

تفريغ ميديسنال 2



المحاضرة 1: Cancer Part 1

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الصيدلاني/ة:



لجان الترقيات

Cancer molecular biology

- Increased knowledge of intercellular and intracellular communication has led to the development of several newer agents that have shown some effectiveness in treating several cancers, especially when used in combination with more traditional agents.
- These have included several monoclonal antibodies that target the overproduction of growth factor receptors and Tyrosine Kinase inhibitors that target the transduction process involved in growth factor stimulation
- You have to refer to the youtube lectures in your moodle.

Cancer Types

categorized based on the functions/locations of the cells from which they originate:

- **Carcinoma**: a tumor derived from epithelial cells, those cells that line the surface of our skin and organs (80-90% of all cancer cases reported)
- **Sarcoma**: a tumor derived from muscle, bone, cartilage, fat or connective tissues.
- **Leukemia**: a cancer derived from white blood cells or their precursors.
- **Lymphoma**: a cancer of bone marrow derived cells that affects the lymphatic system.
- **Myelomas**: a cancer involving the white blood cells responsible for the production of antibodies (B lymphocytes).

كارسينوما (Carcinoma)	الخلايا الظهارية (Epithelial cells)	ورم ينشأ من الخلايا التي تُبطن سطح الجلد والأعضاء. يشكل هذا النوع 80-90% من جميع حالات السرطان
ساركوما (Sarcoma)	الأنسجة الضامة والداعمة	ورم ينشأ من العضلات، أو العظام، أو الغضاريف، أو الدهون، أو الأنسجة
لوكيميا (Leukemia)	خلايا الدم البيضاء	سرطان مشتق من خلايا الدم البيضاء أو طلائعها (Precursors).
ليمفوما (Lymphoma)	خلايا مشتقة من نخاع العظم	سرطان يؤثر على الجهاز اللمفاوي.
مايلوما (Myelomas)	خلايا الدم البيضاء (الخلايا البائية)	سرطان يشمل خلايا الدم البيضاء المسؤولة عن إنتاج الأجسام المضادة (B)

Antineoplastic Agents

مميزاتهم انهم يعملون على الalkylation
for DNA

▲ **Alkylating agents** → make covalent bond with nucleic acid
S-phase لا تؤثر على

(Form bonds with nucleic acids and proteins)

Carboplatin, cyclophosphamide, melphalan, thiotepa

▲ **Antimetabolites** → metabolite تدخل في DNA في انهم الخلية
وبعد ما تدخلهم تكتشف انهم مختلفين والفروقات تقسم 2 ووقفوا

(similar to metabolites involved in nucleic acid synthesis)

Polate بيشبه Uracil بيشبه

Methotrexate, fluorouracil, gemcitabine

▲ **Natural Products** → هدفه ال S-phase من انهم تقسم الخلية

(anti tumour antibiotics, microtubule stabilizer, mitotic inhibitor, topoisomerase inhibitor)

doxorubicin, docetaxel, vinorelbine, topotecan

▲ **Endocrine agents** → Cancer الهرمونات الانثوية يزيد ال
الانثوية وتعالج ال Cancer الذكورية

(Aromatase inhibitors, oestrogen antagonist, corticosteroids, LHRH agonist)

Anastrozole, tamoxifen, prednisolone, goserelin

▲ **Molecularly targeted agents** → Kinase-inhibitor

(gene expression, monoclonal antibody, tyrosine kinase inhibitor)

Retinoids, trastuzumab, gefitinib → وجودها يعني
anti-body ↑ Kinase inhibitor

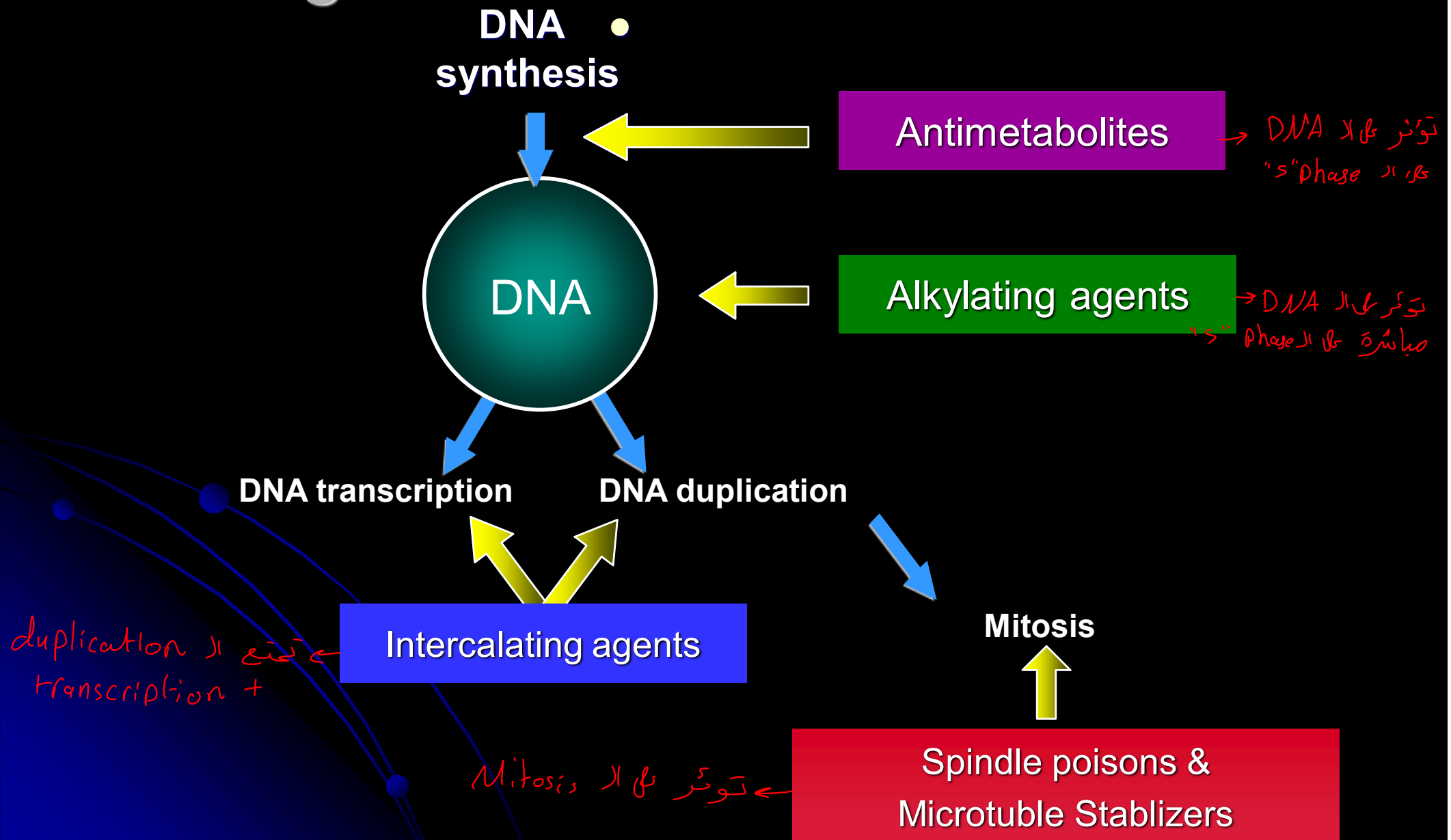
▲ **Biologic response modifiers**

Interferon, thalidomide, filgrastim

زمان كانوا تاخذوه الحامل عشان الرجاء بس
في سنة 2 isomers R - يمنة والخللايا
S - الوحام

بس زمان كانوا ياخذوا R isomer عشان
صديق الاطفال صار ينولوا يتشوهات ووقفوا استعماله
للرجاء و زي الدكتور قواز عبد الحق و بعدها صاروا يستعملوه ال Cancer لانه يمنة نو الخللايا

Sites of Action of Cytotoxic Agents – Cellular Level



Antineoplastic Agents

Alkylating agents	Topoisomerase inhibitors	Antimetabolites	Molecularly targeted
busulfan	dactinomycin	cytarabine	erlotinib
carboplatin	daunomycin	clofarabine	imatinib
carmustine ✓	doxorubicin	fludarabine	sorafenib
cisplatin	etoposide	gemcitabine	sunitinib
cyclophosphamide ✓	etoposide phosphate	mercaptopurine	tretinoin
dacarbazine	idarubicin	methotrexate	Herceptin
ifosfamide ✓	irinotecan	nelarabine	Miscellaneous
lomustine ✓	liposomal daunomycin	thioguanine	arsenic trioxide
mechlorethamine ✓	liposomal doxorubicin	Tubulin binders	asparaginase
melphalan ✓	mitoxantrone	docetaxel	bleomycin
oxaliplatin	teniposide	ixabepilone	dexamethasone
procarbazine ✓	topotecan	vinblastine	hydroxyurea
temozolomide		vincristine	mitotane
thiotepa		vinorelbine	PEG-asparaginase
		paclitaxel	prednisone

side effect

Problems with chemotherapy

resistance

- Treatments are non-specific, attack healthy cells as well as normal cells since cancer cells are derived from normal cells.
- Cancers can develop resistance: for example with platinum-drugs, cancer cells became resistant by many

ways:

من الـ Alkylation agent ويعتبر من الأدوية القوية
نستخدمه لعلاج سرطان الكلى ويصير عليه resistance لصاي
الأسباب

يدخل الخلية بس يطلع أكثر ← Decreased drug uptake/increased efflux ← ما يقدر يدخل الخلية

– Enhanced tolerance of DNA adducts → الـ Covalent bond موجودة بس

الـ cancer cell مبسوطة لا نه رت تحت الـ bond بس
رقت تفتتت

الـ الخلية تعالج نفسها
بجيت بغير عندها enzyme

تقوى المنطقة كـ DNA
الـ Covalent bond و
تكمّل شغلها الطبيعي

Enhanced repair of DNA adducts

Increased drug deactivation by intracellular glutathione

الـ glutathione مسؤول على انه يخلصنا من المواد الضارة بس اذا الـ cancer cell منعتة بشغل أكبر
رقت تطلع الـ دا لبرا الخلية

Alkylating Agents

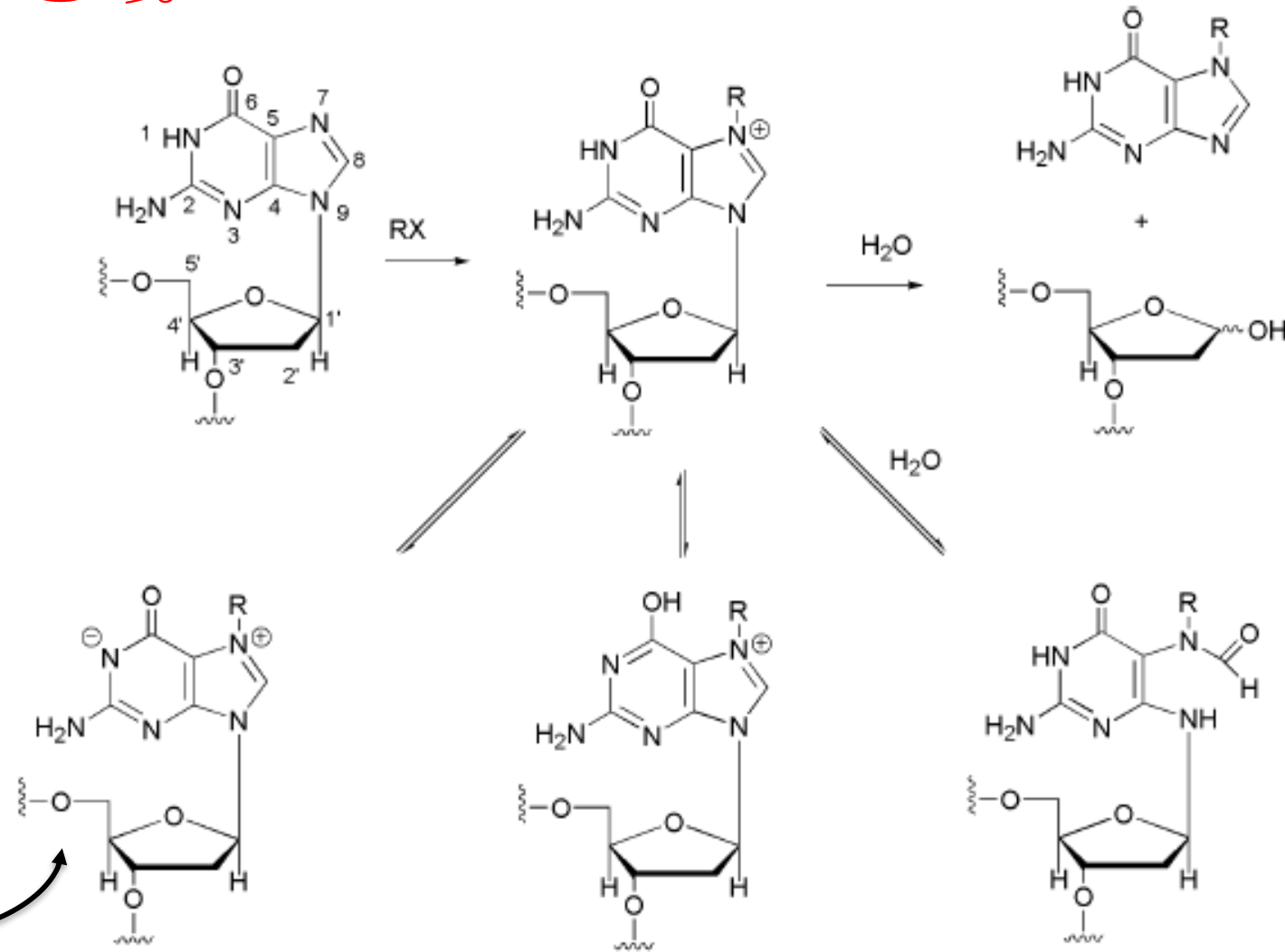
- The alkylating agents are a class of drugs that are capable of forming **covalent bonds** with important biomolecules. The major targets of drug action are nucleophilic groups present on DNA (especially the 7-position of guanine)
- proteins and RNA among others may also be alkylated.
- Alkylation of DNA is thought to lead to cell death, although the exact mechanism is uncertain. Potential mechanisms of cell death include activation of apoptosis caused by p53 activation and disruption of the template function of DNA.

عمل الـ Alkylation agent مثل مقبض على الـ DNA بس ،
يشغل على الـ RNA ، ويرفض بتشجعوا الـ Apoptosis عن طريق

activation of p53 وهو العامل المرتبط بالوت المبرمج للخلايا

لكن الـ Caphion نفس السلسلة مختلف

Alkylating Agents



Scheme 10.1 • Alkylation of guanine N-7 and subsequent depurination of DNA.

Additionally, alkylation has been proposed to result in **altered base pairing** away from the normal G-C: A-T hydrogen bonds because of alterations in tautomerization.

The alkylation also leads to increased acidity of the N-1 nitrogen reducing the pKa from 9 to 7 to 8 giving rise to a zwitterionic form that may also mispair

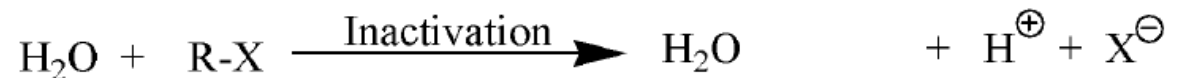
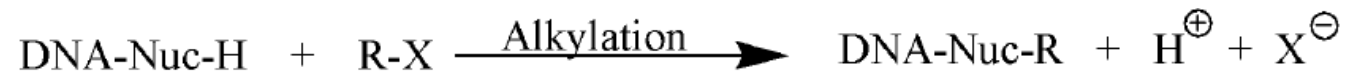
Resistance to alkylating agents

- In many cases, however, the cancer cells have dysfunctional p53 so that even though the cell has been unable to replicate DNA error free, cell death via apoptosis does not occur.
- In this way, cancer cells may become resistant to the effect of alkylating agents.
- Another possibility is that the cancer cells, like normal cells, have various mechanisms by which alkylated DNA bases can be excised.

موجودہ السلايدات
إلى تحديث

- The general mechanism for alkylation involves nucleophilic attack by

$\text{—N=}, \text{—NH}_2, \text{—OH}, \text{—O—PO}_3\text{H}$ of DNA and RNA



Scheme 10.2 • General reaction for alkylation and inactivation of alkylating agents.

Where X = a leaving group

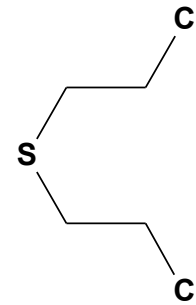
NITROGEN MUSTARDS



- The nitrogen mustards are compounds that are chemically similar to sulfur mustard or mustard gas developed and used in World War I. The term “mustard” comes from the similarity in the blisters produced by the compound and those seen upon exposure to the oil of black mustard seeds.
- Investigation of sulfur mustard revealed that it possessed antineoplastic properties but because the compound existed as a gas at room temperature, handling and administration of the material were difficult.
- Conversion of the sulfide to a tertiary amine allowed for the formation of salts, which exist as solids at room temperature allowing for easier handling and dosing. The term mustard was then extended to the nitrogen analogs (nitrogen mustards) given their chemical similarity.
- Mustards such as mechlorethamine are classified as **dialkylating** agents in that one mustard molecule can alkylate two nucleophiles.
- The initial acid–base reaction is necessary to release the lone pair of electrons on nitrogen, which subsequently displaces chloride to give the highly reactive aziridinium cation (see figure next page).
- Nucleophilic attack can then occur at the aziridinium carbon to relieve the small ring strain and neutralize the charge on nitrogen.
- This process can then be repeated provided a second leaving group is present

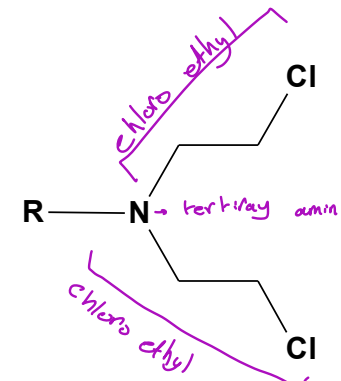
Chemical Warfare – circa 1914

- Two most common agents:
 - Chlorine gas
 - Mustard gas



Sulfur Mustard (غاز)

(chemical weapon) not used clinically



Nitrogen Analog

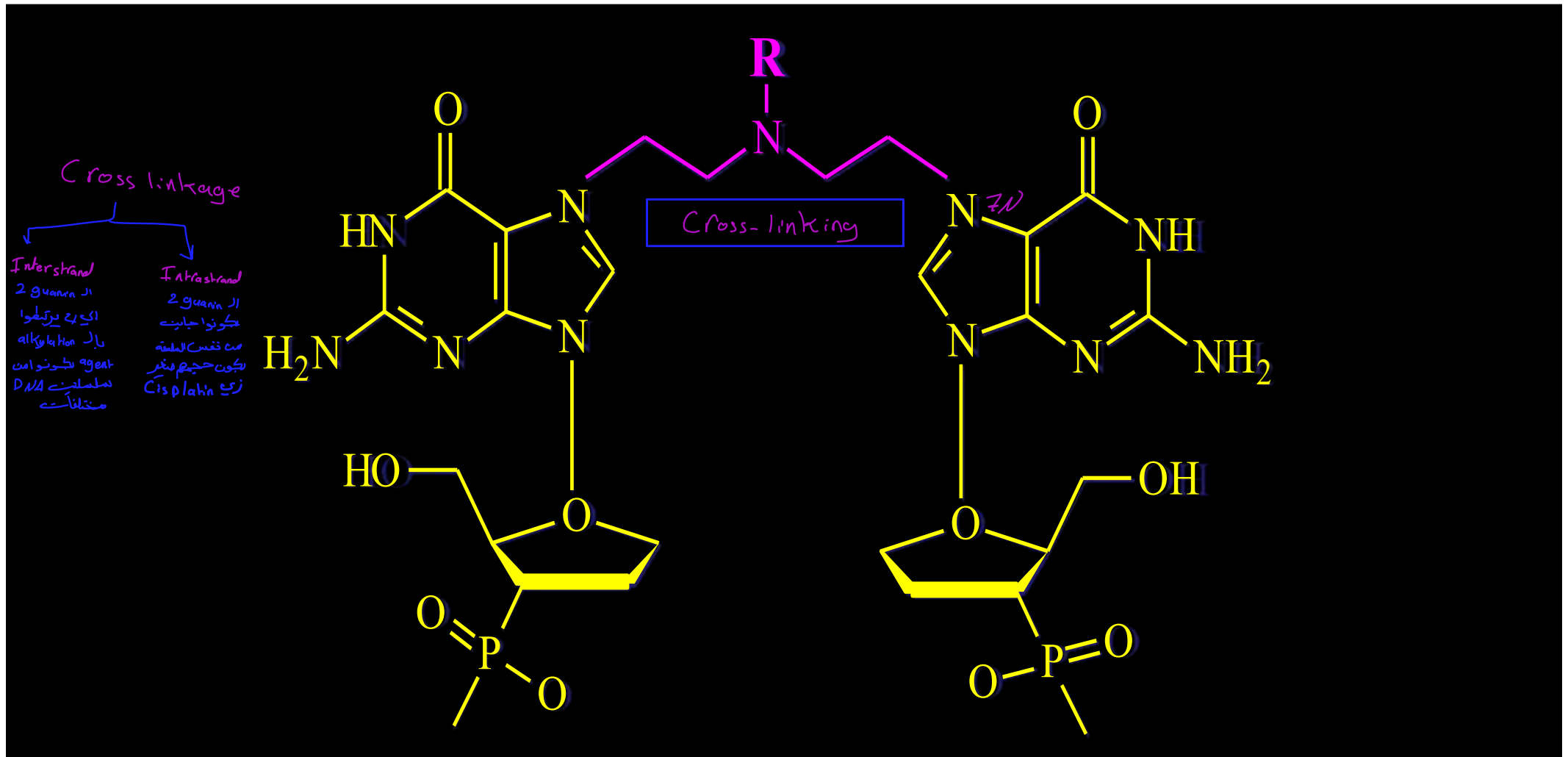
هي الـ analogy أي اخذوه
من الـ Sulfur Mustard بحيث
بدلوا الـ S بالـ N
وهو اضعف من Sulfur Mustard
لكن بقدر استعماله Clinically فبالإضافة
منه Powder و Tablet حتى حقن

بالحرب العالمية تم إطلاق
هذا الغاز وصار نتيجة ذلك
حروق جلدية للجند و
صار في ملائكي بالانسجة
الجلدية، تم تسخينه صلبه
لأنه لو تركه في الماسترد، ويقلو
الـ sterility قروو يجربوا يهتجروا
بـ analogy منه اقدر استعماله Clinically
لأنه Sulfur-mustard غاز و صا في ادويه هيسو في الـ



Lieut. Col. William Mook, an army skin expert, treating a soldier burned by mustard gas

An Example of DNA Crosslinking



Crosslinking: Joining two or more molecules by a covalent bond. This can either occur in the same strand (intrastrand crosslink) or in the opposite strands of the DNA (interstrand crosslink). Crosslinks also occur between DNA and protein. DNA replication is blocked by crosslinks, which causes replication arrest and cell death if the crosslink is not repaired.

Alkylating Agents (Covalent DNA binding drugs)

إذا تغير التركيب الجيني

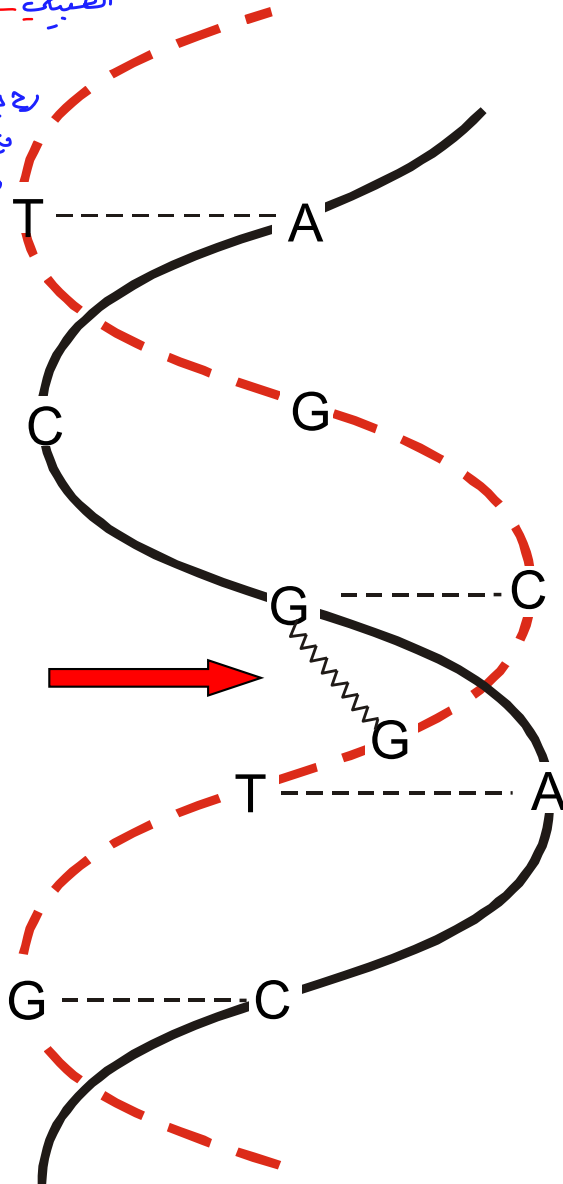
أو إذا صار ترتيبه بالشكل

الطبيعي ← G-C
T-A

مismatching

بغية إصلاح G-G

وهذا نتيجة الـ Zwitterion

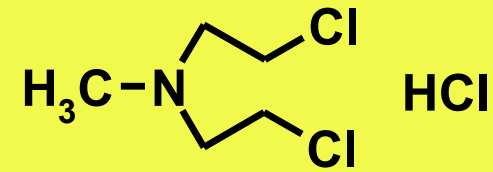


الدكتور جانتة سؤال سنوات طلبتهم على الترتيب

1. The first class of chemotherapy agents used.
2. They stop tumour growth by cross-linking guanine nucleobases in DNA double-helix strands - directly attacking DNA.
3. This makes the strands unable to uncoil and separate.
4. As this is necessary in DNA replication, the cells can no longer divide.
5. Cell-cycle nonspecific effect → ممكن يؤثر على M, S, G₂, G₁, G₀.
6. Alkylating agents are also mutagenic and carcinogenic → التأثير المزمن صوت

الـ Chemotherapy! كى محتوية
فى الـ alkylation agent بتأثرهم للأطفال
عشان هيلجى السيرة إلى رح نأخذهم يفضل
انها ما تنجب ليجد 5 سنوات عشان المبيضة ما
يكون متأثر

Mechlorethamine (or Chlormethine)



Mechlorethamine HCl - Mustargen®



➤ Mechlorethamine is highly reactive, in fact, too reactive and therefore. In cases of **extravasation** (drug escapes from the tumor into the underlying tissue), the antidote

الحقن ومرفق
ال Cancer الأثر
عرضه إلى جانب
الأوعية عندهم
ضعيفه

sodium thiosulfate

الدواء يوصل إلى fissure
حواليه tumor

($\text{Na}_2\text{S}_2\text{O}_3$), a strong nucleophile, may be administered. → anti dot



➤ It is capable of reacting with electrophilic sites on the mustard, and once reaction has occurred, the resulting adduct has increased water solubility and may be readily eliminated (Scheme 10.4).

➤ Cancer patients are at an increased risk of extravasation because of the fragility of their veins resulting from ^①radiation, ^②previous chemotherapy treatments, or ^③malnutrition.

ل زمان اخذوا alkylation
agent عشان هيلجى بهر ال
Vein

له لانه يكون
عندهم! كتاب
ما بياكلوا منج

ال Thiosulfate تعطيه
antidote لا يفر عنه
الحريفة extravasation

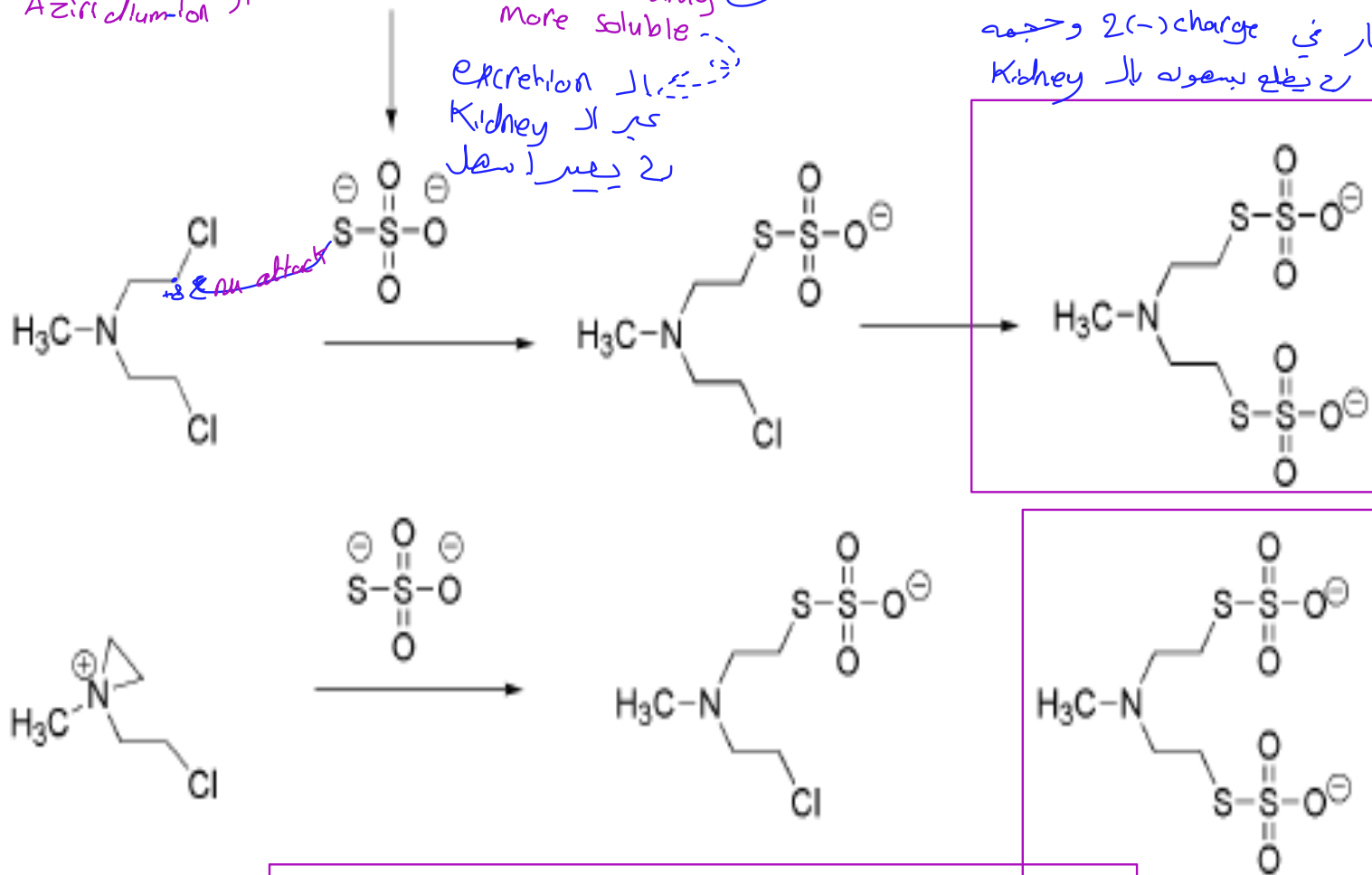
Prison and Chapter 3: Textbook of Organic Medicines and Pharmaceutical Chemistry

2 يجعل ① Aziridiazation
② make the drug more soluble
ممكن اذيقه قبل او بعد تكون
Aziridiazation

لانه صار بي charge (-) 2 وحجمه
صغير بي يطلع بسهولة بال Kidney

قبل تكون
aziridium ion

بعد تكون ال
Aziridium ion



Scheme 10.4 • Thiosulfate Inactivation of mechlorethamine.

الناتج نفسه بالحالتين
بس الاختلاف بوقت التكوين

Nitrogen Mustards

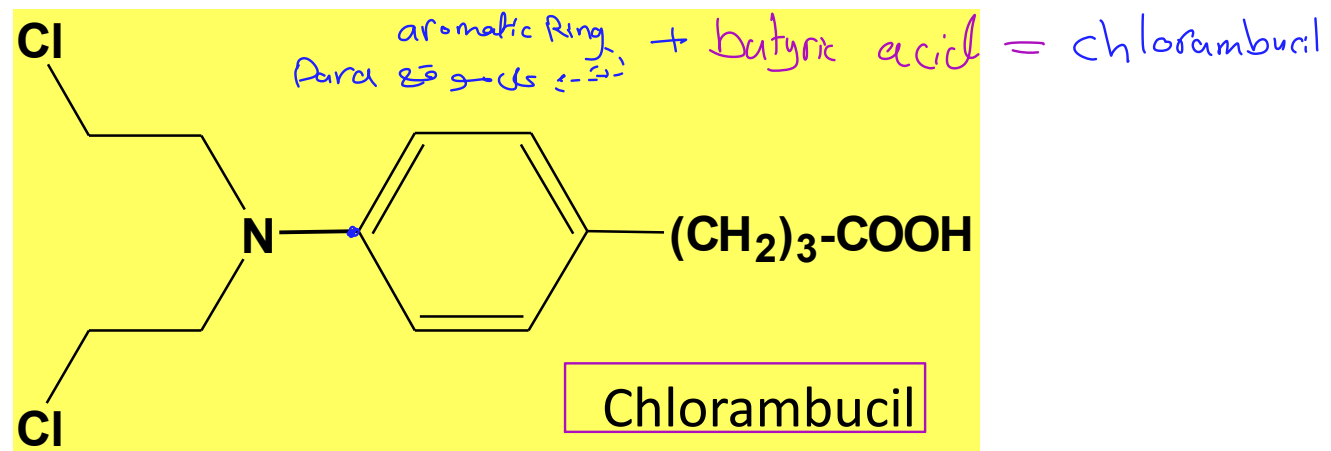
الـ Aziridium ion
رديطلا تكون
يسهوه وسره

Theoretical rationales used to improve nitrogen mustards

-Substituting an aromatic ring for methyl group can be predicted to increase chemical stability and thereby decrease the rate of alkylation because of electron-withdrawing effect.

This also, will lead to good oral bioavailability, tissue distribution, before alkylation is widespread.

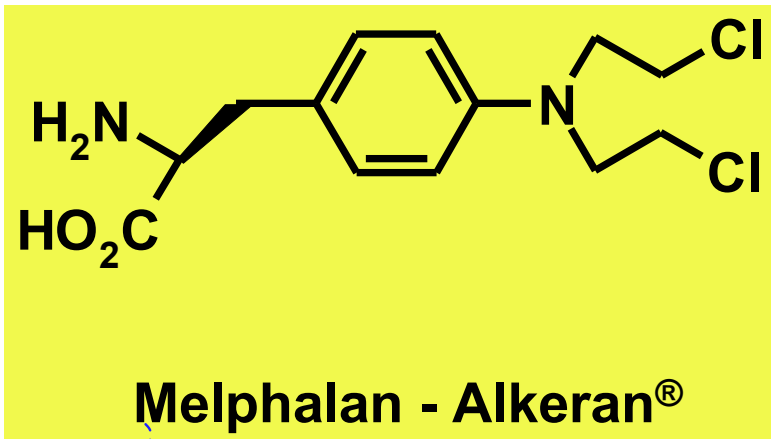
E.g. Chlorambucil, and melphalan.



4-(p-bis(2-Chloroethylamino)phenyl)butyric acid.

Para
تكون الـ aziridium مرتبته جوع 2 ما

Nitrogen Mustards



Side effect
alkylation agent

① Oral or IV, severe bone marrow suppression resulting in infection and bleeding

② Dosage reduction may be necessary in renal failure as measured by BUN

③ Known to cause chromosome abnormalities



IV



tab

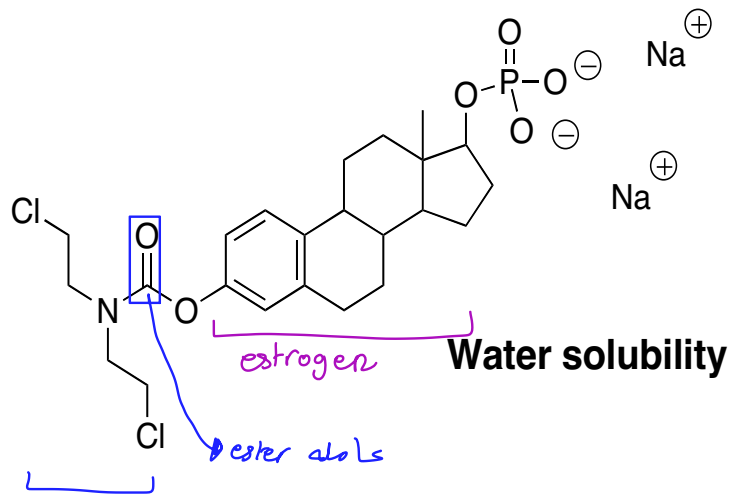
Nitrogen Mustards

To increase selectivity, nitrogen mustards was bonded with natural ^① carrier e.g. estramustine which is active against prostate cancer, another ^② examples is the bonding with antimetabolites e.g. uracil mustard.

Estramustine phosphate

Estracyt®

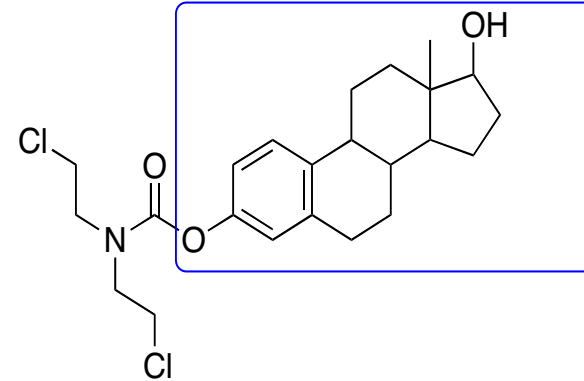
بنزید النائية عشات
orally active
هيكلة لا يكون



- 1) Oral absorb
- 2) Fast metabol.

Pro-drug

ليس تنكسر لا يحل الدواء
لا يحل الدواء لا يحل الدواء
estrogen
[estrogen active] - Prostate cancer



Estradiol
Carry to cells with
estrogenic receptors

Main comp. plasma

Estrogenic (Anti-androgenic) effect prostate cancer
Cleaved to active alkylating agent?

mustard + ester + estrogen + phosphate

لا يميز
Selectivity

