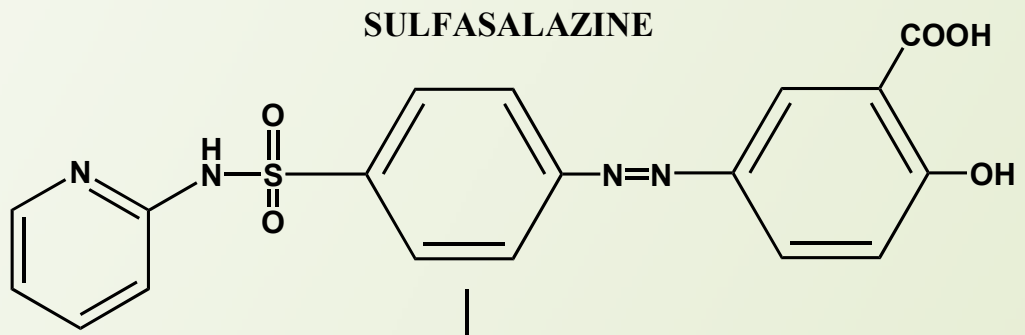
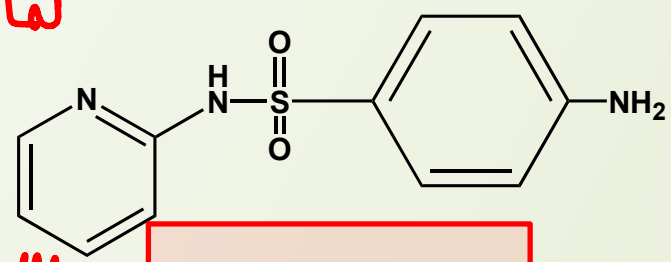
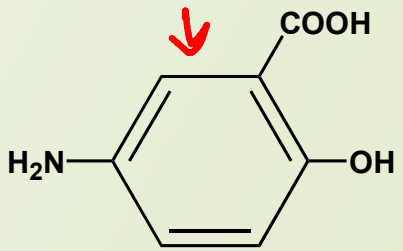
Adverse Effects to Sulfasalazine in Patients with Inflammatory Bowel Disease





SULFAPYRIDINE



5-AMINOSALICYLIC ACID

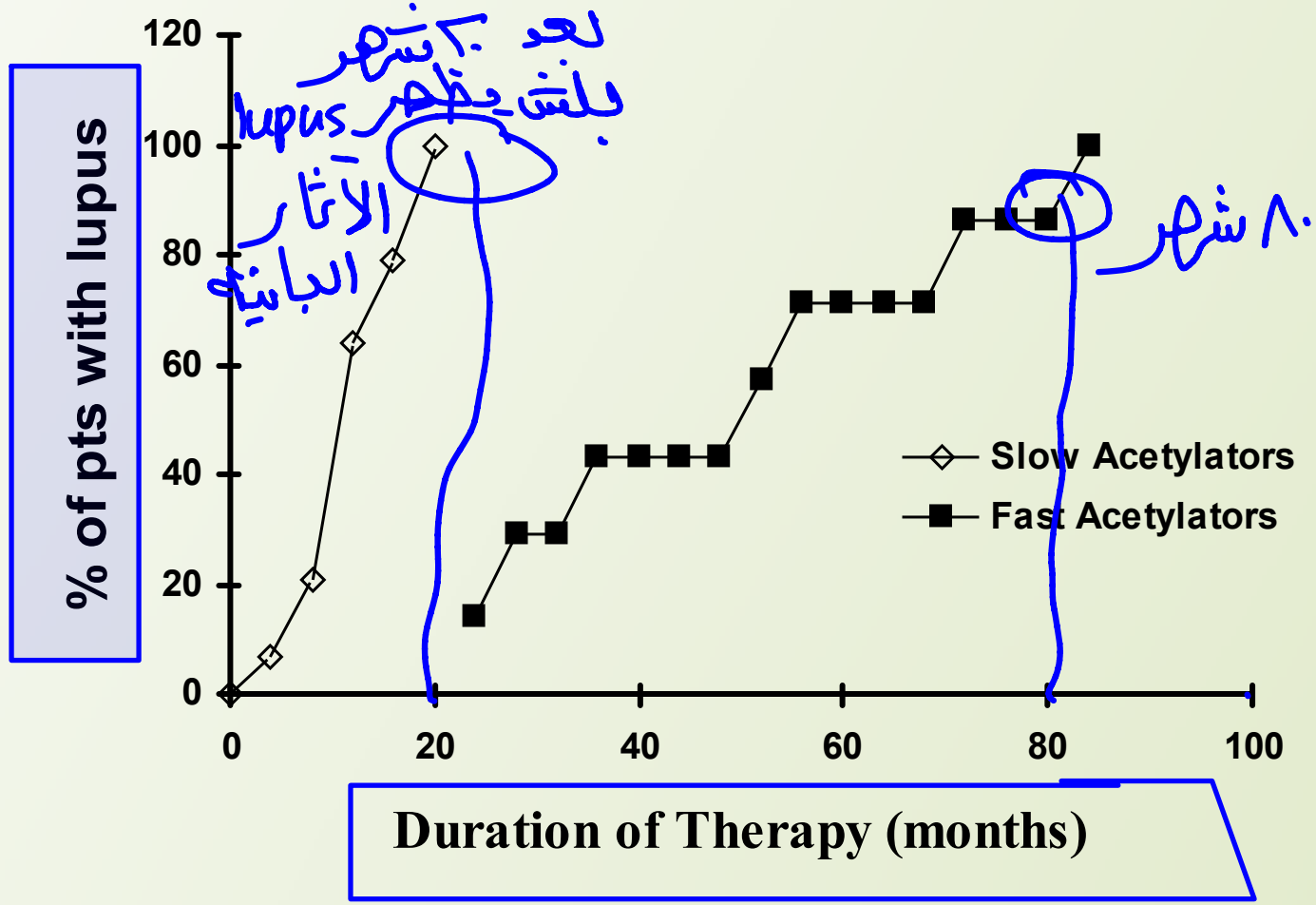
Adverse effects to sulfasalazine in patients with inflammatory bowel disease

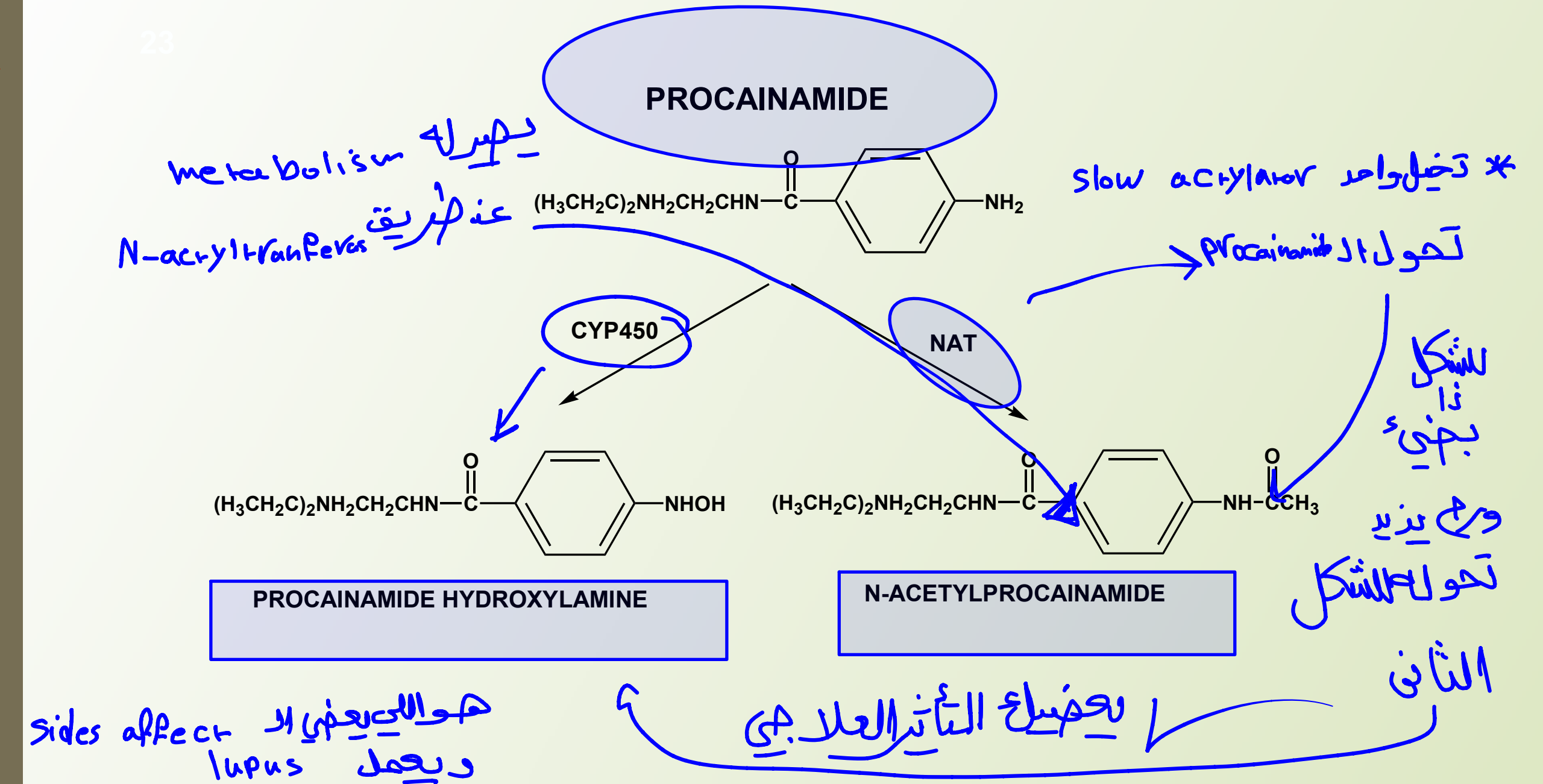
Side Effect	Frequency of side effect	
	Slow Acetylators	Fast Acetylators
cyanosis	9	1
hemolysis	5	0
transient reticulocytosis	6	0

Data from: Das et al. *N Engl J Med* 289:491-495, 1973.

Relationship Between Onset of Lupus Syndrome in Fast and Slow Acetylators Receiving Procainamide.

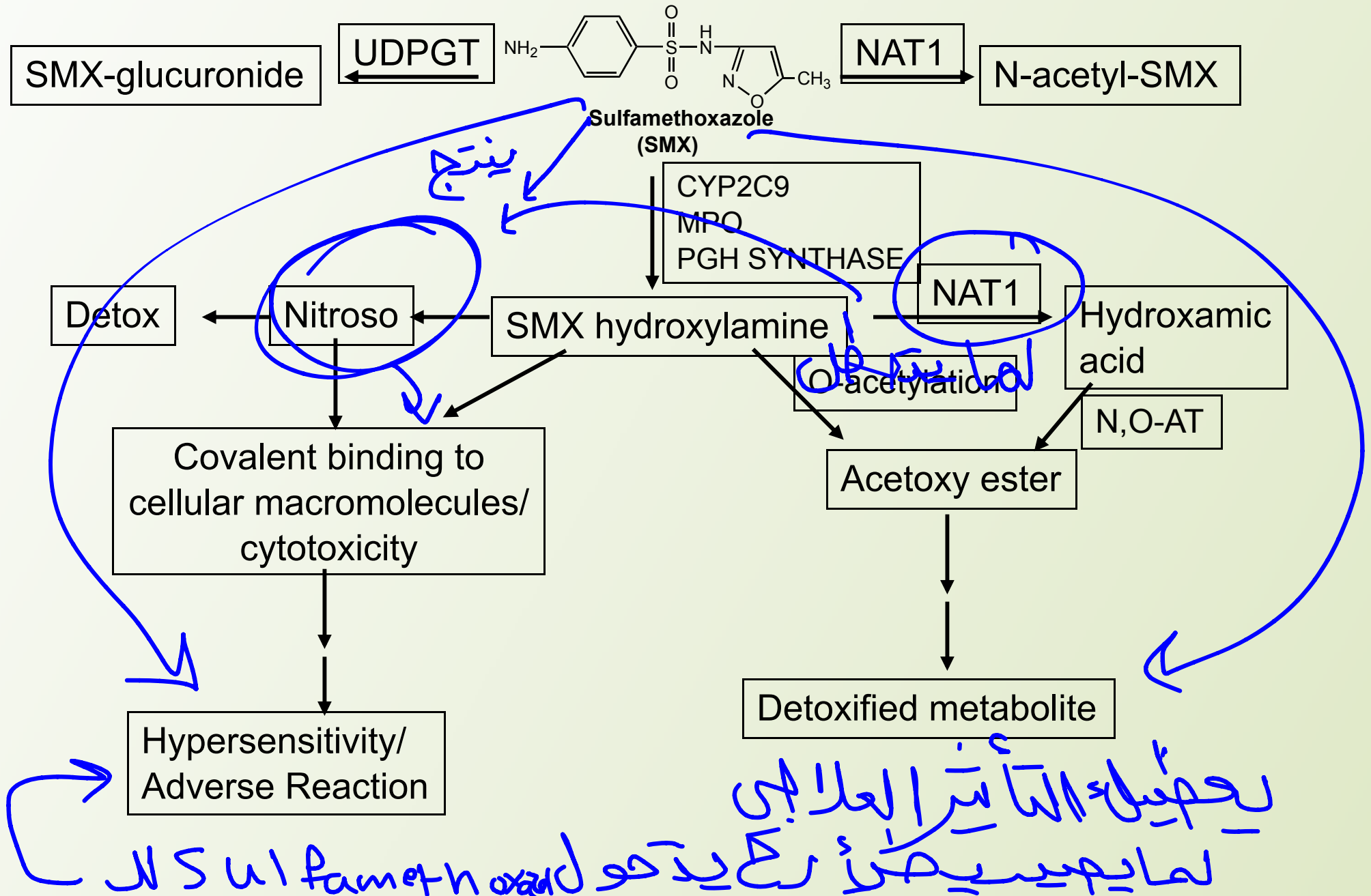
Data from: Woosley RL, et al. *N Engl J Med* 298:1157-1159, 1978.




PROCAINAMIDE
metabolism يطرأ عليه
N-acyltranferas عن طريق
$(H_3CH_2C)_2NH_2CH_2CHN-C(=O)-C_6H_4-NH_2$
slow acylator * تحليل واحد
Procainamide تحول الـ
CYP450
NAT
للشكل
ذا
بخفي
ورح يزيد
تحول الشكل
الثاني
$(H_3CH_2C)_2NH_2CH_2CHN-C(=O)-C_6H_4-NHOH$
$(H_3CH_2C)_2NH_2CH_2CHN-C(=O)-C_6H_4-NH-C(=O)CH_3$
PROCAINAMIDE HYDROXYLAMINE
N-ACETYLPROCAINAMIDE
يعطي التأثير العلاجي
sides affect هو اللي يعطي الـ
lupus ويعمل

Distribution of Acetylator Phenotype in Control Subjects and Those Experiencing a Sulfonamide Hypersensitivity Reaction.

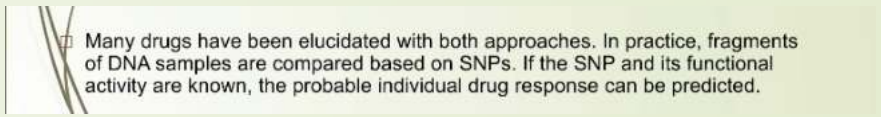
Rieder et al. *Clin Pharmacol Ther* 49:13-17, 1991.


SMX-glucuronide
UDPGT
NAT1
N-acetyl-SMX
Sulfamethoxazole
(SMX)
CYP2C9
MPO
PGH SYNTHASE
Detox
Nitroso
SMX hydroxylamine
NAT1
Hydroxamic acid
O-acetylation
N,O-AT
Covalent binding to cellular macromolecules/ cytotoxicity
Acetoxy ester
Detoxified metabolite
Hypersensitivity/ Adverse Reaction

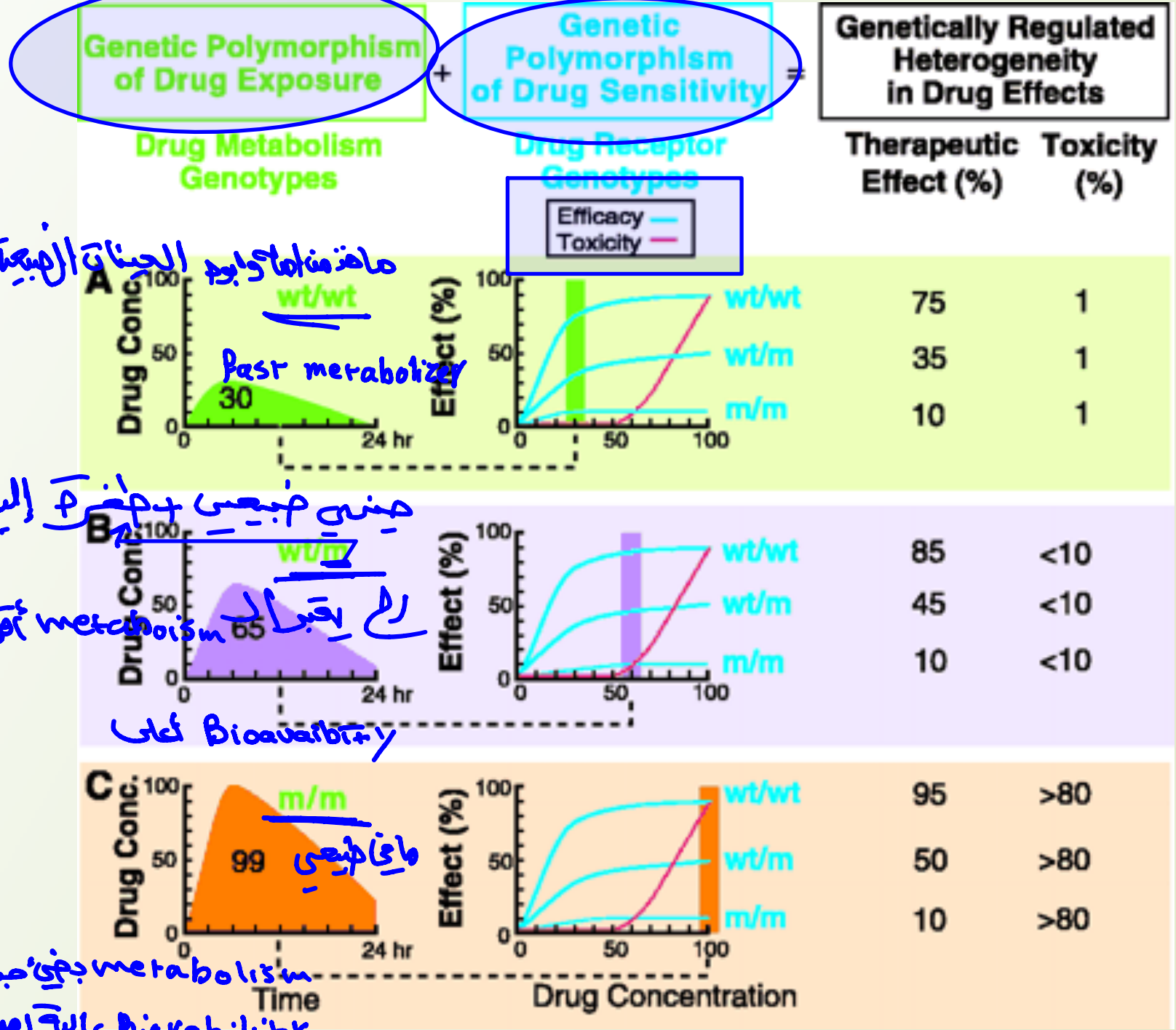
Polymorphism

- To determine whether a patient is a rapid or slow metabolizer, the patient is given a known substrate for that enzyme and the patient's intrinsic clearance is measured.

- Traditionally, intersubject variation in metabolism has been investigated by this method followed by in-vitro verification of enzyme level. Alternatively, it is possible to determine metabolic-status genotype directly from subjects' DNA. The latter approach is more definitive and offers much insight during drug development into how genes affect the metabolism of drugs.


Many drugs have been elucidated with both approaches. In practice, fragments of DNA samples are compared based on SNPs. If the SNP and its functional activity are known, the probable individual drug response can be predicted.

- Many drugs have been elucidated with both approaches. In practice,



From: Evans WE, Relling MV. Pharmacogenomics: Translating functional genomics into rational therapeutics. *Science* 286:487-491, 1999.

أستغفرك ربي وأتوب إليك

Table 12.2 Clinically Important Genetic Polymorphisms of Drug Metabolism that Influence Drug Response

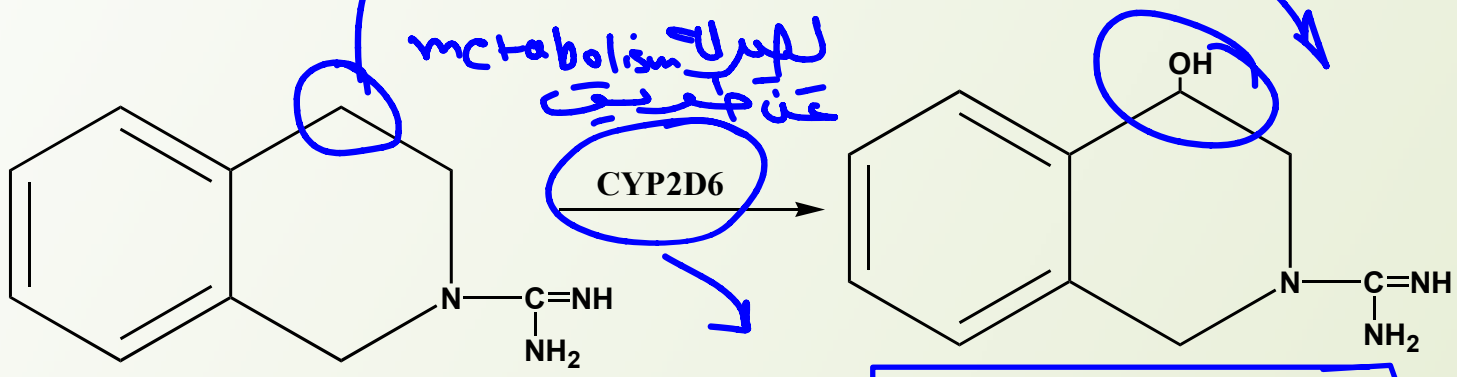
الأدوية اللي بتحصل

Enzyme/Receptor	Frequency of Polymorphism	Drug	Drug Effect/Side Effect
CYP2C9	14â€"28% (heterozygotes)	Warfarin	Hemorrhage
	0.2â€"1% (homozygotes)	Tolbutamide	Hypoglycemia
		Phenytoin	Phenytoin toxicity
		Glipizide	Hypoglycemia
		Losartan	Decreased antihypertensive effect
CYP2D6	5â€"10% (poor metabolizers)	Antiarrhythmics	Proarrhythmic and other toxic effects
	Polymorphism		Toxicity in poor metabolizers
	1â€"10% (ultrarapid metabolizers)	Antidepressants	Inefficacy in ultrarapid metabolizers
		Antipsychotics	Tardive dyskinesia
		Opioids	Inefficacy of codeine as analgesic, narcotic side effects, dependence
		Beta-adrenoceptor antagonists	Increasedâ€"blockade

ايش رح يصير على المريض لو كان عنده اختلاف جيني في هذا الانزيم واعطيته الدوا

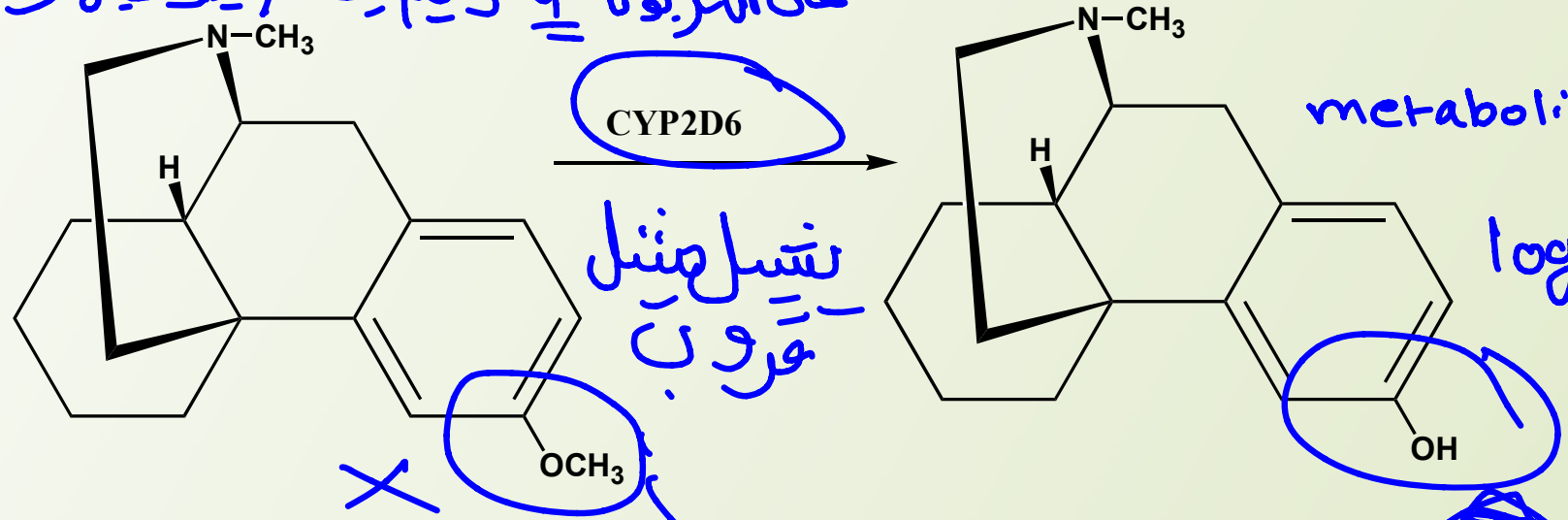
CYP2C19	3â€“6% (whites)	Omeprazole	Higher cure rates when given with clarithromycin
	8â€“23% (Asians)		
		Diazepam	Prolonged sedation
Dihydropyrimidine dehydrogenase	0.1%	Fluorouracil	Myelotoxicity, Neurotoxicity
Plasma pseudo-cholinesterase	1.5%	Succinylcholine	Prolonged apnea
N-acetyltransferase	40â€“70% (whites)	Sulphonamides	Hypersensitivity
	10â€“20% (Asians)	Amonafide	Mylelotoxicity (rapid acetylators)
		Procainamide, hydralazine, isoniazid	Drug-induced lupus erythematosus
Thiopurine Methyltransferase	0.3%	Mercaptopurine, thioguanine, azothioprine	Myelotoxicity
UDP-glucuronosyl-transferase	10â€“15%	Irinotecan	Diarrhea, myelosuppression
ACE		Enalapril, lisinapril captopril	Renoprotective effect, cardiac indexes, blood pressure
Potassium channels		Quinidine	Drug-induced QT syndrome
HERG		Cisapride	Drug-induced torsade de pointes
KvLQT1		Terfenadine	Drug-induced long-QT syndrome
		Disopyramide	
HKCNE2		Mefloquine	Drug-induced arrhythmia
		Clarithromycin	

2. CYP2D6 ACTIVITY



DEBRISOQUINE

4-HYDROXYDEBRISOQUINE



DEXTROMETHORPHAN

DEXTRORPHAN

* metabolic Ratio

$$\log 10 \frac{\text{drug}}{\text{metabolic}}$$

كيف أعرف الشخص slow or fast metabolizer

عن طريق حساب metabolic Ratio

تعطي الدوا للمريض وتعرف إنه يمر بـ metabolism عن طريق إنزيم معين

تاخد عينات بول وتشوف كمية الدوا اللي طلعت سواء دوا أصلي زي ما هو أو metabolic

metabolic تشوف التركيز بالدم وتركيز ←

* كلما كانت metabolic ratio أعلى ← Slow metabolizer

لأن كلما زاد الدواء الجهاز ← metabolize يـ

metabolic ratio يزيد ←

* // // // // أقل ← Fast metabolizer

* مكان الـ Fast والـ low يختلف حسب معطيات المحاور

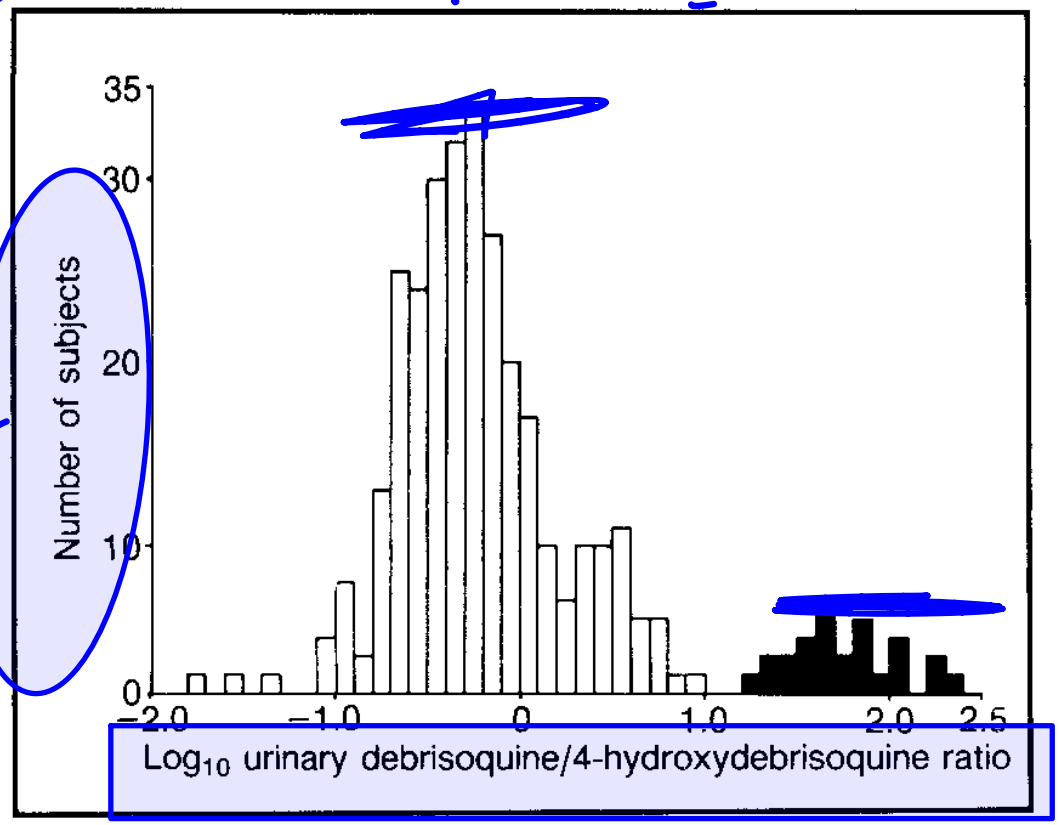


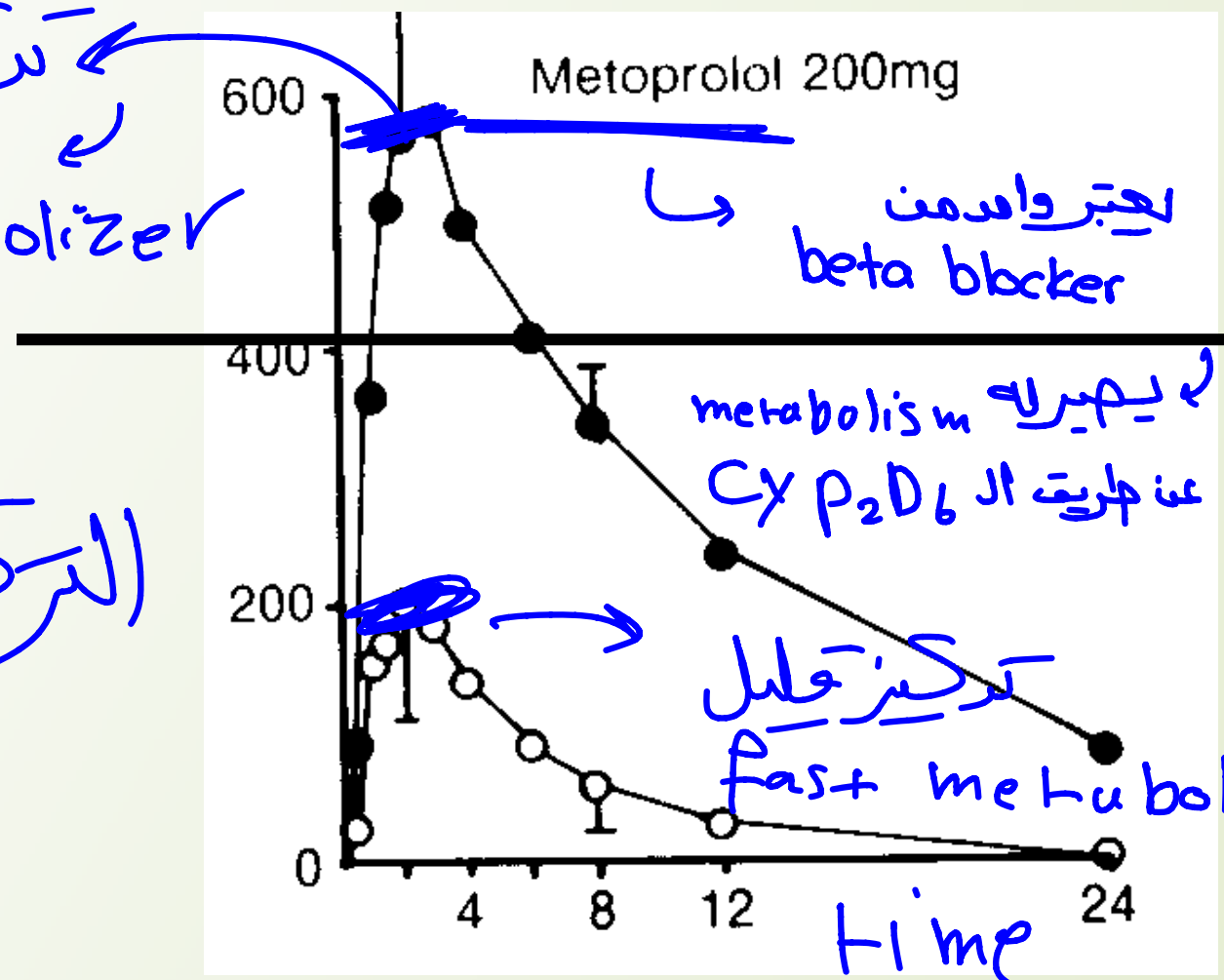
Fig. 1. Frequency distribution of the $\log_{10}$ 0- to 8-hour urinary debrisoquine to 4-hydroxydebrisoquine ratio in an unselected group of white British subjects (n = 324) after a 10mg oral dose of debrisoquine hemisulphate (Lennard et al. unpublished data). Debrisoquine 4-hydroxylation is controlled by 2 alleles at a single gene locus. Poor metabolisers (■) are homozygous for an autosomal recessive allele and usually have ratios > 20 (Evans et al. 1980).

* اذا normal بالوسط

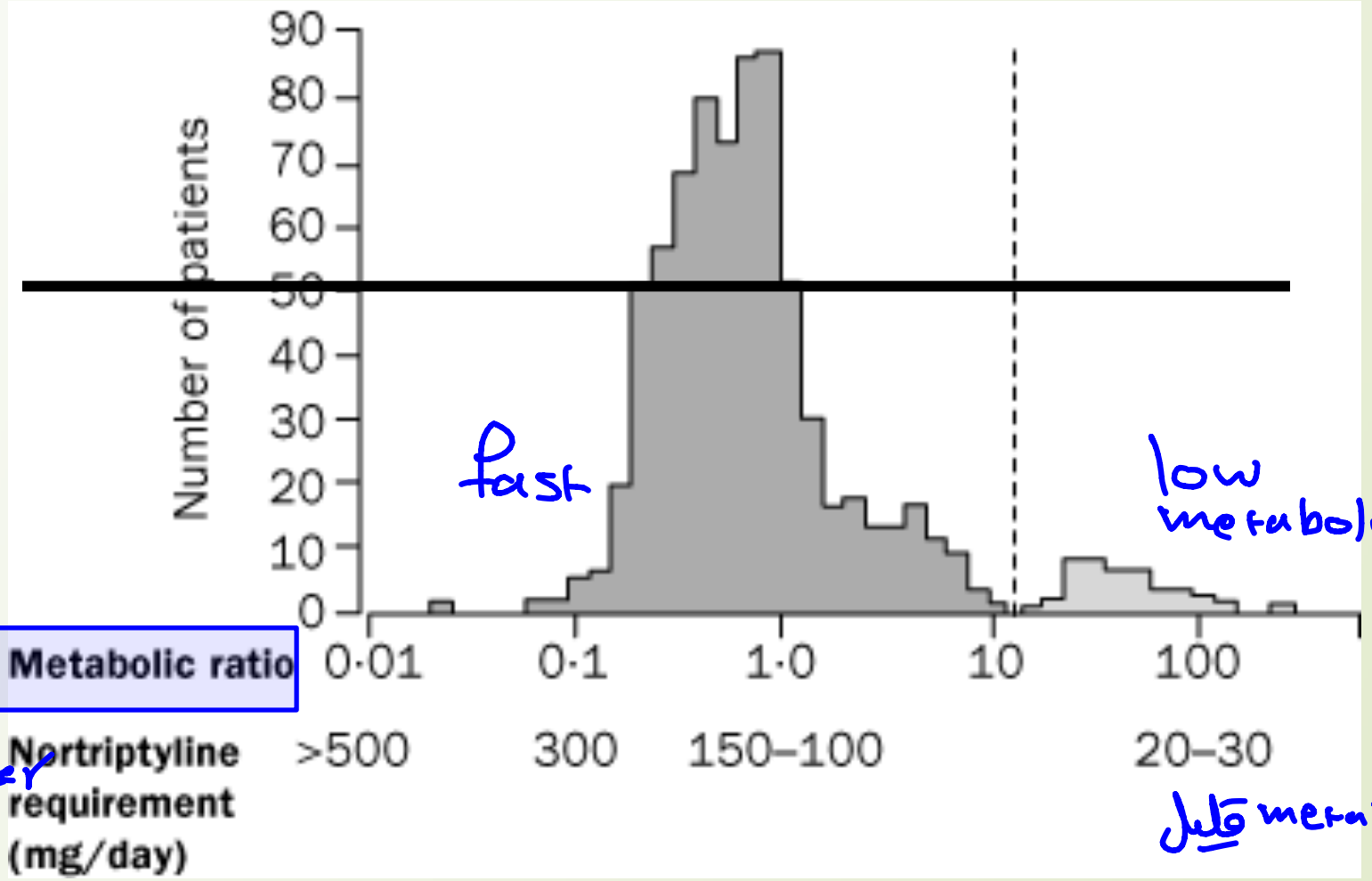
Drugs Whose Metabolism Co-segregates with Debrisoquine

alprenolol amitriptyline bufuralol clomipramine
codeine desipramine encainide ethylmorphine
flecainide fluoxetine guanoxan imipramine
metoprolol nortriptyline paroxetine phenformin
propafenone propranolol

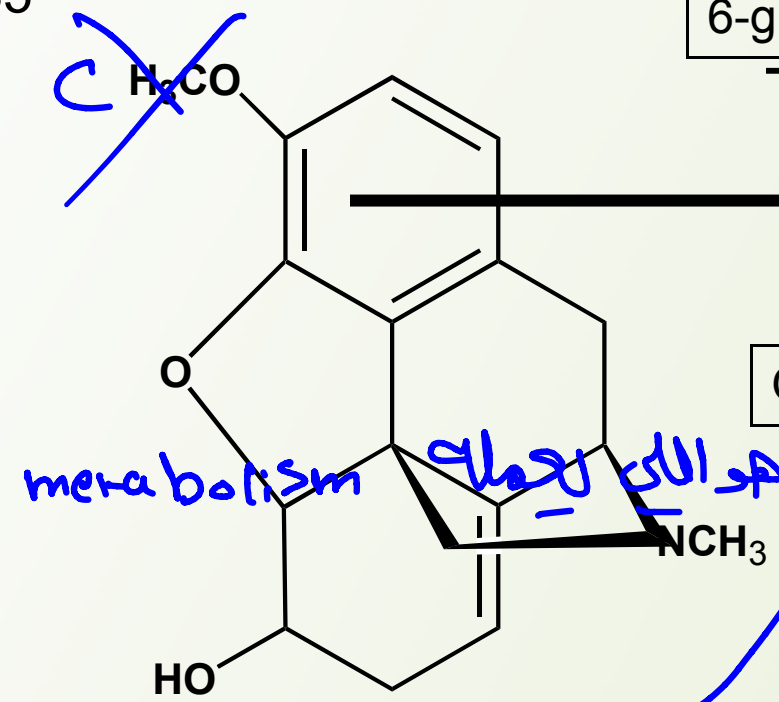
* يحسبلهم عن طريق CYP2d6 metabolism
metabolism لنفس التأثير ونفس ال
للـ Debrisoquine



Plasma metoprolol concentrations in poor (□) and extensive (□) metabolizers of debrisoquine after 200 mg of metoprolol tartrate administered orally. Redrawn from Lennard MS, et al. *NEJM* 307:1558-1560, 1982.



Dose requirements for nortriptyline in patients with different CYP2D6 Phenotypes. From: Meyer U. *Lancet* 356:1667, 2000.



CODEINE

6-glucuronidation → codeine-6-glucuronide → M-6-G

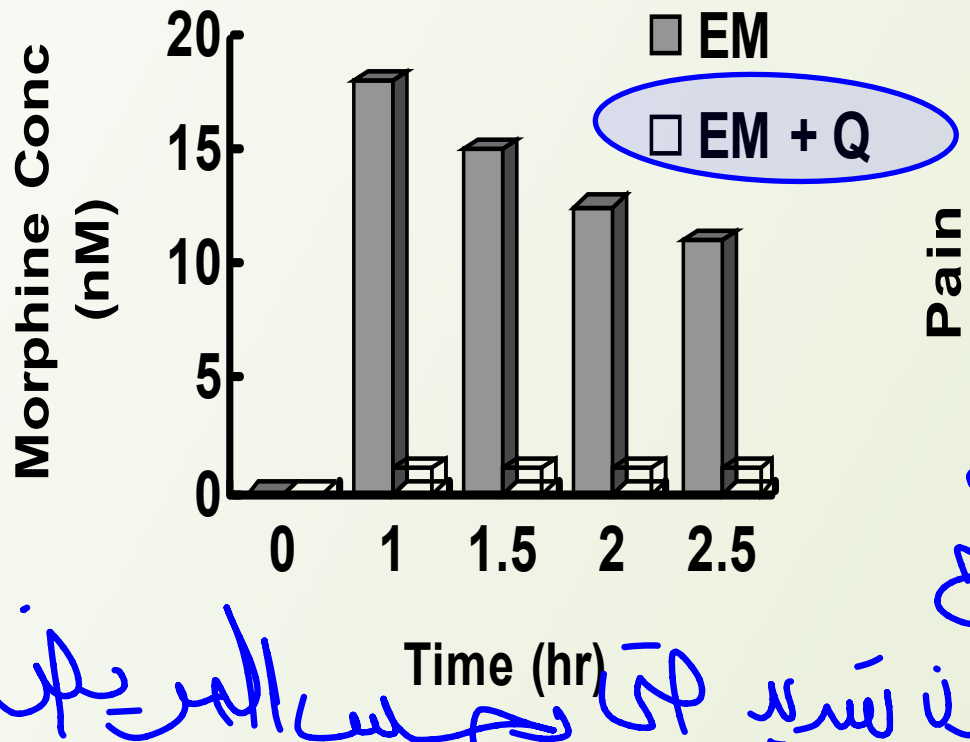
O-demethylation (CYP2D6) → morphine → M-6-G, M-3-G, normorphine

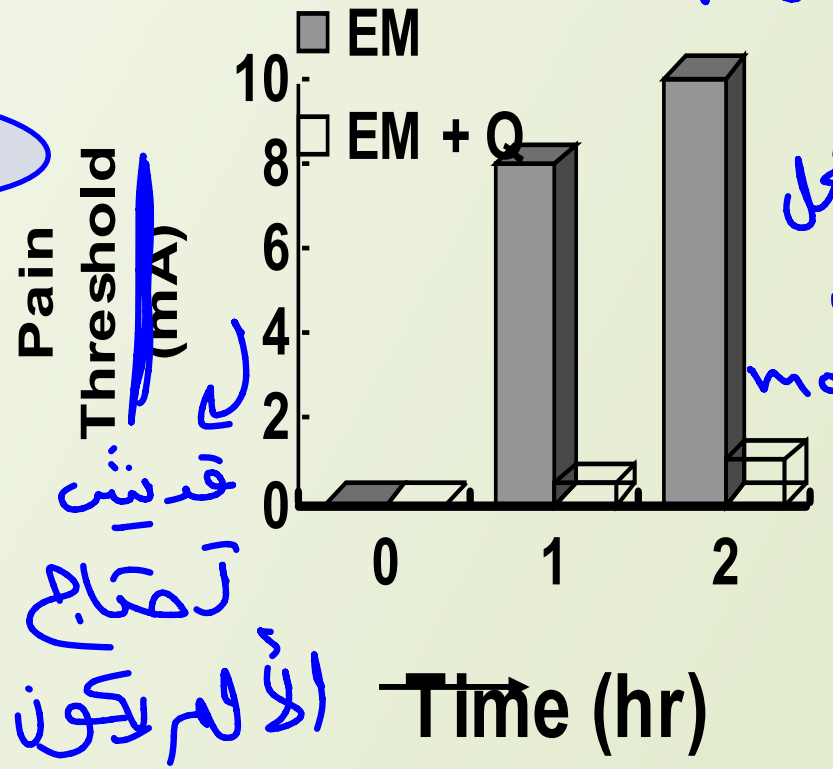
N-demethylation → norcodeine → norcodeine-6-glucuronide

Past metabolism

Effect of Quinidine on the Analgesic Response to Codeine in Extensive Metabolizers of CYP2D6 (Phenotyped with Dextromethorphan)

Data from: Desmeules J, et al. *Eur J Clin Pharmacol* 41:23:26, 1991

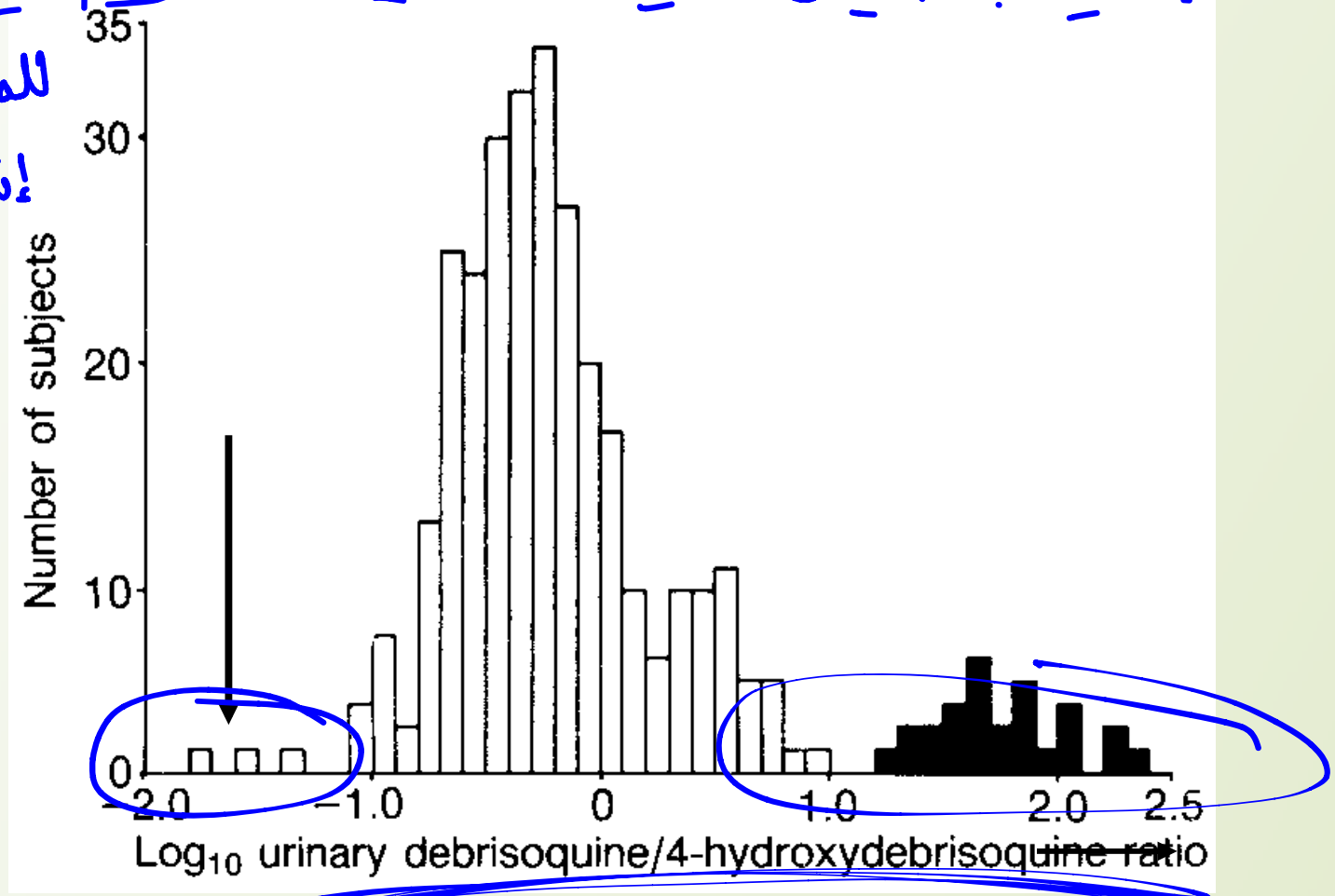




The polymorphic O-demethylation of codeine is of clinical importance when this drug is given as an analgesic.

About 10% of codeine is O-demethylated by CYP2D6 to morphine, and this conversion is deficient in poor metabolizers. Poor metabolizers therefore experience no analgesic effects of codeine

* فكرة الضيب اللي جده يعمل العملية ← بيخلي الانزيم اللي مسؤول عن الـ metabolism للمخدر عشان يحرق المخدر يشتغل أولا!



What is the cause of 'hypermetabolizers'?

Debrisoquine phenotype in subjects with different *CYP2D6* genotypes

Genotype	# of Subjects	Metabolic Ratio
CYP2D6wt/(CYP2D6L)$_2$	9	0.33
CYP2D6wt/CYP2D6wt	12	1.50
CYP2D6wt/CYP2D6(A or B)	9	2.14
CYP2D6B/CYP2D6B	6	48.84

(CYP2D6L)2 - gene duplication; *CYP2D6A* - single base deletion

CYP2D6B - multiple point mutations

Data from: Agundez JG et al. *Clin Pharmacol Ther* 57:265, 1995.

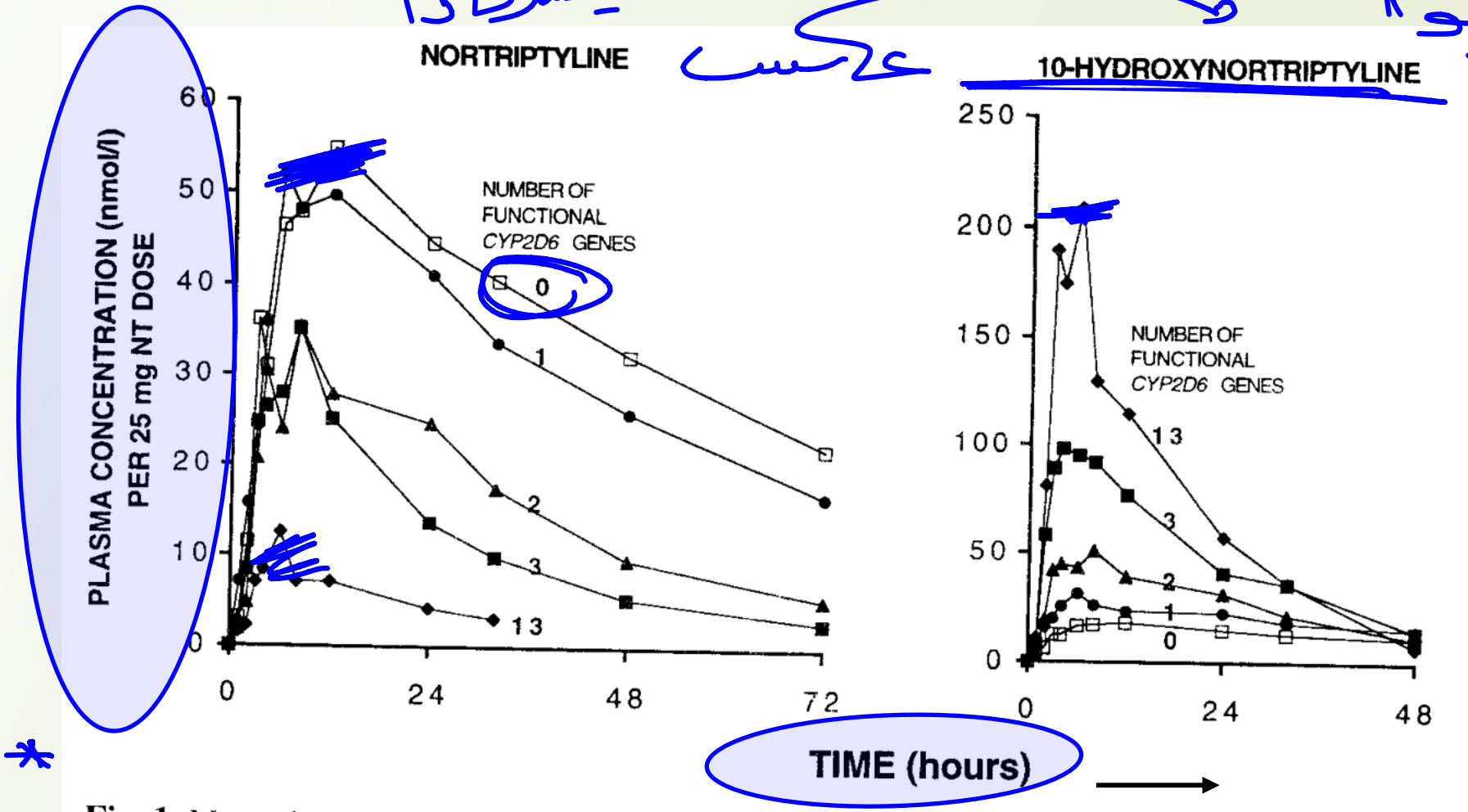


Fig. 1. Mean plasma concentrations of nortriptyline and 10-hydroxynortriptyline in different genotype groups after a single oral dose of nortriptyline. For subjects with 3 and 13 functional genes, plasma concentrations are adjusted to the 25 mg dose by means of division of the values by 2. The numerals close to the curves represent the number of functional *CYP2D6* genes in each genotype group.

From: Dalen P, et al. *Clin Pharmacol Ther* 63:444-452, 1998.

3. CYP2C9 ACTIVITY

يكون له كذا genotype

Prescribed Daily Warfarin Dose and CYP2C9 Genotype

Warfarin Dose*	Genotype
5.63 (2.56)	*1/*1
4.88 (2.57)	*1/*2
3.32 (0.94)	*1/*3
4.07 (1.48)	*2/*2
2.34 (0.35)	*2/*3
1.60 (0.81)	*3/*3

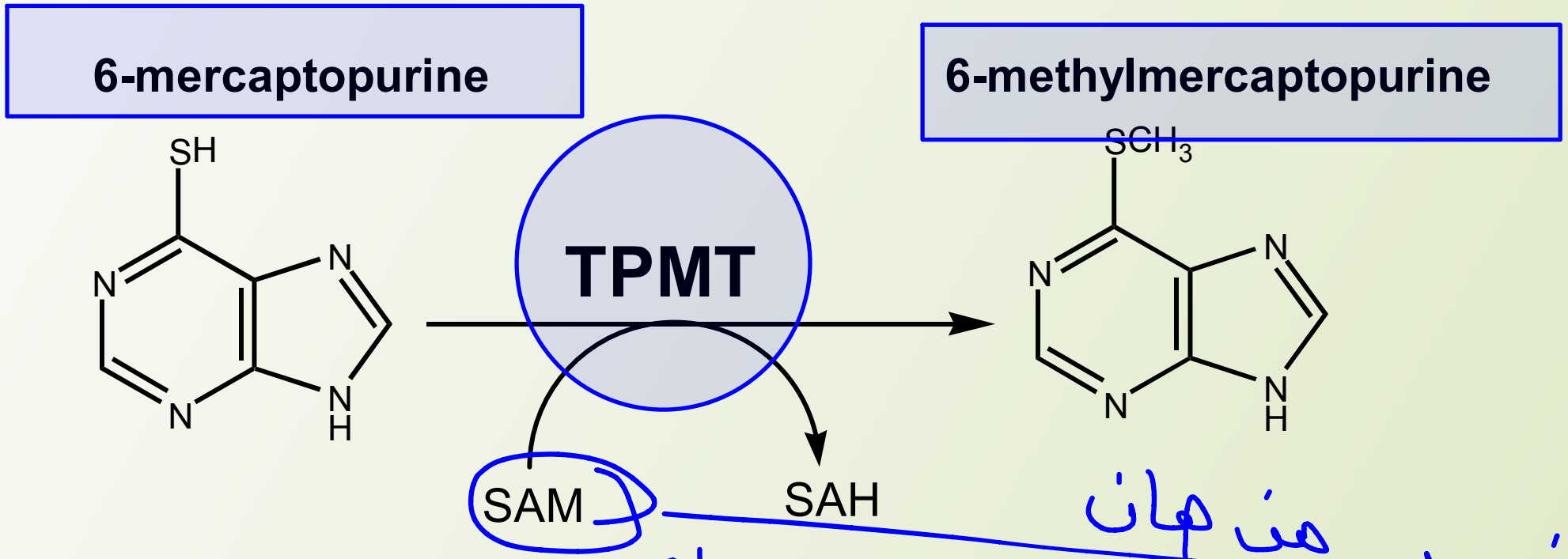
*1/*1 → metabolism عالي جدًا → يحتاج كمية warfarin عالية

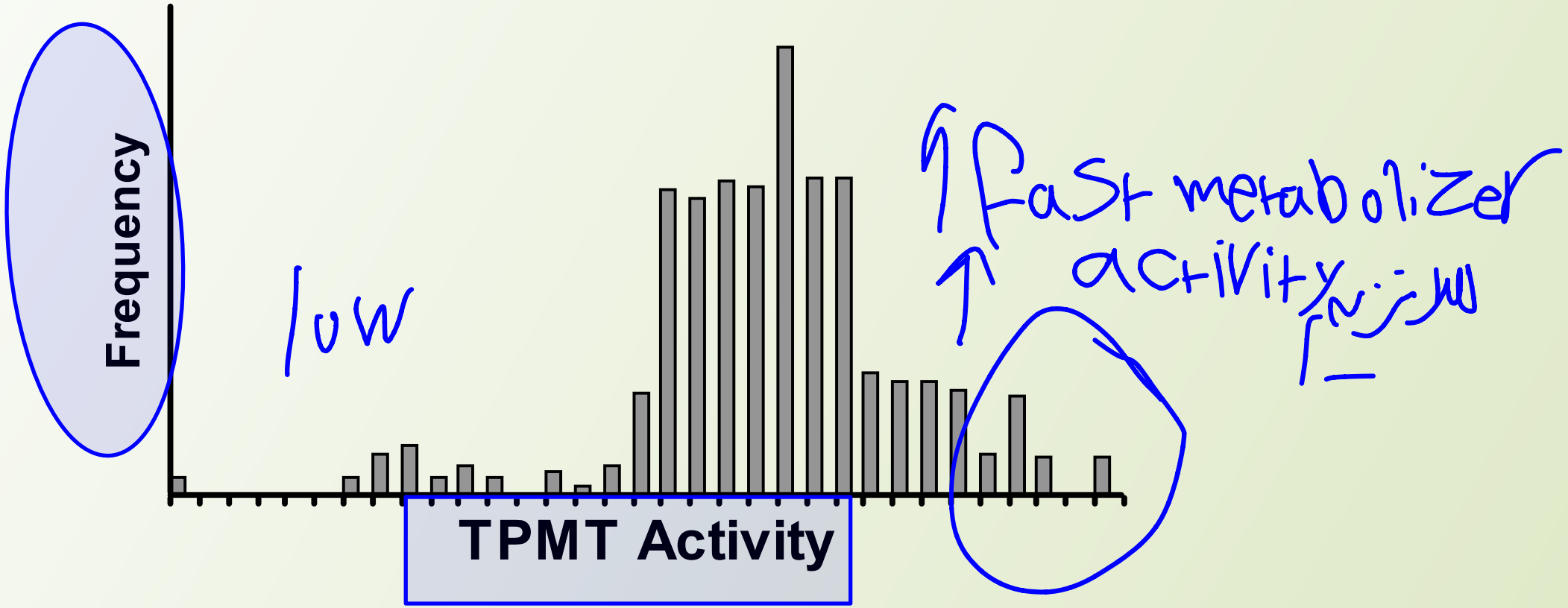
*3/*3 → slow metabolizer → كمية قليلة

*Data presented as mean (SD) daily dose in mg

From: Higashi MK, et al. *JAMA* 287:1690-1698, 2002.

4. Thiopurine Methyltransferase (TPMT)





Distribution of Thiopurine Methyl-transferase Activity.

Reproduced from: Weinshelboum RM, Sladek SL. *Am J Hum Genet* 32:651-662, 1980.

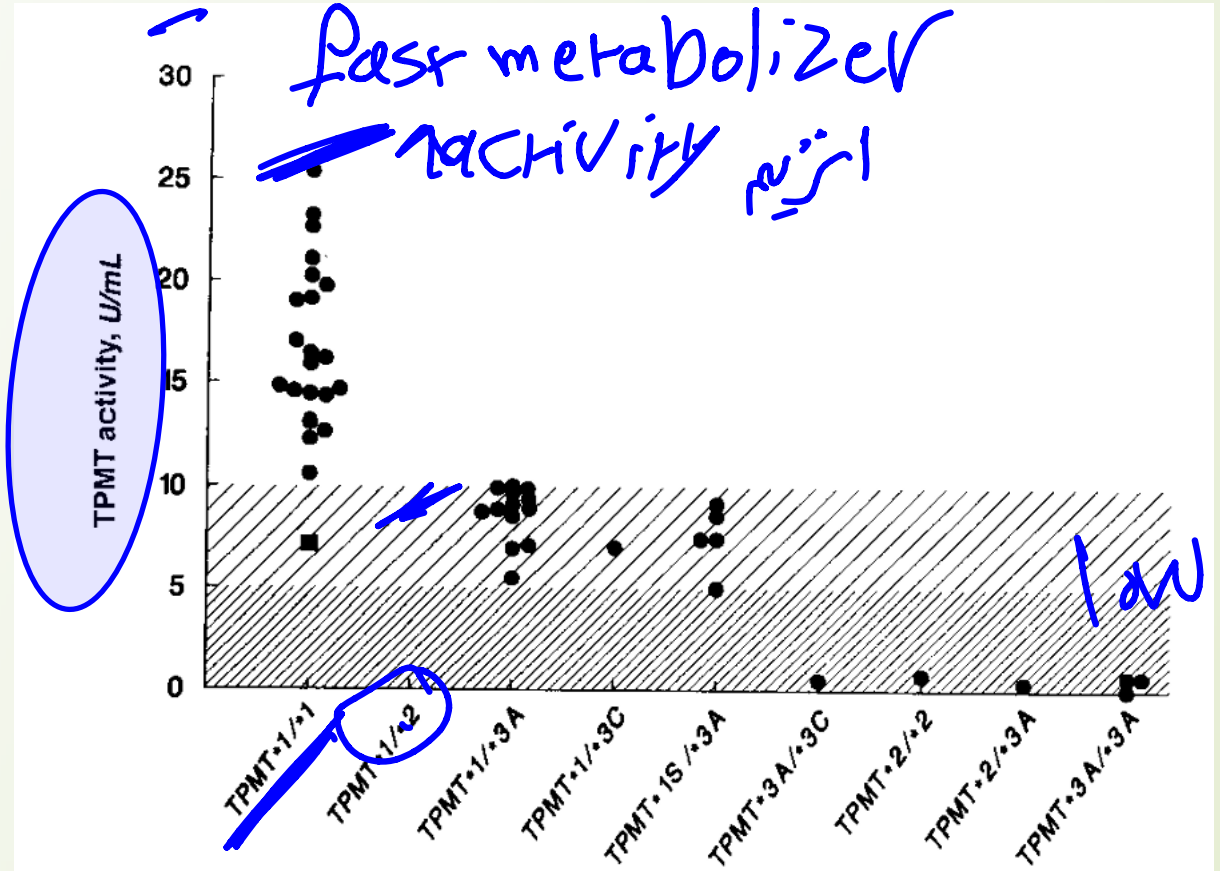


Figure 3. Thiopurine S-methyltransferase (*TPMT*) activity in patients with different TPMT genotypes determined by mutation-specific polymerase chain reaction methods. The heavily shaded area depicts the range of TPMT activity in erythrocytes that defines TPMT deficiency (<5 U/mL of packed red blood cells), the lightly shaded area depicts intermediate activity that defines TPMT heterozygous phenotypes (5 to 10 U/mL of packed red blood cells), and the unshaded area depicts the range of TPMT activity in patients who have homozygous wild-type phenotypes. Black circles indicate patients with concordant genotype and phenotype; the black square indicates one patient with discordant genotype and phenotype.

CYP2C19

- The 4'-hydroxylation of the (S)-enantiomer of **mephenytoin** is catalyzed by CYP2C19. The polymorphic enzyme has a poor metabolizer (PM) frequency of about 3% in Caucasians, 15-25% among Asians, and 4-7% among Black Africans. The major defective allele responsible for the PM phenotype is CYP2C19***2,** which is found among 13% and 32% of Caucasians and Asians, respectively.
- A second allele, CYP2C19***3,** is found mostly among Asians and rarely in Caucasians.
- Interestingly, few polymorphisms are reported for the isozyme subfamily CYP3A. This isozyme is involved in the metabolism of endogenous steroid and testosterone. Mutations of this vital enzyme may not be compatible with life.

معظم التغيرات والآثار الجانبية موجودة بسبب الإختلاف الجيني فبعض الأشخاص لديهم بطء في تمثيل الدواء
Poor drug metabolizer

- Not all therapeutic variations and side effects result from genetic differences in the receptor or drug metabolism. Drug response (including therapeutic and unintended side effects) is influenced by many direct and indirect factors, including modifying effects from environmental factors on the disease process and drug disposition.
- As a result, some researchers are unsure whether prescribing drugs based on a pharmacogenetic profile will significantly reduce side effects for most drugs, since many side effects and therapeutic failures may be the result of **incorrect diagnosis** or **failure to account for other influencing variables such as the nature and severity of the disease, the individual's age and race, organ function, concomitant therapy, drug interactions, and concomitant illnesses**

بعض العلماء مو متأكدين إذا كان ممكن نوصف الدواء على أساس جينات الشخص لأنه يقلل عدد الآثار الجانبية!
في كثير عوامل تأثر على الـ side effect
diet / العادات الغذائية lifestyle / age

Genetic Polymorphism in Drug Transport: p-Glycoprotein and Multidrug Resistance

- *Transporter pharmacogenetics* is a rapidly developing field that is concerned with drug uptake and efflux into or through tissues. Significant problems in the clinical application of drugs result from poor or variable oral drug bioavailability, and high intra- and inter-individual variation in pharmacokinetics.
- Several membrane transporter proteins are involved in the absorption of drugs from the intestinal tract into the body, into nonintestinal tissues, or into specific target sites of action.
- *Drug efflux* is an important cause of drug resistance in certain types of cells.
- In cytotoxic chemotherapy for several human cancerous diseases, drugs are generally very effective, but in the case of *intrinsic* or *acquired multidrug resistance*, usually highly effective antineoplastic compounds, eg, vincristine, vinblastine, daunorubicin, or doxorubicin, fail to produce cures.
- One of the major causes of such multidrug resistance is the appearance of special integral membrane proteins, the *P-glycoprotein multidrug transporter*, or MDR1, which is one of the major causes of low drug level in targeted cells.

- The multidrug resistance-associated proteins (MRPs) are members of the ATP-binding cassette (ABC) superfamily with six members currently, of which MRP1, MRP2, and MRP3 are commonly known to affect drug disposition. MRP1 is ubiquitous in the body.
- Substrates for MRP1 include glutathione, glucuronide, and sulfate. MRP1 is expressed basolaterally in the intestine, although its role in extruding drugs out of the enterocytes is still uncertain.
- There is some substrate overlap between MRP1 and apically located P-glycoprotein. The amino acid homology between MDR1 and P-glycoprotein was reported to be 15% in some cell lines

GENETIC POLYMORPHISM IN DRUG TARGETS

In the future, proteins involved in disease will become identified as important biomarkers for pharmacodynamic studies. Genomics has led to the development of proteonomics, which involves the study of biologically interesting proteins and their variants. Proteins can be used as probes for drug discovery or as biomarkers for drug safety, such as cell surface proteins (eg, COX-2, D-2R), intracellular proteins (eg, troponin I), and secreted proteins (eg, MCP-1).

- The physiologic response of the body to a drug is generally the result of interaction of the drug at a specific target site in the body. It is estimated that **about 50% of drugs act on membrane receptors, about 30% act on enzymes, and about 5% act on ion channels**.
- Many of the genes encoding these target proteins exhibit polymorphisms that may alter drug response. Clinically relevant examples of polymorphism leading to variable responses are listed. For example, the **beta-2-adrenergic receptor**, and its common mutation of Arg /Gly at amino acid 16, greatly reduces the bronchodilator response of albuterol.

- In addition, mutations in the **angiotensin-converting enzyme** (ACE) gene have been proposed to account for variations in the response to ACE inhibitors.
- Another study has shown that a combination of two mutations in the gene encoding a high **affinity sulphonylurea receptor** leads to a 40% reduction in the insulin response to tolbutamide.

اختلاف جيني ← اختلاف بالسلسلة ← اختلاف بتأثير الدوا

- The response to clozapine in patients with schizophrenia appears to involve genetic polymorphisms in the **5- hydroxytryptamine (serotonin) receptor**, HTR2A.
- Finally, mutations in five genes involved in the **cardiac ion channels** affect the risk of drug-induced long-QT syndrome, a potential cause of **sudden cardiac death** in young individuals without structural heart disease. The prevalence of long-QT syndrome is about 1 in 10,000.
- All five genes code for membrane ion channels affecting sodium or potassium transport and are influenced by antiarrhythmics and other drugs

Table 12.3 Clinically Important Genetic Polymorphisms of Drug Targets and Drug Transporters

Gene	Frequency	Drug	Drug Effect
Multidrug resistance gene (*MDR1*)	24%	Digoxin	Increased concentrations of digoxin in plasma
Beta-2 adrenergic receptor gene (*2AR*)	37%	Albuterol	Decreased response to Beta-2 adrenergic agonists
Sulphonylurea receptor gene (*SUR1*)	2â€"3%	Tolbutamide	Decreased insulin response
Five genes coding for cardiac ion channels	1â€"2%	Antiarrhythmics, terfenadine, many other drugs	Sudden cardiac death due to long-QT syndrome

ملخص للجدول اللي فوق

C