Clinical and High-Dose Alkylating Agents

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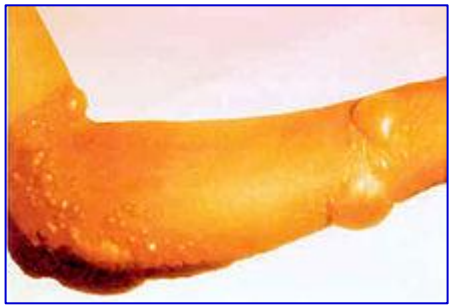
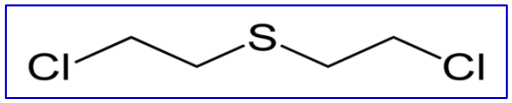
HISTORY

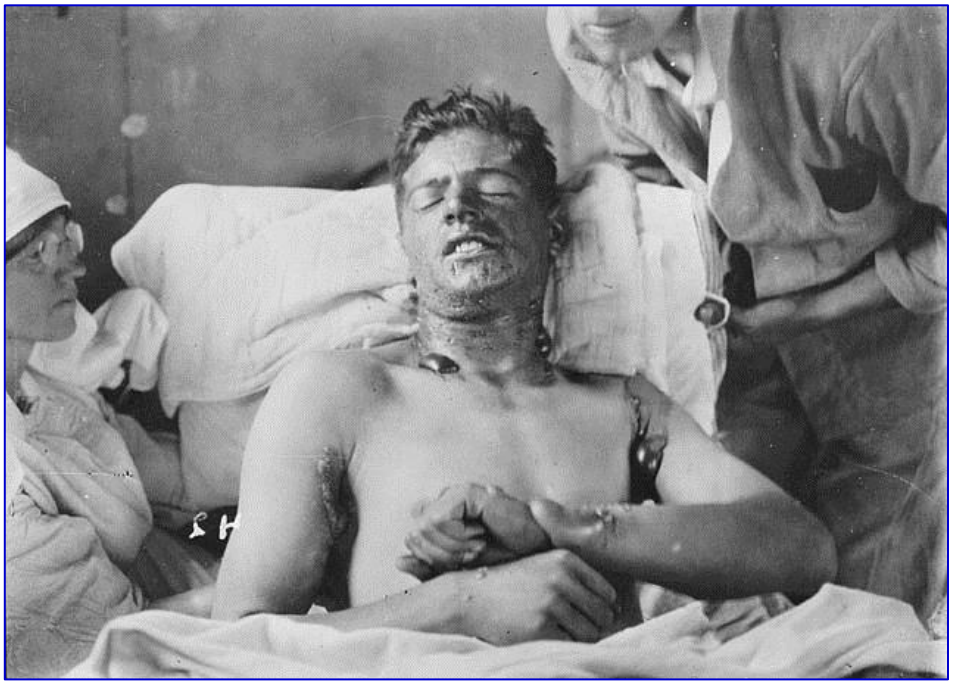
- Clinical trials of nitrogen mustards in patients with lymphomas evolved from clinical observations of the effects of **sulfur mustard gas** used in the First World War.



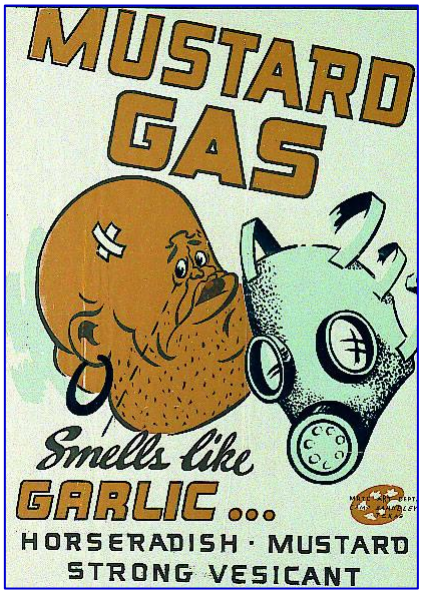
Typical appearance of bullae on arm caused by blister agent burns



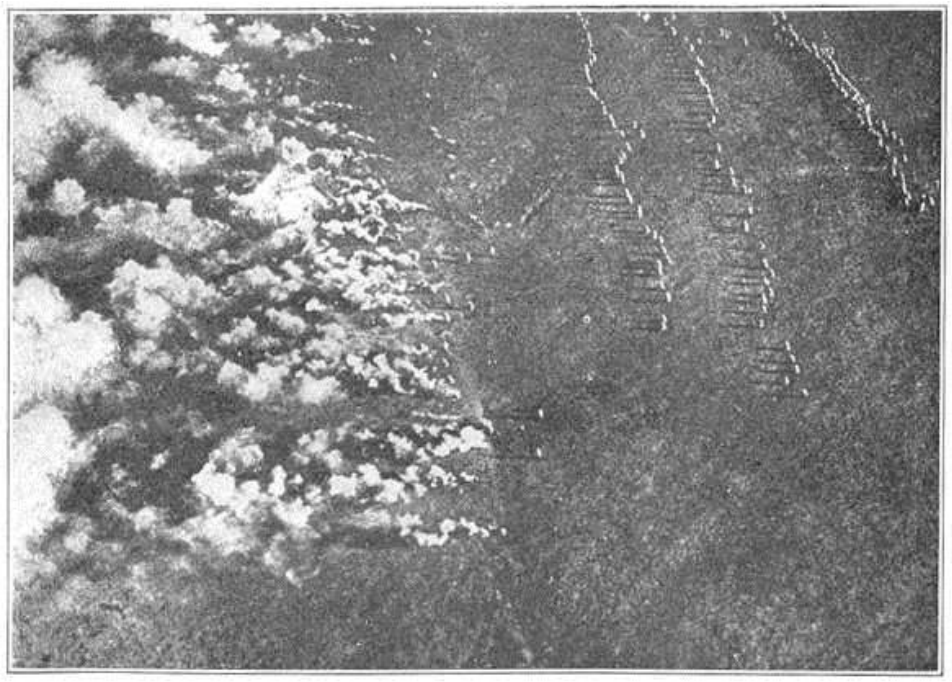
Sulfur mustard



Soldier with moderate mustard gas burns sustained during World War I showing characteristic bullae on neck, armpit and hands



Pallets of 155 mm artillery shells containing "HD" (distilled sulfur mustard agent) at Pueblo chemical weapons storage facility.

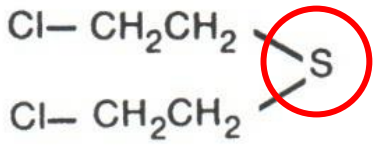


동부전선에서 독가스를 살포중인 독일군

- 1차세계대전: 1914.7.28 – 1918.11.1
- 가스공격 → 화학전
- 독일군, 연합군 모두 사용
- 1차세계대전 당시 50,965톤 가량의 화학무기 사용
- 85,000명 사망자
- 1,176,500명 부상자

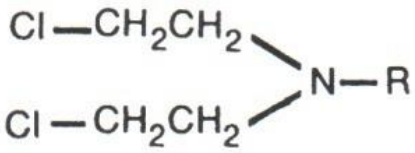
HISTORY

- **Nitrogen mustards mechlorethamine (HN_2) and tris(β-chloroethyl) amine (HN_3)** were the 1st non-hormonal agents to show significant antitumor activity in humans.
- During WWII nitrogen mustards were studied at Yale University and classified human clinical trials of nitrogen mustards for the treatment of lymphoma started in December 1942.
- The compound was found to produce lymphoid aplasia, irritation of lungs & mucous membranes and hence was evaluated as *antitumor agent*.



A

Bischloroethylsulfide (sulfur mustard).



B

Bischloroethylamine (nitrogen mustard general structure). —R = —CH_3 in mechlorethamine. —R = —CH_2CH_2Cl in tris(β-chloroethyl)amine.

Figure 12.1 Structures of bischloroethylsulfide and bischloroethylamine. **A.** Bischloroethylsulfide (sulfur mustard). **B.** Bischloroethylamine (nitrogen mustard general structure).

- HN1: Bis(2-chloroethyl)ethylamine
- HN2: Bis(2-chloroethyl)methylamine
- HN3: Tris(2-chloroethyl)amine

MODE OF ACTION OF ALKYLATING AGENTS (AAs)

- As a class share a common target (DNA) & are cytotoxic, mutagenic, and carcinogenic.
- Activity enhanced by radiation, hyperthermia, nitroimidazoles, and by glutathione (GSH) depletion.
- Differ greatly in toxicity profiles and antitumor activity, due to difference in pharmacokinetic features, lipid solubility, ability to penetrate the CNS, membrane transport properties, detoxification properties and enzymatic reactions capable of repairing alkylation sites on DNA.
- Major AAs: cyclophosphamide, ifosfamide, melphalan, bischloroethylnitrosourea (BCNU), busulfan

KEY FEATURES OF SELECTED ALKYLATING AGENTS

	Cyclophosphamide	Chlorambucil	Melphalan	BCNU	Busulfan
Mechanism of action:	All agents produce alkylation of DNA through the formation of reactive intermediates that attack nucleophilic sites.				
Mechanisms of resistance:	Increased capacity to repair alkylated lesions, e.g., guanine O^6-alkyl transferase (nitrosoureas, busulfan) Increased expression of glutathione-associated enzymes, including γ-glutamyl cysteine synthetase, γ-glutamyl transpeptidase, and glutathione-*S*-transferases Increased aldehyde dehydrogenase (cyclosphamide) Decreased expression or mutation of p53				
Dose/schedule (mg/m^2):	400–2,000 i.v. 100 p.o. qd	1–3 p.o. qd	8 p.o. qd × 5 d	200 i.v.	2–4 mg daily
Oral bioavailability:	100%	50%	30% (variable)	Not known	50% or greater
Pharmacokinetics: primary elimination $t_{1/2}$ (h)	3–10 (parent) 1.6 (aldophosphamide) 8.7 (phosphoramide mustard)	1.5 (parent) 2.5 (phenylacetic acid)	1.5 (parent)	0.25 to 0.75[a] (nonlinear increase with dose from 170 to 720 mg/m^2)	
Metabolism:	Microsomal hydroxylation Hydrolysis to phosphoramide mustard (active) and acrolein Excretion as inactive oxidation products	Chemical decomposition to active phenyl acetic acid mustard and to inert dechlorination products	Chemical decomposition to inert dechlorination products 20–35% excreted unchanged in urine	Chemical decomposition to active and inert products	Enzymatic conjugation with glutathione
Toxicity:					
Myelosuppression	Acute, platelets spared	Acute	Delayed, nadir at 4 wk	Delayed, nadir 4–6 wk	Acute and delayed
Alopecia Pulmonary fibrosis Venoocclusive disease Leukemogenesis Infertility Teratogenesis	Seen with all alkylating agents →				
Other	Cystitis; cardiac toxicity; IADH	—	—	Renal injury	Addisonian syndrome, seizures
Precautions:	Use MESNA with high-dose therapy	—	$t_{1/2}$ prolonged in patients with renal dysfunction	—	Monitor AUC with high-dose therapy
Drug interactions:	Expect increased cytotoxicity with radiation sensitizers, and glutathione depletion		Cimetidine decreases bioavailability by 30%	—	Induces phenytoin (Dilantin) metabolism

AUC, area under the concentration × time curve; BCNU, bischloroethylnitrosourea; IADH, inappropriate antidiuretic hormone syndrome; MESNA, 2-mercaptoethane sulfonate; $t_{1/2}$, half-life.
[a]See reference 276a.

TRADITIONAL CLASSIFICATION BASED ON MECHANISM OF ACTION

SN1 (Nucleophilic substitution, first order)

- Highly reactive intermediate, reacts rapidly with a nucleophile to produce alkylated product.
- First order kinetics, dependent on concentration of original alkylating agent.
- Less selective in their alkylation targets than SN2 reagents.
- e.g., **nitrogen mustard, mechlorethamine.**

$$RX \rightarrow R^+ + X^- \xrightarrow{+\ Y^-} RY + X^-$$

SN2 (Nucleophilic substitution, second order)

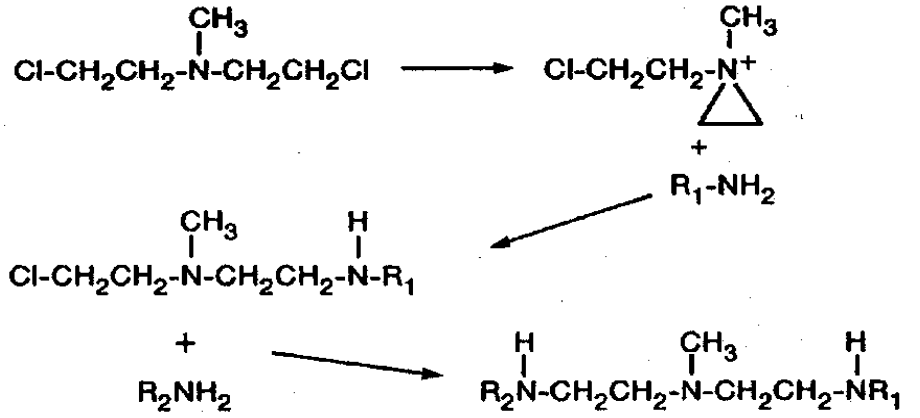
- Biomolecular nucleophilic displacement.
- Dependent on concentration of both alkylating agent and target nucleophile.
- More selective in their alkylation targets than SN1 reagents.
- e.g., **alkyl alkane sulfonate, busulfan.**

$$RX + Y^- \rightarrow [X \ldots R \ldots Y] \rightarrow X^- + RY$$

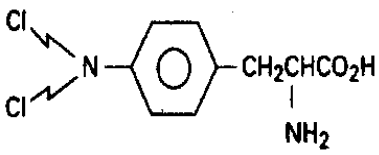
Types of ALKYLATING AGENTS Used Clinically

NITROGEN MUSTARDS

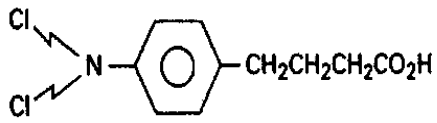
- Mechlorethamine
- Cyclophosphamide: against a variety of tumors.
- Ifosfamide: against testicular cancer and soft tissue sarcomas.
- Melphalan: against ovarian cancer, multiple myeloma & carcinoma of breast.
- Chlorambucil: against chronic lymphocytic leukemia, lymphomas and ovarian carcinoma.



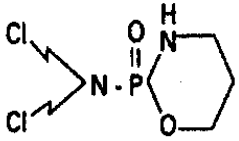
Alkylation mechanism of nitrogen mustards. (From Colvin M. Molecular pharmacology of alkylating agents. In: Cooke ST, Prestayko AW. *Cancer and chemotherapy*, vol 3. New York: Academic Press, 1981:291.)



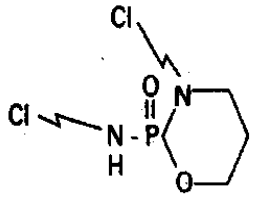
Melphalan



Chlorambucil



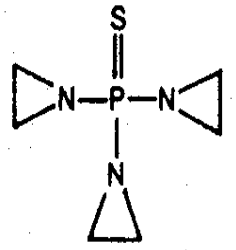
Cyclophosphamide



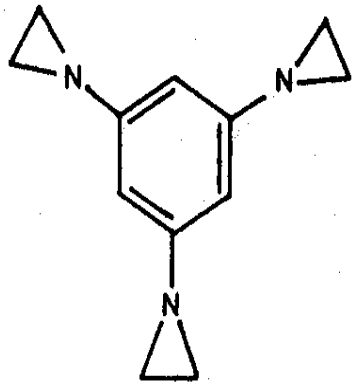
Ifosfamide

AZIRIDINES

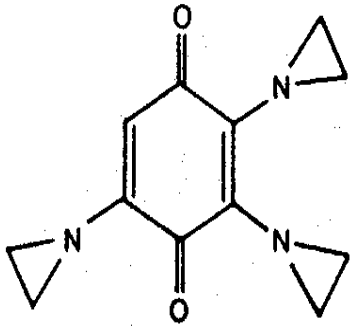
- Triethylenethiophosphoramide (Thiotepa), triethylenenemelamine and trenimon.
- Analogs of ring-closed intermediates of nitrogen mustards.
- Breast & ovary carcinoma and for intrathecal treatment of meningeal carcinomatosis.
- Possible mechanism of action that they alkylate by opening aziridine rings.
- Activity is increased by protonation and at low pH.



Thio-TEPA

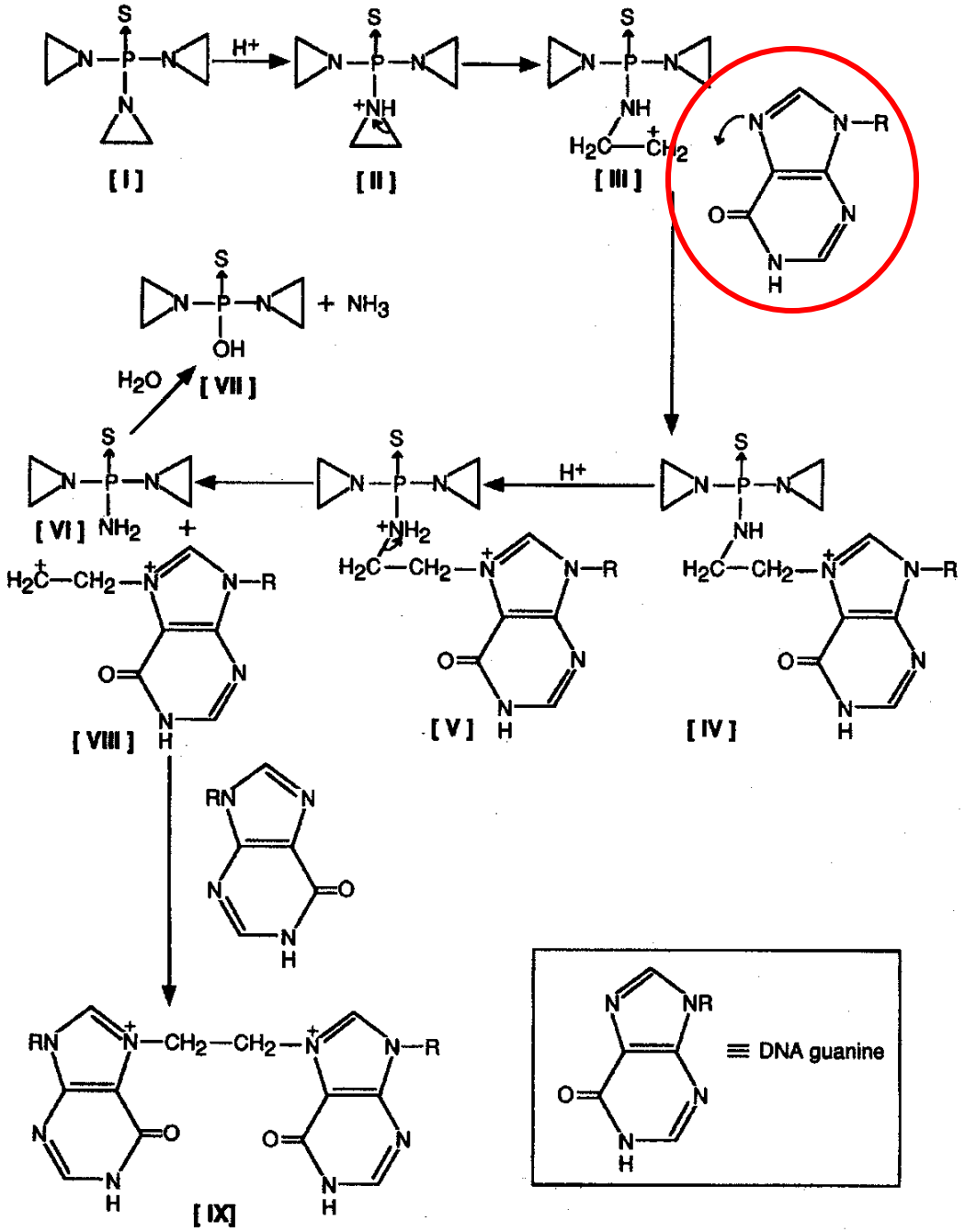


Triethylenemelamine

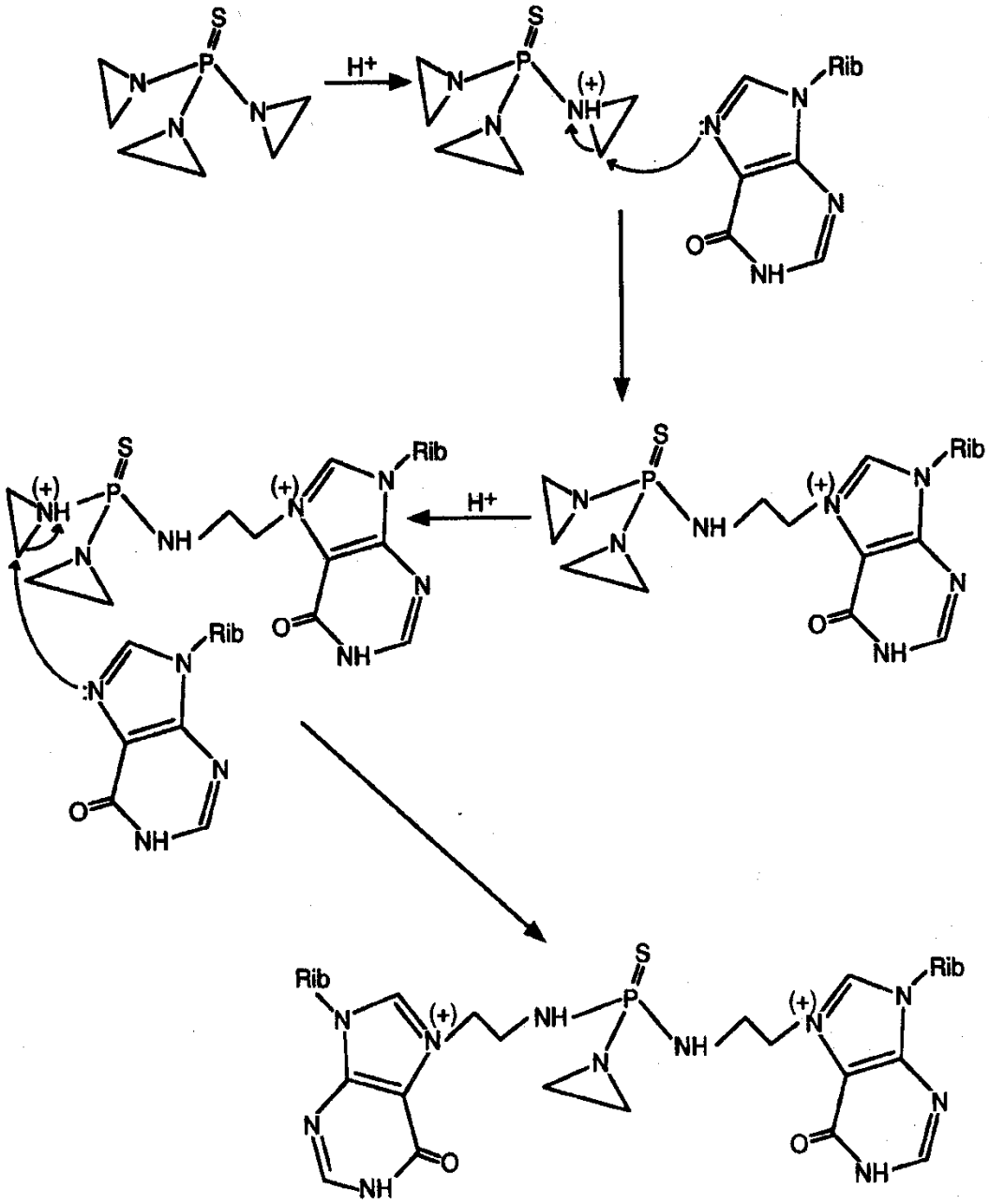


Trenimon

Aziridine antitumor agents.



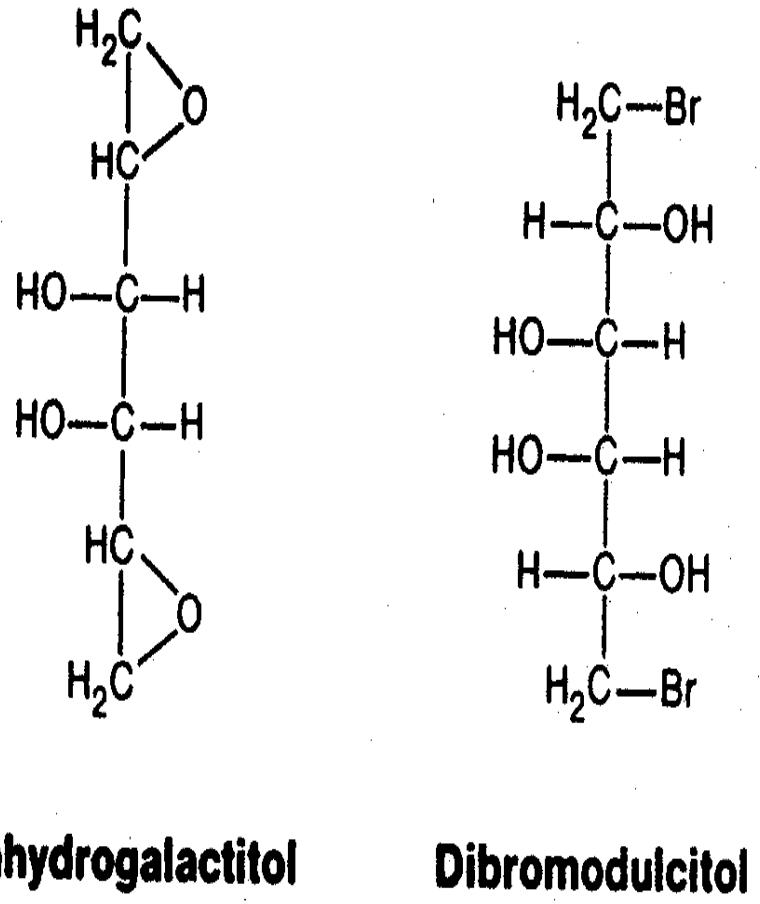
Alternative mechanisms of cross-linking by thiotepa. **A:** Alkylation and cross-linking by sequential reactions of a single aziridine group. (*continued*)



(*continued*) **B:** Cross-linking produced by sequential alkylating reactions of two aziridine groups from the same parent drug molecule.

EPOXIDES

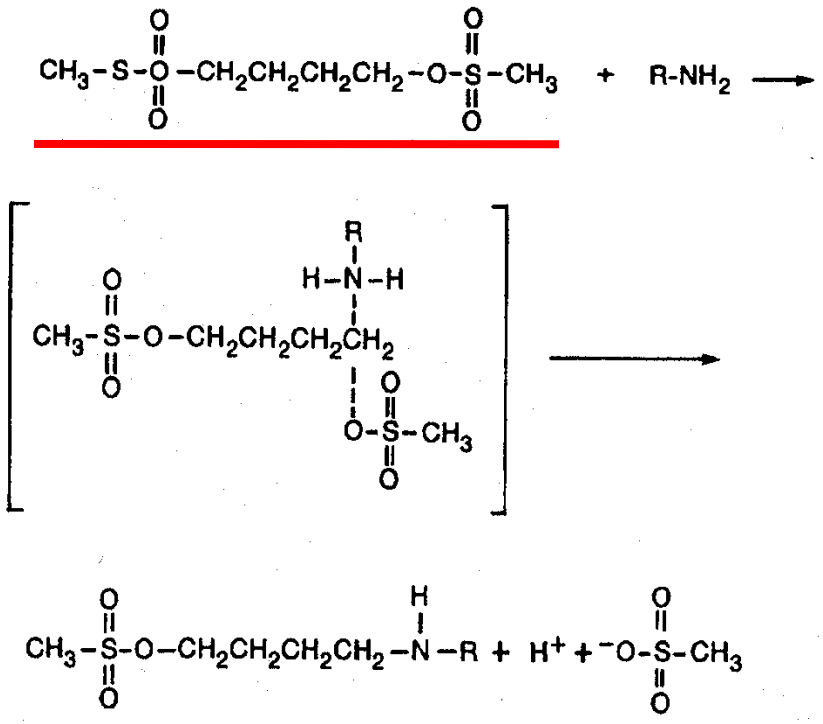
- Dianhydrogalactitol: activity against brain tumors.
- Dibromodulcitol: modest activity against breast cancer.
- Possibly similar in mechanism of action as aziridines.
- Less pH dependent as they protonate less readily.



Structures of epoxides.

ALKYL ALKANE SULFONATES

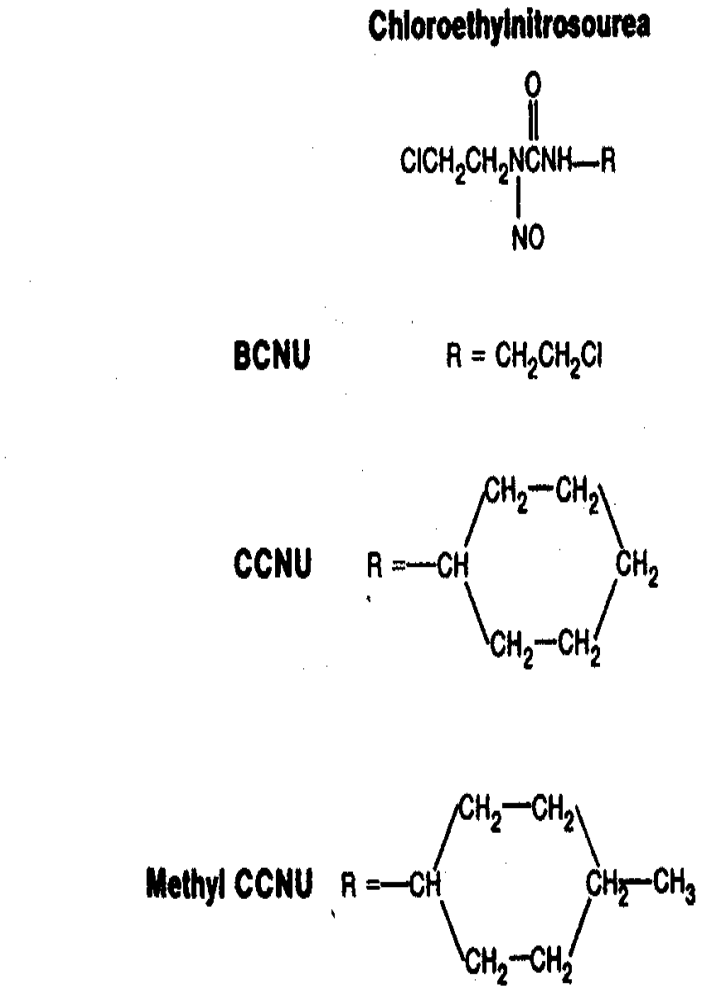
- Busulfan: widely used for acute and chronic myelogenous leukemia.
- Reacts more extensively with thiol groups of amino acids and proteins than nitrogen mustards.
- Busulfan exhibits second-order alkylation kinetics.
- Displays a more marked effect on myeloid cells than on lymphoid cells, so used against chronic myelogenous leukemia.



Alkylation mechanism of alkane sulfonates. (From Colvin M. Molecular pharmacology of alkylating agents. In: Cooke ST, Prestayko AW. *Cancer and chemotherapy*, vol 3. New York: Academic Press, 1981:291.)

NITROSOUREAS

- Chloroethylnitrosourea: eradicated intracranially inoculated tumors because of their lipophilic character and the ability to cross blood brain barrier.
- BCNU: brain tumors, colon cancer and lymphomas.
- CCNU, Methyl-CCNU: greater activity against solid tumors



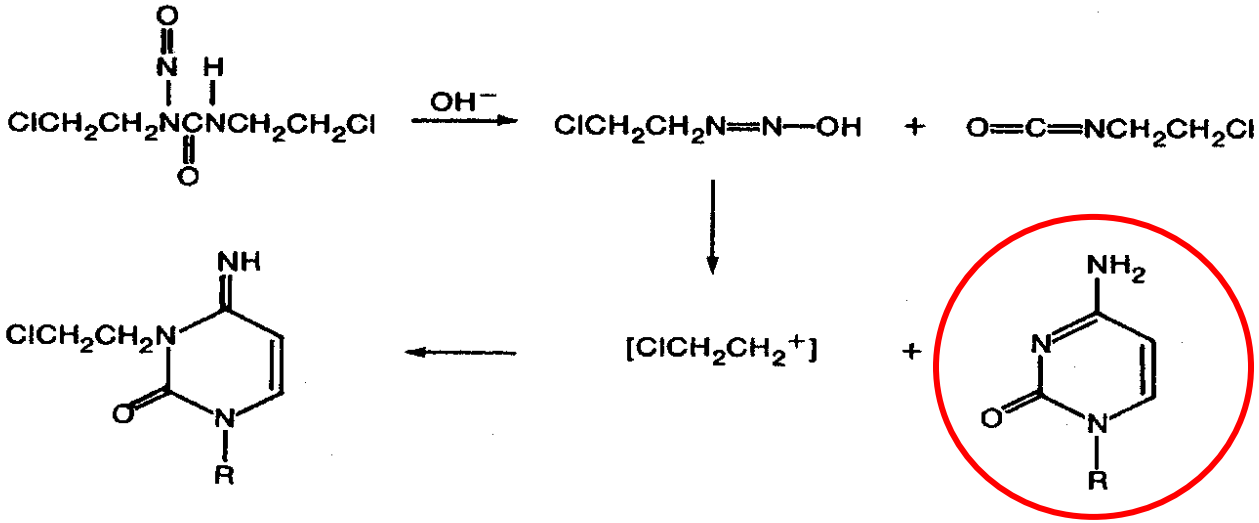
Structures of nitrosoureas. (BCNU, bischloroethyl-nitrosourea; CCNU, cyclohexylchloroethylnitrosourea.)

PLATINUM AGENTS

- **Cisplatin:** heavy organic metal complex
- Cell-cycle-phase-nonspecific alkylating agent
- Intrastrand & interstrand DNA cross links and adducts

ALKYLATION OF NUCLEOSIDE BY BCNU

- Decomposed into diazonium hydroxide molecule and isocyanate compound.
- Chloroethyldiazonium ion or chloroethyl carbonium ion alkylate DNA, producing chloroethyl amino groups on nucleotide, which produce DNA-DNA & DNA-protein cross links through a dehalogenation step.
- Isocyantes inhibit DNA polymerase, DNA ligase, RNA synthetic and processing enzymes & glutathione reductase



. Alkylation of nucleoside by bischloroethylnitrosourea (BCNU).

CELLULAR PHARMACOLOGY

Cellular Targets:

- Nucleic acids, Proteins, Amino acids, and Nucleoides

Sites of Alkylation:

- Oxygens of phosphates,
- Oxygens of bases,
- Amino groups of purines,
- Amino groups of proteins,
- Sulfur atoms of methionine &
- Thiol groups of cysteinyl residues of glutathione.

CYTOTOXICITY IS MOST LIKELY DUE TO ALKYLATION OF DNA:

In DNA molecule alkylation targets are,

- Electron-rich phosphoryl oxygens of sugar phosphate &
- All oxygens and nitrogen atoms of purine and pyrimidine bases can be alkylated to varying degrees, e.g., alkylation of the O-6 atom and of extracyclic nitrogen of guanosine is of particular importance for carcinogenesis.

DNA Cross-Linking

- Bifunctional alkylating agents such as the nitrogen mustards produced **interstrand and intrastrand DNA-DNA cross-links** and that these cross-links were responsible for the inactivation of the DNA and cytotoxicity.
- Cell check point proteins, including most prominently **p53**, are responsible for recognition of DNA alkylation & strand breaks.
- Recognition of DNA damage leads to a halt in cell-cycle progression & initiation of programmed cell death.

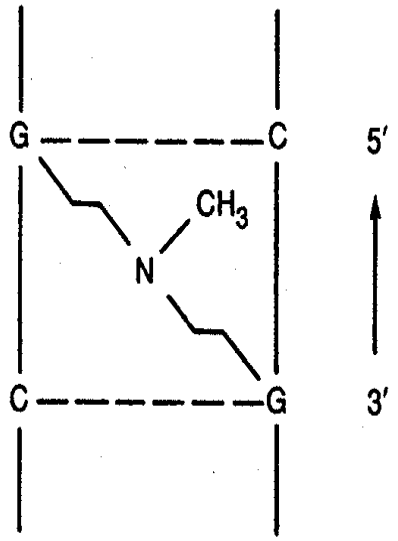


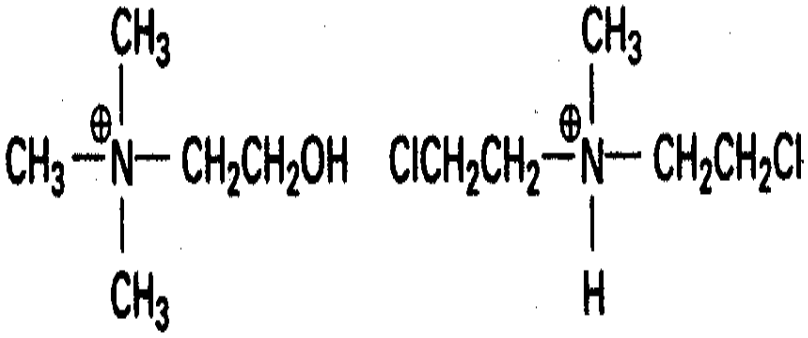
FIGURE 13-13. Cross-linking of DNA by nitrogen mustard. (Modified and reproduced from Brookes P, Lawley PD. The reaction of mono- and di-functional alkylating agents with nucleic acids. *Biochem J* 1961;80:486, with permission.)

CELLULAR UPTAKE

ACTIVE TRANSPORT SYSTEM:

Temp. dependent, accumulate drug against a conc. gradient & sensitive to metabolic inhibitors.

- **Mechlorethamine:** Choline, because of structural resemblance.
- **Melphalan:** active transporter for leucine and other neutral amino acids



Structures of choline and mechlorethamine.

PASSIVE DIFFUSION:

- Highly lipid soluble nitrosoureas BCNU and CCNU enter cells by **passive diffusion**.

TUMOR RESISTANCE : Major Problems

- Decreased drug entry into the cell.
- Increased thiol content to inactivate AA.
- Enzymatic detoxification mechanisms conjugate intermediates or metabolize them to inactive intermediates.
- Enhanced repair of alkyl agent DNA lesions generated by alkylation.
  - AGT (guanine-O^6-alkyl transferase) repair
  - nucleotide excision repair (NER)

REVERAL OF RESISTANCE: 1. DRUG MODULATION

Reduced GSH metabolism have been implicated in resistance

- Precursors (e.g., cysteine, GSH-monoethyl ester) of GSH have been given to replete GSH in normal tissues, thus reducing the host toxicity.
- Specific inhibitors of GSH biosynthetic enzymes have been administered to decrease intracellular GSH.
- Inhibitors (e.g., ethacrynic acid) of detoxifying enzymes such as GSTs have been given to decrease the tumor cell's ability to protect itself against alkylating metabolites.
- Administration of thiol precursors to protect normal tissues.

REVERAL OF RESISTANCE: 2. NITROSOUREA MODUALTION

- A modulatory approach specific for nitrosoureas has resulted from studies of DNA repair.
- Alkyl guanine alkyl transferase (AGT) binds irreversibly to O^6-guanine alkyl adducts and removes them from DNA, inactivating itself in the process.
- Methylation of guanine at O^6 position serves irreversibly to consume and inactivate AGT.
- Usual order of reactivity for alkylation displacement reactions is

  Benzyl > methyl > *n*-propyl > isobutyl

CLINICAL PHARMACOLOGY

Decomposition vs. Metabolism

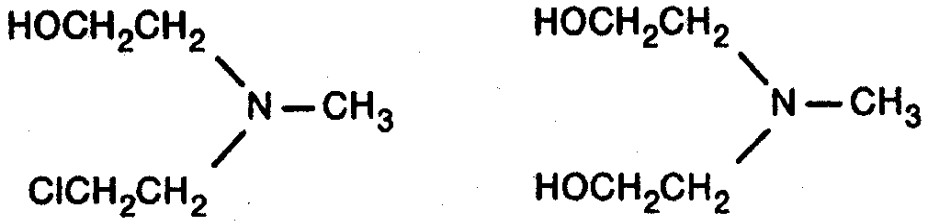
Degradation:

- Spontaneous hydrolysis of alkylating entity (i.e., alkylation by water): e.g., mechlorethamine.

Metabolism:

- Enzymatic metabolism: e.g., mechlorethamine.
- Oxidation: e.g., chlorambucil.

2-hydroxyethyl-2-chloroethylmethylamine	Bis-2-hydroxy ethylmethylamine



Hydrolysis products of mechlorethamine.

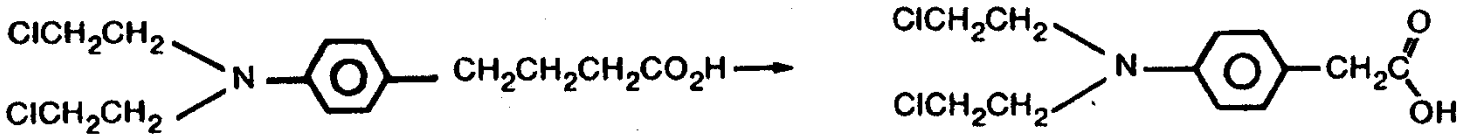


FIGURE 13-16. Oxidation of the butyric acid side chain of chlorambucil to produce phenylacetic acid mustard.

CYCLOPHOSPHAMIDE METABOLISM

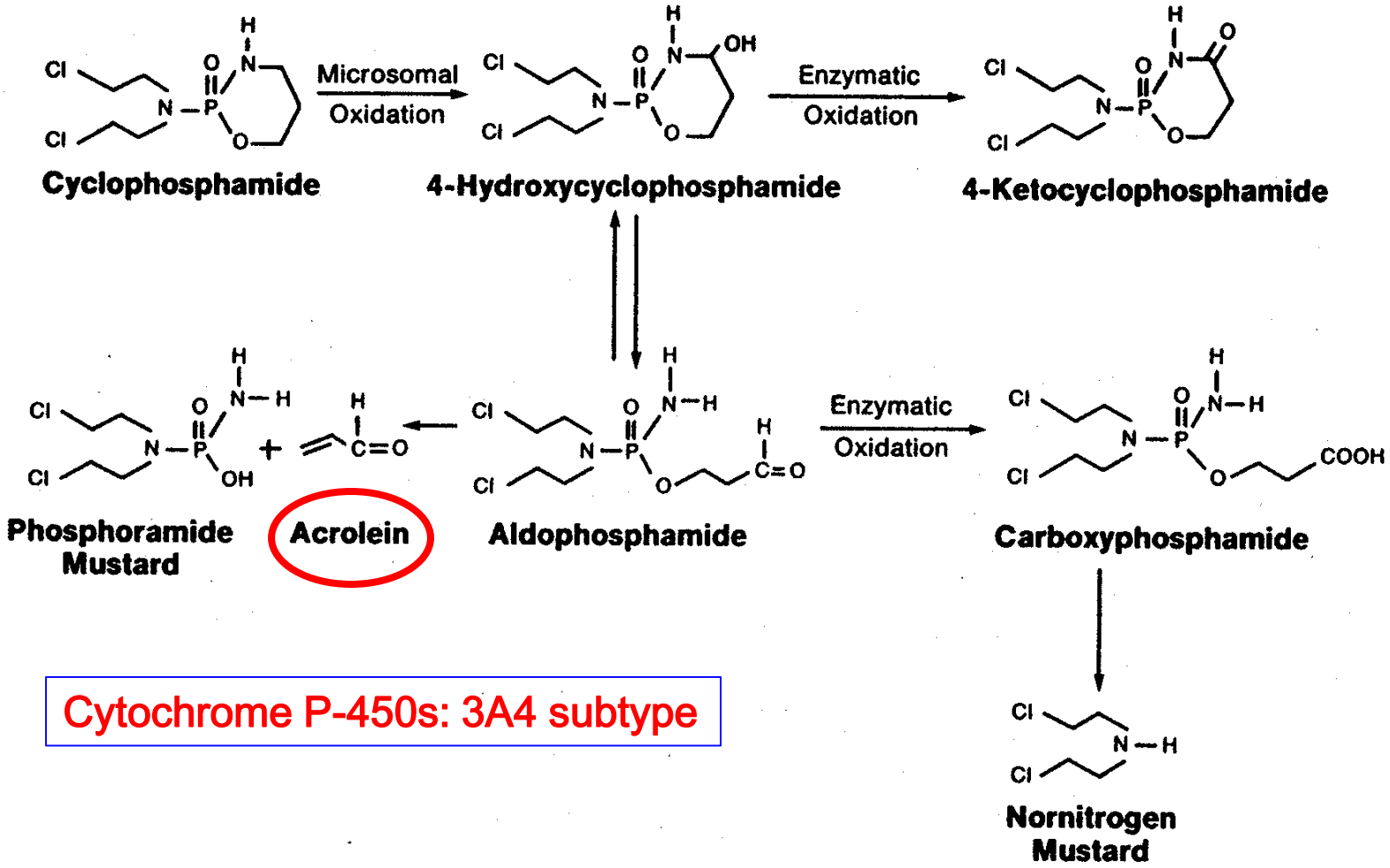
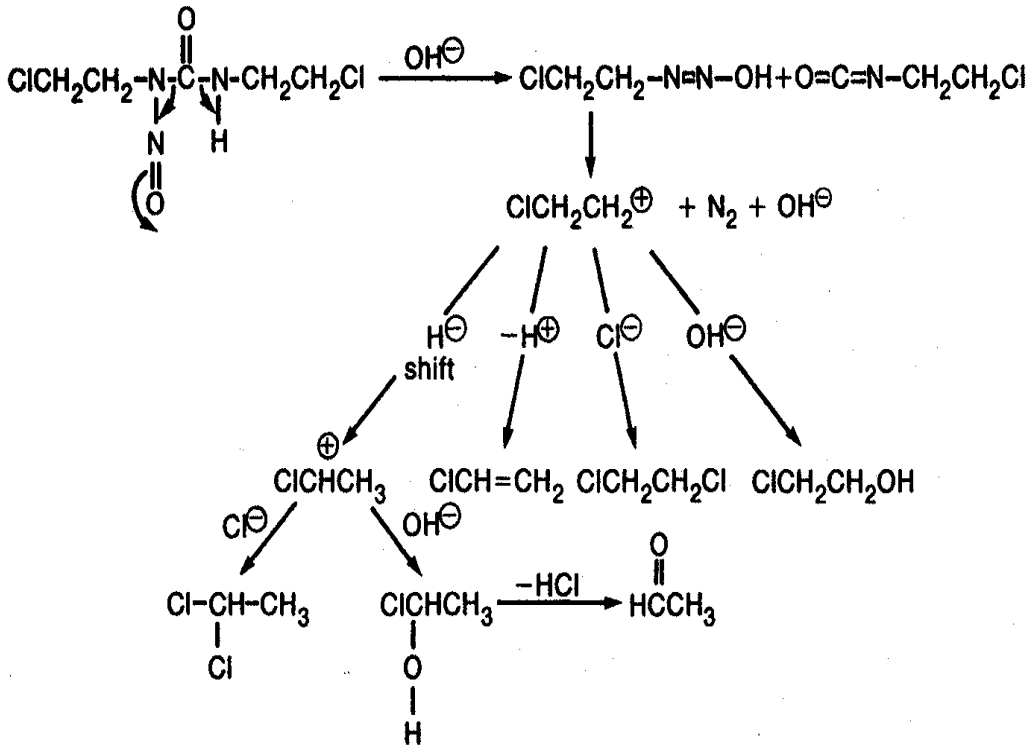


FIGURE 13-17. Metabolism of cyclophosphamide.

BCNU DECOMPOSITION IN BUFFERED AQUEOUS SOLUTION



Decomposition of bischloroethylnitrosourea (BCNU) in buffered aqueous solution.

BCNU: enzymatically denitrosated by hepatic microsomes.

CLINICAL PHARMACOKINETICS

MELPHALAN

DOSE	CONC.	HALF LIFE	EXCRETION
0.6 mg/kg (I/V)	4.5-13 μmol/L	1.8 hrs	13%, 24 hrs (urine)
0.6 mg/kg (oral)	1 μmol/L 6 hrs		20-50% (feces)

I/V- Myelosupression, blood urea level greater than 30 mg/dL, 50% reduced

Ovarian cancer

In-transit limb metastases of malignant melanoma

CHLORAMBUCIL

0.6 mg/kg (oral)	2.0-6.3 μmol/L	1 hr	less than 1%

absorbed more completely & rapidly than melphalan

CYCLOPHOSPHMIDE & METABOLITES

CLINICAL PHARMACOKINETICS OF CYCLOPHOSPHAMIDE AND METABOLITES

Subject of Study	Cyclophosphamide Dose (mg/kg)	Peak Plasma Concentration, (μmol/L)	Plasma $t_{1/2}$ (h)	References
Cyclophosphamide	1–2	4	—	236
	6–15	50	3–10	237
	60	500	—	238
Total alkylating activity	40–60	10–80	7.7	237, 244, 245
Phosphoramide mustard	60–75	50–100	—	238
	4–12	3–18	8.7	247
Nornitrogen mustard	60–75	200–500	—	238, 247
	4–9	4–15	3.31	—
Aldophosphamide/4-hydroxycyclophosphamide	10	1.4	1–5	242, 243, 248, 250, 251
	20	2.6	—	

$t_{1/2}$, half-life.

- Prolonged plasma levels renal failure, reduction is dose recommended.
- Patients with severe renal impairment doesn't result in increase in hematologic & other toxicity

IFOSFAMIDE

- Single dose 3.8-5 g/m ~ terminal half life is 15 hour, longer than that of cyclophosphamide (3-10 hrs)
- 1.6-2.4 g/m similar to cyclophosphamide
- 3.8 g/m is similar to 1.1 g/m cyclophosphamide
- 6-15% is excreted through urine, although urinary excretion may approach 50% at high single dose.
- Cleavage of chloroethyl group from side chain & ring nitrogen is quantitatively more significant pathway for metabolism

THIOTEPA

- 30-300 mg/m, half life ranges from 1.2-2 to 24 hours.
- 15% of administered thiotepa is excreted in urine with 4.2% as TEPA and 23.5 % as other alkylating species

NITROSOUREA

BCNU:

- 60-170 mg dose with initial peak levels of 5 µmol/L with retention time 15-75 minutes
- A new analogue, fotemustine, has longer half life & greater ability to penetrate into the tumor cells.

BUSULFAN

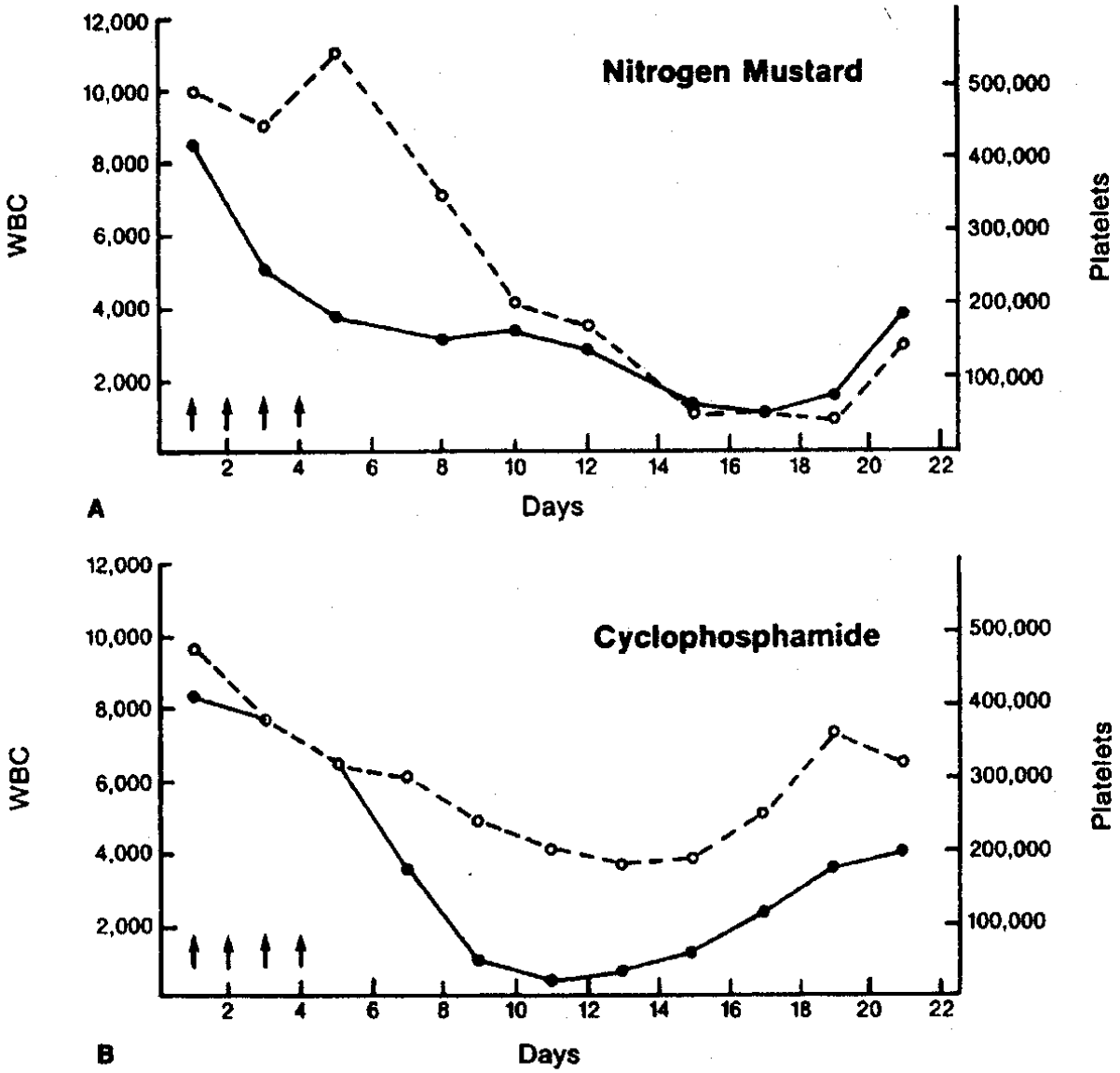
- Well absorbed. i.e., 100% for standard doses of 2-6 mg/day
- Primary elimination half life is ~2.5 hours
- Volume of distribution
  - 0.6 L/kg in adults
  - 1 L/kg children aged 2-14
  - 1.4-1.6 L/kg in infants
- High lipid solubility & low protein binding

TOXICITY

1. HEMATPPOIETIC SUPRESSION

- Suppression of leukocytes, platelets & red cells
- Significant depression when dose of drug exceeds 30 mg per kg
- Cyclophosphamide, spare hematopoietic stem cells
- Busulfan and melphalan especially damage to bone marrow stem cells
- Phenylalanine mustard seems to be more damaging to stem cells than that of cyclophosphamide
- Nitrosourea damage hematopoietic precursor (leukocyte & platelet) whose differentiation or maturation period is 3-4 weeks

LEUCOPENIA & THROMBOCYTOPENIA AFTER ADMINISTRATION MECHLORETHAMINE AND CYCLOPHOSPHAMIDE



Leukopenia and thrombocytopenia after administration of mechlorethamine, 0.1 mg per kg per day for 4 days **(A)**, or cyclophosphamide, 60 mg per kg per day for 4 days **(B)**. [●, white blood count (WBC); ○, platelets.] (Modified and reproduced from Nissen-Meyer R, Host H. A comparison between the hematologic side effects of cyclophosphamide and nitrogen mustard. *Cancer Chemother Rep* 1960;9:51, with permission.)

2. NAUSEA & VOMITING

- Frequent side effect, but not life threatening
- Poorly controlled by antiemetics
- Major source of patient discomfort
- Centrally mediated not due to direct gastrointestinal toxicity
- Frequency & degree of reaction variable
- Increase with the increase of dose of alkylating agent
- Time onset of these reactions is also variable
- Sustained use of antiemetics is important during the alkylating agent chemotherapy

3. INTERSTITIAL PNEUMONITIS & PULMONARY FIBROSIS

- Cytotoxicity to the pulmonary epithelium
- Pulmonary fibrosis, atypia of alveolar & bronchiolar epithelia, hyperplasia of type2 pneumocytes & interstitial and intraalveolar edema by busulfan, cyclophosphamide, BCNU, methyl-CCNU, melphalan, chlorambucil & mitomycin C.

4. RENAL & BLADDER TOXICITY

- Cyclophosphamide & ifosfamide, mild cystitis to severe bladder damage with massive hemorrhage
- Due to toxic metabolite (may be acrolein) irritation with bladder mucosa
- Adequate hydration and frequent bladder emptying may lessen the complication
- Prevention agent for this is 2-mecraptoethane sulfonate (MENSA).
- If all local measures fail, cystectomy necessary to prevent the fatal hemorrhage
- Damage may extend up the ureters to the renal pelvis
- Water retention in patients receiving cyclophosphamide, characterized by a marked fall in urinary out put.
- Continuous infusion of furosemide necessary for diuresis and free water clearance

5. ALOPECIA

- Associated with cyclophosphamide, infrequently with busulfan.
- Severe, especially when combined with vincristine sulfate or doxorubicin hydrochloride
- Regrowth of occurs after therapy but change in color & greater curl
- Use of tourniquet or ice pack may reduce the alopecia

6. *ALLERGIC REACTIONS*

- Skin eruptions, angioneurotic edema, urticaria & anaphyllactic reactions

7. GONADAL ATROPHY

- Depletion of testicular germ cells and its functional counterpart of aspermia reported in human and animals, e.g., cyclophosphamide
- Testicular damage by alkylating agents is reversible
- Amenorrhea due to busulfan, cyclophosphamide, melphalan
- Decreased levels of estrogen & progesterone and increased levels of serum FSH and luteinizing hormone

8. TERATOGENESIS

- All alkyling agents are teratogenic both *in vivo* and *in vitro*
- Effect is due to the direct cytotoxicity to the developing embryo
- Administration of alkyling agents during the 1st trimester presents a definite risk of a malformed viable infant while not in 2nd and 3rd trimesters.

9. CARCINOGENESIS

- Multiple myeloma, lymphomas and acute leukemia.
- Melphalan, cyclophosphamide, chlorambucil and nitrosourea
- Occurrence of acute leukemia in patients treated with alkylating agents for cancer

10. ORGAN TOXICITY IN HIGH DOSE CHEMOTHERAPY

- Alkylating agents produce myelosuppresion as their dose limiting toxicity
- These toxicities results from long treatment, rarely with initial therapy
- Logical tool either alone or in combination for high-dose chemotherapy regimens.
- High dose setting toxicities affect gut, heart, lung, liver, CNS become dose limiting and life threatening

ALKYLATING AGENTS IN HIGH-DOSE CHEMOTHERAPY

Dose-Limiting Extramedullary Toxicities of Single Agents

Drug	MTD[a] (mg/m²)	Fold Increase Over Standard Dose	Major Organ Toxicities
Cyclophosphamide	7,000	7.0	Cardiac
Ifosfamide	16,000	2.7	Renal, CNS
Thiotepa	1,000	18.0	GI, CNS
Melphalan	180	5.6	GI
Busulfan	640	9.0	GI, hepatic
BCNU	1,050	5.3	Lung, hepatic
Cisplatin	200	2.0	PN, renal
Carboplatin	2,000	5.0	Renal, PN, hepatic
Etoposide	3,000	6.0	GI

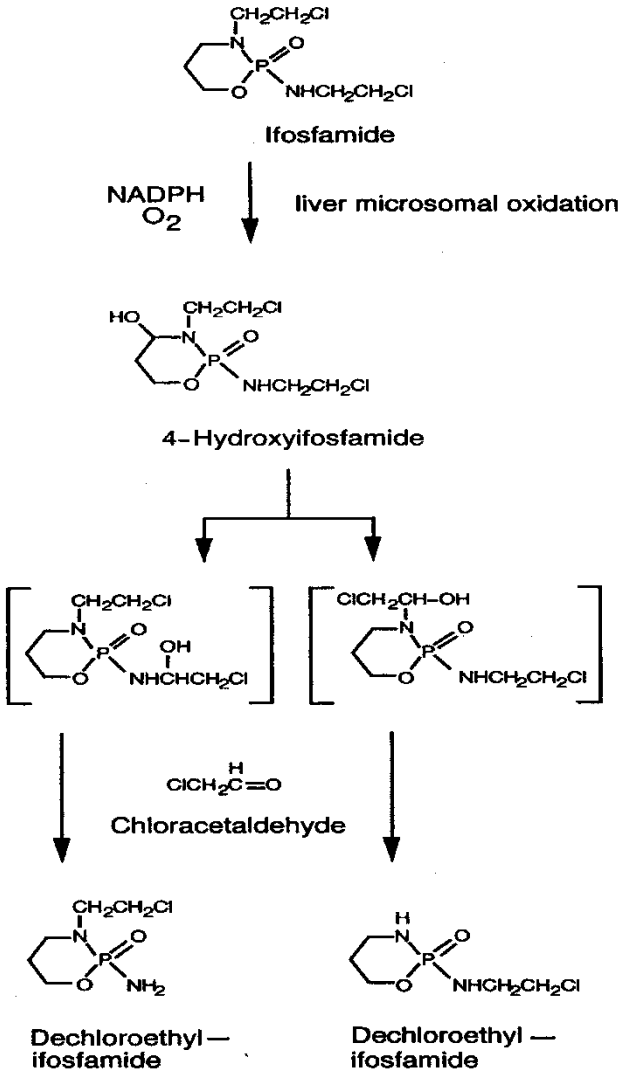
Combination High-Dose Chemotherapy Regimens

Regimen	Dose	Major Toxicities	Regimen MTD[b]	References
Cyclophosphamide BCNU Etoposide	6,000 300 750	Lung, GI	0.47	445
Busulfan Cyclophosphamide	640 8,000	Lung, GI, hepatic	1.0	446
Ifosfamide Carboplatin Etoposide	16,000 1,800 1,500	Renal, hepatic, GI	0.8	447
Cyclophosphamide Etoposide Cisplatin	5,250 1,200 180	GI, renal	0.68	448
Cyclophosphamide Thiotepa Carboplatin	6,000 500 800	GI, cardiac	0.59	449
Cyclophosphamide BCNU Cisplatin	5,625 600 165	Lung, hepatic, renal	0.57	450

BCNU, bischloroethylnitrosourea; CNS, central nervous system; GI, gastrointestinal; MTD, maximum tolerated dose; PN, peripheral neuropathy.
[a]See references 91, 438–444.
[b]See Eder et al.[449] for calculation of regimen MTD.

11. NEUROTOXICITY BY IFOSFAMIDE

- High dose ifosfamide; most frequent cause of neurotoxicity
- CNS toxicities include varying degrees of confusion, aphasia, hallucinations, cerebellar and motor system dysfunction, seizures and coma
- Presence of side chain N-linked chloroethy moiety, which after oxidation and N-dethylation form chloracetaldehyde



Metabolic activation of ifosfamide to its active form, 4-hydroxyifosfamide, and further metabolic transformation to chloracetaldehyde and other end products. (NADPH, reduced form of nicotinamide-adenine dinucleotide phosphate.)

12. IMMUNOSUPPRESSION

- Alkylating agents suppress both humoral and cellular immunity.
- Most immunosuppressive anticancer drug is cyclophosphamide.
- Recovery for the immune response is usually prompt, however, continuous drug therapy may lead to severe lymphocyte depletion and profound immunosuppression, associated with increase fungal, viral, and protozoal infections.
- Fludarabine or cladribine drugs combined with drugs made from interferon boost up immune system and prevents from infections.

- Immunosuppressive activity of alkyling agents, particularly cyclophosphamide used for two clinical applications:

  - Suppression of immune response before organ transplantation. e.g., bone marrow transplantation, kidney graft rejection.
  - In patients with nonmalignant disease for treatment of immunologic disorders e.g., lupus erythematosus, rheumatoid arthritis, membranous glomerulonephritis

REFERENCES

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