable > 2 jours	Intolérable demandant traitement	Hémorragique - Déshydratation	
Urée						
Urémie ou Créatinémie	< 1.25×N	1.26-2.5×N	2.6-5×N	5-10×N	> 10×N	
Protéinurie	Sans changement	1 + < 0.3 g < 3 g/L	2-3 + 0.3-1.0 g 3-10 g/L	4 + > 1.0 g > 10 g/L	Syndrome néphrotique	
Hématurie	Sans changement	Microscopique	Macroscopique	Macroscopique + caillots	Anurie	
Pulmonaire	Sans changement	Léger symptôme	Dyspnée d'effort	Dyspnée de repos	Repos au lit complet	
Fièvre	Absente	< 38°C	38°-40°C	> 40°C	Fièvre avec hypotension	
Réaction allergique	Sans changement	Œdème	Bronchospasme n'appelant pas réanimation	Bronchospasme appelant réanimation	Choc anaphylactique	
Cutané	Sans changement	Erythème	Desquamation Vésicules Prurit	Suintement Desquamation Ulcération	Dermatite exfoliative Nécrose appelant exérèse	
Effet alopéciant	Sans changement	Perte de cheveux	Alopécie modérée par plaques	Alopécie complète mais réversible	Alopécie irréversible	
Infection	Absence	Mineure	Modérée	Majeure	Choc infectieux	
Neurotoxicité						
Etat de conscience	Vigile	Assoupissements	Somnolence < 50% des heures d'éveil	Somnolence > 50% des heures d'éveil	Coma	
Périphérique	Absence	Paresthésies et/ou diminution des réflexes tendineux	Paresthésies sévères et/ou faiblesse modérée	Paresthésies intolérables et/ou diminution importante de la force motrice	Paralysie	
Constipation (b)	Absence	Légère	Modérée	Météorisme abdominal	Météorisme et vomissements	
Douleur (c)	Absence	Légère	Modérée	Sévère	Intolérable	

N: Limite supérieure de la valeur normale.
(b): A l'exclusion des ralentissements de transit secondaires à l'emploi de narcotiques.
(c): Seules sont considérées les douleurs en rapport avec le traitement et non les douleurs liées à la maladie.

NB. — **Toxicité cardiaque:** Grade 0 Absence de toxicité.
Grade 1 Toxicité ne nécessitant pas l'arrêt du traitement (à détailler).
Grade 2 Toxicité nécessitant l'arrêt du traitement (à détailler).

TABLEAU IV. — **Risques potentiels des médicaments anticancéreux utilisés en thérapeutique : risques et précautions à prendre en considération par les personnels manipulant des médicaments**

Dénomination commune internationale	*Causticité*	*Allergie*	*Mutagénicité*	*Carcinogénicité*	*Tératogénicité*
ıcinomycine	—	?	±	inconnue	± (animal)
nomycine	+ +	+	±	inconnue	+ (animal)
étamine	+	+	+	inconnue	+ (animal)
Amsacrine	+	—	+	inconnue	+ (animal)
Asparaginase	—	+	±	improbable	+ (animal)
Bléomycine	—	+	+	inconnue	+ (animal)
Busulfan	—	—	+	probable	inconstante (humain)
Carmustine	+	—	+	certaine	probable (animal)
Chlorambucil	—	—	+	certaine	+ (animal)
Cisplatine	—	+/—	+	inconnue	+ (animal)
Cyclophosphamide	—	+ +	+	certaine	+ (homme)
Cytarabine	+/—	+/—	+	improbable	+ (animal)
Dacarbazine	+ +	+	+	inconnue	+ (animal)
Dactinomycine	+	—	+	improbable	+ (animal)
Daunorubicine	+ +	—	+	inconnue	+ (animal)
Doxorubicine	+ +	+/—	+	improbable	+ (animal)
Ellipticinium	+ +	+	+	inconnue	+ (animal)
Étoposide	+	+	±	inconnue	+ (animal)
Fluoro-uracile	—	+	+	inconnue	+ (animal)
Hydroxyurée	—	—	±	improbable	± (animal)
Ifosfamide	—	—	+	inconnue	+ (animal)
Lomustine	+	+	+	probable	+ (animal)
Méchloréthamine	+	+	+	probable	+ (animal)
Melphalan	+	+/—	+	probable	+ (animal)
Mercaptopurine	—	—	+/—	improbable	+/— (animal)
hotrexate	—	+	+	improbable	+/— (animal)
guazone	—	—	+	inconnue	+/— (animal)
mycine	+ +	+	+	probable	+ (animal)
Mitoxantrone	+/—	—	+/—	inconnue	+/— (animal)
Procarbazine	+	+	+	probable	+ (animal)
Streptozocine	—	—	+	possible	+ (animal)
Téniposide	—	—	+	inconnue	+ (animal)
Thioguanine	—	—	±	inconnue	+ (animal)
Thiotépa	—	—	+	inconnue	+ (animal)
Vinblastine	+ +	—	+	improbable	+ (animal)
Vincristine	+ +	—	+	improbable	+ (animal)
Vindésine	+ +	—	+	inconnue	+ (animal)

Notions essentielles

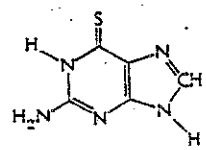
- Les immunodépresseurs chimiques classiques sont des agents anti-prolifératifs, sélectionnés sur leur relative sélectivité pour la lignée lymphoïde : essentiellement l'azathioprine (analogue des purines) et le cyclophosphamide (agent alcoylant).
- La ciclosporine est un polypeptide d'origine fongique, ayant un effet sélectif sur la lignée lymphoïde. Elle agit préférentiellement sur les réponses T-dépendantes, en inhibant la production d'interleukine 2.
- Les glucocorticoïdes, utilisés à dose forte (1 mg/kg en équivalent de prednisone) inhibent : l'immunité à médiation cellulaire (en inhibant la production d'interleukine 1 et d'interleukine 2), la phagocytose dans le système réticulo-endothélial d'hématies ou de plaquettes recouvertes d'anticorps, la bactéricidie par les cellules phagocytaires.
- Les anticorps monoclonaux antilymphocytes agissent en éliminant les lymphocytes porteurs des molécules qu'ils reconnaissent, et surtout en interférant avec la fonction de celles-ci.
- Les thérapeutiques immunodépressives ont deux ordres de complications communes à tous les produits : augmentation de la fréquence et de la gravité des infections ; augmentation du risque pour certaines affections malignes.
- Chaque immunodépresseur peut avoir, en outre, des complications qui lui sont propres. Les plus importantes sont : la toxicité hématopoïétique des agents antiprolifératifs (nettement plus marquée pour le cyclophosphamide que pour l'azathioprine) ; la néphrotoxicité de la ciclosporine.
- La pharmacocinétique très variable et la toxicité rénale de la ciclosporine imposent le recours régulier à des dosages sanguins et à des adaptations de posologie.
- Dans le domaine des greffes allogéniques, la ciclosporine a constitué un progrès considérable : amélioration du pronostic des greffes de moelle ; extension des indications des greffes cardiaques et hépatiques ; mise en place d'études visant à améliorer (par ciclosporine ou anticorps monoclonaux) les résultats des greffes de rein.
- Dans le domaine de l'auto-immunité, les glucocorticoïdes sont la thérapeutique essentielle, éventuellement associés à ou relayés par le cyclophosphamide, la ciclosporine ou des méthodes non pharmacologiques.
- Dans l'avenir, d'importantes perspectives sont ouvertes par les progrès de la définition moléculaire des mécanismes de la réponse immunitaire : définition de la distribution et du rôle biologique des molécules cibles des anticorps monoclonaux antilymphocytes, caractérisation et production d'interleukines et de médiateurs des interactions lymphocytaires.

TABLEAU III. — Synthèse

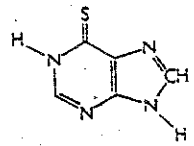
	Mécanisme d'action schématique	*Indications*	*Effets secondaires*[1]
• **Azathioprine**	(par mercaptopurine) — Inhibition au stade inductif de certaines réponses lymphocytaires — Effet prédominant sur les réponses à médiation cellulaire	— Transplantation d'organe — Auto-immunité ?	— Neutropénie — Augmentation de la fréquence de certaines tumeurs
• **Cyclophosphamide**	(par métabolites actifs) — Effet sur les cellules en renouvellement — Effet prédominant sur cellules B si dose unique — Effet sur réponses cellulaires et humorales	— Transplantation d'organe — Préparation à la greffe de moelle — Auto-immunité ?	— Neutropénie, cystite, alopécie, azoospermie — Augmentation de la fréquence de leucémies
• **Ciclosporine**	— Effet sélectif sur lymphocytes — Effet prédominant sur lymphocytes T	— Transplantation d'organe — Greffe de moelle — Auto-immunité ?	— Néphrotoxicité — Augmentation de la fréquence des lymphomes
• **Corticoïdes**	— Inhibition de la production des interleukines — Inhibition de certaines fonctions des macrophages — Redistribution des lymphocytes et des monocytes — Effet sur réponses cellulaires	— Greffes — Auto-immunité	Voir chapitre correspondant
• **Anticorps anti-lymphocytes**	— Élimination des lymphocytes recirculants (T à vie longue) — Interférence avec les fonctions des molécules reconnues	— Greffes de moelle ? — Transplantations d'organes ?	Anticorps anti-immunoglobulines

1. Dans tous les cas : diminution de la résistance aux agents infectieux.

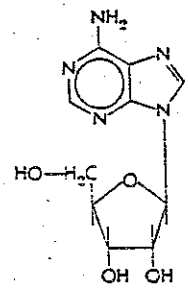
Table 52–4. STRUCTURAL FORMULAS OF ADENOSINE AND VARIOUS PURINE ANALOGS



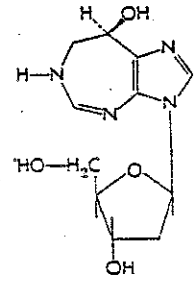
Thioguanine



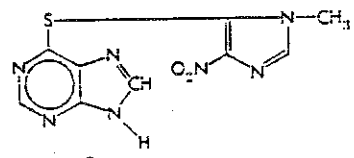
Mercaptopurine



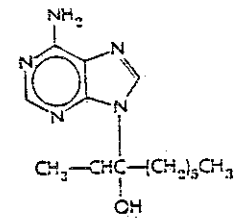
Adenosine



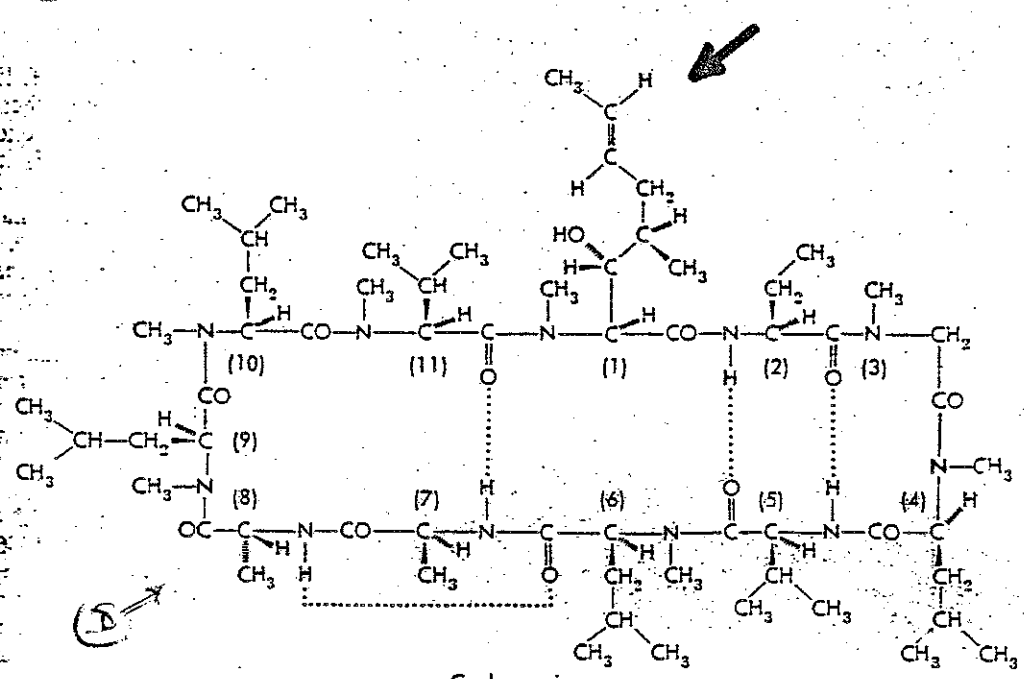
Pentostatin
(2'-Deoxycoformycin)



Azathioprine



Erythrohydroxynonyladenine
(EHNA)



Cyclosporine

hydrophobe !

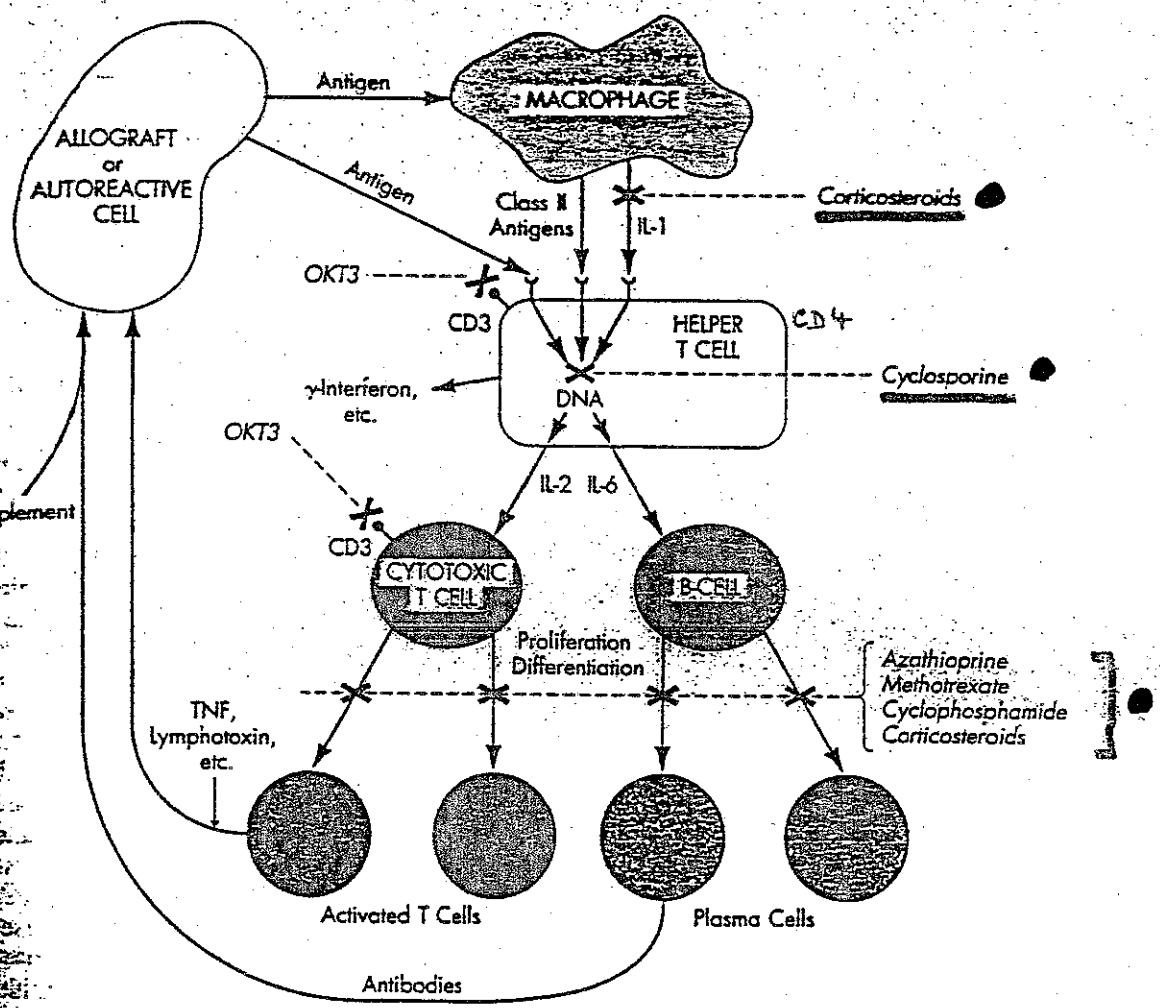


Figure 53–1. *Potential targets for immunosuppressive agents.*

The figure depicts the salient features of cellular and humoral immune responses and indicates the apparent sites of action of various immunosuppressive agents (*see* text for details). Abbreviations are: IL, interleukin; CD3, cell differentiation complex 3; OKT3, murine monoclonal antibody directed against an epitope in CD3; and TNF, tumor necrosis factor.