تفريغ بيوفارما

اسم الموضوع:

Pharmacogentics

إعداد الصيدلاني/ـة:

لـيان شاهـر

Soul Academy

لجان الدفعات

Pharmacogenetics

Pharmacogenetics

- *Pharmacogenetics* is the study of how genes affect the way people respond to drug therapy.
- The goal of pharmacogenetics is to individualize drug therapy to a person's unique genetic makeup with greater efficacy and safety
- The environment, diet, age, lifestyle, and state of health can influence a person's response to medicine.
- Pharmacogenetics is an established discipline that studies the genetic basis of interindividual variability in the response to drug therapy

- With some drugs, pharmacogenetics allows the recognition of subgroups with different genetic makeup that results in alterations in drug receptors and the pharmacodynamic response to drugs.
- Understanding the genetic and molecular differences in disease etiology and drug mechanism produce insight on how a patient will respond to a given drug.
- For example, the monoclonal antibody Herceptin was designed to treat a subset of breast cancer patients who overexpress the HER-2 (human epidermal growth factor receptor-2) gene. Patients who lack HER-2 overexpression are considered to be nonresponders to Herceptin therapy.
- In the past, such differences would be apparent only after a trial-and-error period.

This genetic knowledge improves our ability to select or design the proper drug for individuals suffering from a disease with a varying range of molecular defects.

People react differently to drugs

"One size does not fit all …"

Toxic responders

Non-responders

Responders

Patient population with same disease phenotype

Genotyping

Patients with drug toxicity

Patients with non-response to drug therapy

Patients with normal response to drug therapy

Due to individual variation…

- 20-40% of patients benefit from an approved drug
- 70-80% of drug candidates fail in clinical trials → زابطين بالمختبر ولكن للانسان لأ
- Many approved drugs removed from the market due to adverse drug effects
  في ادوية سحبوها من السوق بسبب اثارها الجانبية.

- The use of DNA sequence information to measure and predict the reaction of individuals to drugs.
  - Personalized drugs
  - Faster clinical trials
  - Less drug side effects

→ Pharmacogenetics

Genetic influences

- PK
  - Drug metabolism Polymorphism in many cytochrome P-450 family enzymes (CYPs) and others
  - P-glycoprotein or other drug transporter (difference in genetic expression)
- Drug receptor (PD)
  - Variation in receptor number, affinity, or response to drug
- Indirect drug response
  - Inherited differences in coagulation may predispose women to deep vein thrombosis when taking oral contraceptives
  - Variations in SCNA receptor predisposes patients to drug induced arrhythmia

Nongenetic influences

- Environmental (PK, PD, or disease prognosis)
  - Cigarette smoking, enzyme induction
  - Exposure to mutagenic agents and occupational or environmental hazards
  - Geographic differences
  - Climate (ultraviolet light on skin tumor)
  - Diet (effect of diet, including grapefruit, and influence on GI enzymes and drug absorption)
  - Drinking water (dissolved minerals and effect on health)
  - Nutrients or supplements

Mixed covariates

شو الاشياء التانية
اللي ممكن تأثر
استجابتنا للادوية

- Gender, age, body weight/surface (PK/PD)
  - Male, female
  - Infant, young adult, or geriatric patient
- Pathophysiology (PK/PD)
  - Renal, hepatic, cardiovascular, or other disease

لما يكون الدواء بكمية، لما الي رح توصل للانسجة.

- Drug-drug interactions (PK/PD)
  - Metabolic, binding, or PD interactions

ممكن يرتبطوا
وقت المستقبل
كمان

Terms to know

مهمان نفرقهم

الاختلاف بـ حبين واحد بس

Monogenic: due to allelic variation at a single gene

Polygenic: due to variations at two or more genes

الاختلاف بـ 2 حبين وطالع

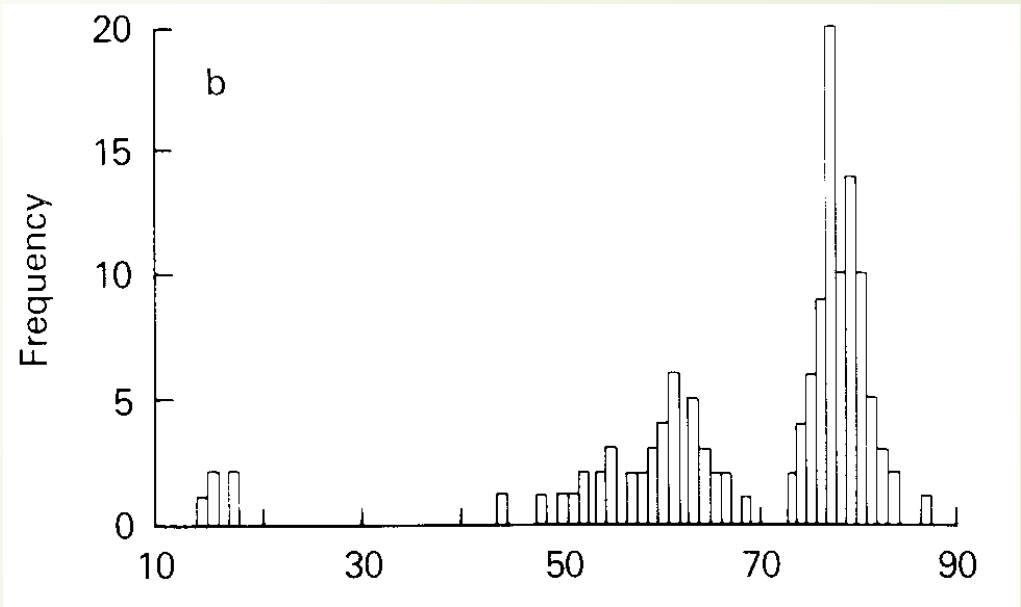
Polymorphism

- *Polymorphisms* or genetic variations with a frequency of greater than 1% of the population, or *mutations*, in less than 1% of the population, in genetic sequences can affect patient therapeutic response or metabolism of a given drug
- Many alleles encoding different drug receptors are being discovered and studied with increasing frequency.
- Pharmacokinetic parameters now known to be influenced by genetic differences include drug bioavailability, distribution, metabolism and tissue binding.
- Polymorphism in cytochrome isozymes is well known in drug metabolism, and the corresponding allele genes involved have been widely studied and are fairly well understood clinically at this time.

Polymorphism

- Genetic polymorphism within a specific genotype may occur with different frequencies depending on racial or population factors, which evolved from selective geographic, regional, and ethnic factors.
- Genetic polymorphisms with higher frequencies are more important because they are likely to affect more people. However, some rare mutations are important because they cause extreme medical consequences or may be fatal for the individual.
- Using genetic polymorphism considerations, drugs may be developed that have less inter-subject variation in pharmacodynamic response and less risk of an adverse event.
- In addition, doses for patients can be based on their metabolic capacity by using the frequency of genotypes of "poor metabolizers" or "ultrarapid metabolizers."
- Molecular studies in pharmacogenetics began with cloning of **CYP2D6** and now have been extended to more than two dozen drug-metabolizing enzymes and several drug transport systems

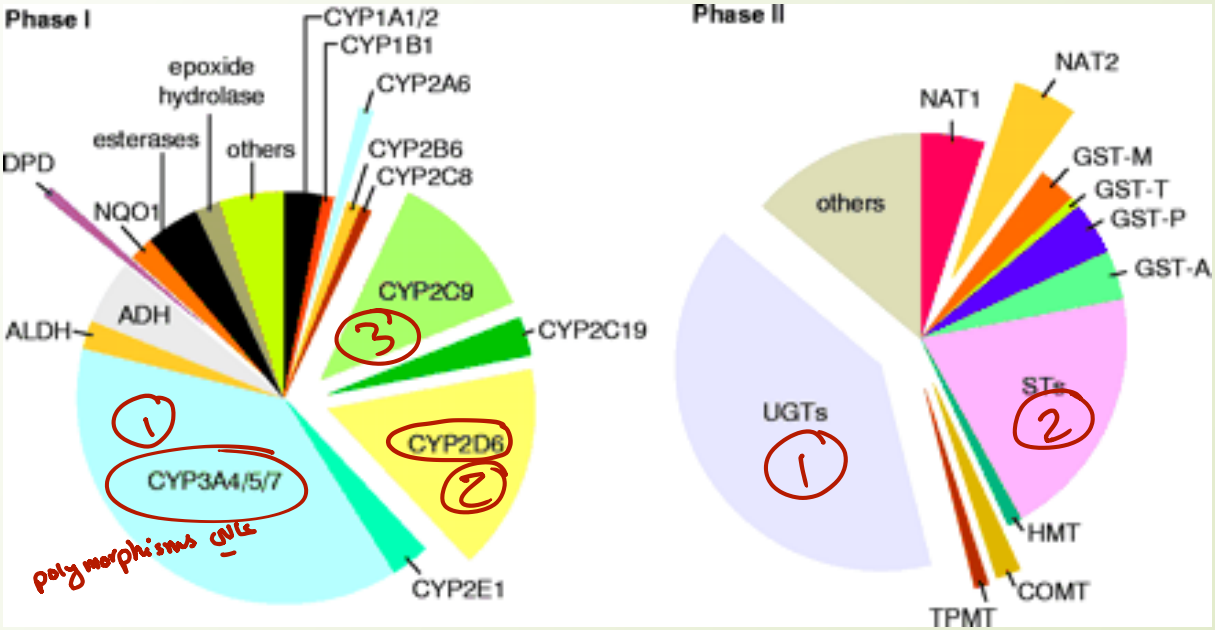
Polymorphic Distribution



Fast meta... اذا كان التركيز قليل + activity عالية

slow / poor meta.. اذا كان التركيز عالي + activity قليلة

Genetic polymorphisms in drug metabolizing enzymes



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

EXAMPLE OF POLYMORPHISMS

Protein	Drugs and Treatment/Action	Drug Responses	Polymorphism Rules and Year of Report
Cytochrome P450 1A2	Antipsychotic agents for schizophrenia patients	Tardive dyskinesia مركبتهم بطيئة وغير منتظمة	Bsp120I (C→A) polymorphism in CYP1A2 gene, 2000 [Basile *et al.*, 2000]
Cytochrome P450 2C9	Anticoagulant agents for the initial phase of phenprocoumon treatment	Severe over-anticoagulation	CYP2C9*2 genotype, 2004 [Schalekamp *et al.*, 2004]
			CYP2C9*3 genotype, 2004 [Schalekamp *et al.*, 2004]
Cytochrome P450 2D6	Neuroleptic agents for chronic schizophrenic patients	Tardive dyskinesia	CYP2D6*4 genotype, 1998 [Kapitany *et al.*, 1998]
Cytochrome P450 2D6	Psychochopic drugs for psychiartric illness	Extrapyramidal drug side effects	CYP2D6 PM phenotypes, 1999 [Vandel *et al.*, 1999]
Cytochrome P450 2D6	CYP2D6-dependent antidepressants	Drug non-response	CYP2D6 EM phenotypes, 2004 [Rau *et al.*, 2004]
UDP-glucuronysltransferase	Capecitabine/irinotecan for the treatment of metastatic colorectal cancer	Greater antitumor response with low toxicity	UGT1A7*2/*2 genotype, 2005 [Carlini *et al.*, 2005]
			UGT1A7*3/*3 genotype, 2005 [Carlini *et al.*, 2005]
UDP-glucuronysltransferase I	Tranilast for the prevention of restenosis following coronary revascularization	Hyperbilirubinemia	Homozygosity for a (TA)7-repeat element within the promotor region of UGT1A1 gene, 2004 [Hosford *et al.*, 2004]
N-acetyltransferase 2	Trimethoprim-sulfamethoxazole for the treatment of infections in infants	Idiosyncratic reactions such as fever, skin rash and multiorgan toxicity	NAT2*5A allele, 1997 [Zielinska *et al.*, 1998]
			NAT2*5C allele, 1997 [Zielinska *et al.*, 1998]
			NAT2*7B, 1997 [Zielinska *et al.*, 1998]
N-acetyltransferase 2	Aromatic amine carcinogens in tobacco smoke	Hepatitis B related hepatocellular carcinoma	NAT2*4 allele, 2000 [Yu *et al.*, 2000]
N-acetyltransferase 2	Isonaiazid for the prophylaxis and treatment of tuberculosis	ADRs such as peripheral neuritis, fever and hepatic toxicity	SA type (NAT2*6/*6, NAT2*6/*7, and NAT2*7/*7), 2002 [Hiratsuka *et al.*, 2002]

EXAMPLE OF POLYMORPHISMS

من أوائل اللي شافو فيها

- Interindividual differences in response to drug therapy due to differences in acetylation of drugs is a well studied example of genetic polymorphism.
- Patients' ability to metabolize certain drugs such as hydralazine, procainamide, and isoniazid can be categorized as either "fast acetylators," "normal acetylators," or "slow acetylators."
- Acetylation status is dependent on the patient's genetic composition, which determines the activity of the acetylation enzyme N-acetyltransferase.
- Acetylation status determines whether a patient is dosed with a correspondingly higher or lower dose compared to "normal acetylators."
- Genetic variations are well known in **bacteria** and other microorganisms because the rapid changes in these organisms are easily observed.
- In humans, mutations and related changes occur to different degrees in thousands of proteins and other macromolecules.

على درجة أولى مقارنة مع الطبيعية

بحكيلك التغيرات ممكن تصير على الأف البروتين macromolecule

- A change or mutation in gene sequence may or may not result in chronically reduced or increased level or activity of a protein or an essential enzyme. In some cases, such changes result in an exaggerated or reduced therapeutic response to a drug.
- The cell is homozygous if the genetic sequences occupying the locus are the same on the maternal and paternal chromosome; if they are different, the cell is heterozygous. When more than one alternative forms of a gene exists, they are referred to as alleles of the gene. The identity of the alleles carried by an individual at a given gene locus is referred to as the genotype.
- Alleles that vary by a single nucleotide change can now be characterized rapidly at the DNA level by single-nucleotide polymorphism (SNP). The physical effect observed as a result of genotype difference is referred to as phenotype.
- Genes are considered functionally polymorphic when allelic variants exist stably in the population and their gene products exhibit altered activity in relation to the wild type ("normal"). Ideally, variation in drug response can be predicted by monitoring changes in phenotype or genotype for a single patient or a group of patients.

1. N-ACETYLTRANSFERASE ACTIVITY

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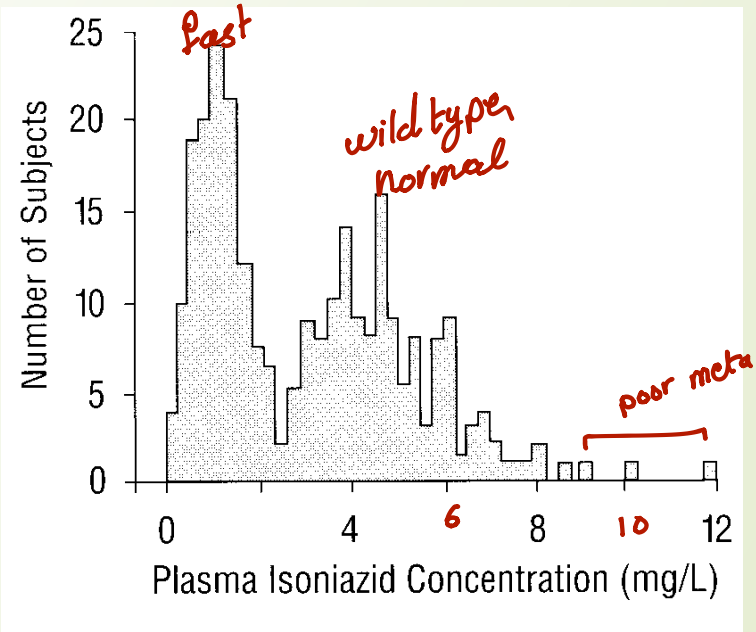


Distribution of plasma isoniazid concentration in 483 subjects after and oral dose. Reproduced from Evans DAP. *Br Med J* 2:485, 1960.

ETHNIC DIFFERENCES IN THE DISTRIBUTION OF ACETYLATOR PHENOTYPE

Population	% Slow	% Hetero Fast	% Homo Fast
South Indians	59	35.6	5.4
Caucasians	58.6	35.9	5.5
Blacks	54.6	38.6	6.8
Eskimos	10.5	43.8	45.7
Japanese	12	45.3	42.7
Chinese	22	49.8	28.2

From: Kalo W. *Clin Pharmacokinet* 7:373-4000, 1982.

Examples

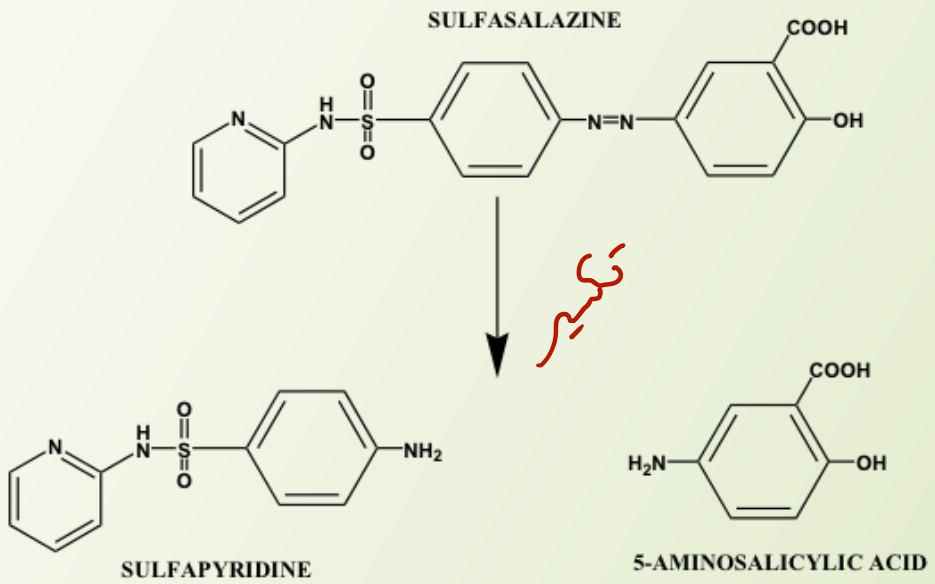
Xenobiotics Subject to Polymorphic Acetylation in Man

Hydrazines	*Arylamines*	*Carcinogenic Arylamines*
isoniazid	dapsone	benzidine
hydralazine	procainamide	-naphthylamine
phenylzine	sulfamethazine	4-aminobiphenyl
acetylhydrazine	sulfapyridine	
hydrazine	aminoglutethimide	

Drugs metabolized to amines

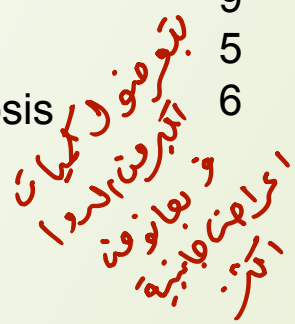
sulfasalazine	nitrazepam
clonazepam	caffeine

Adverse Effects to Sulfasalazine in Patients with Inflammatory Bowel Disease



Adverse effects to sulfasalazine in patients with inflammatory bowel disease

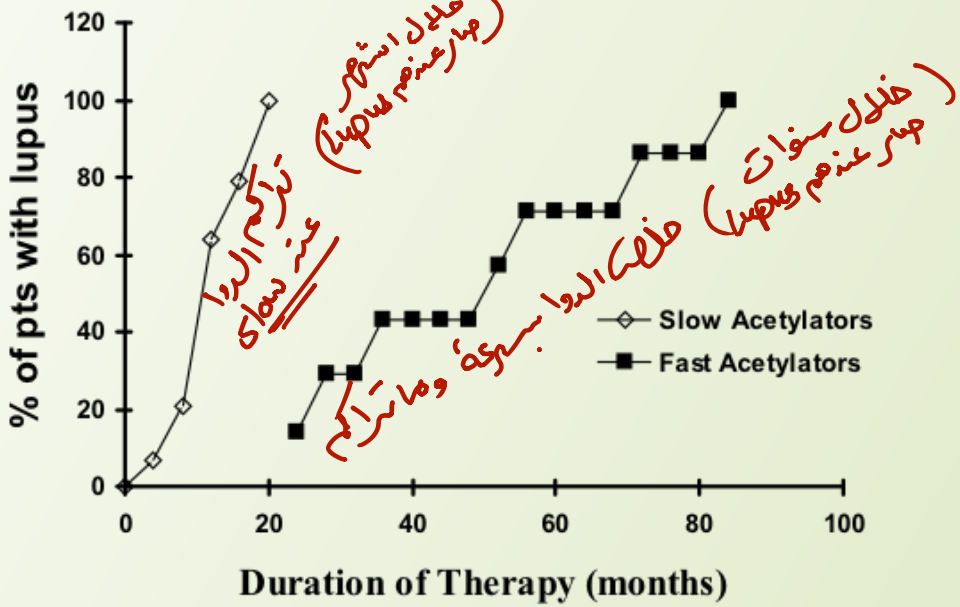
	Frequency of side effect	
Side Effect	*Slow Acetylators*	*Fast Acetylators*
cyanosis	9	1
hemolysis	5	0
transient reticulocytosis	6	0



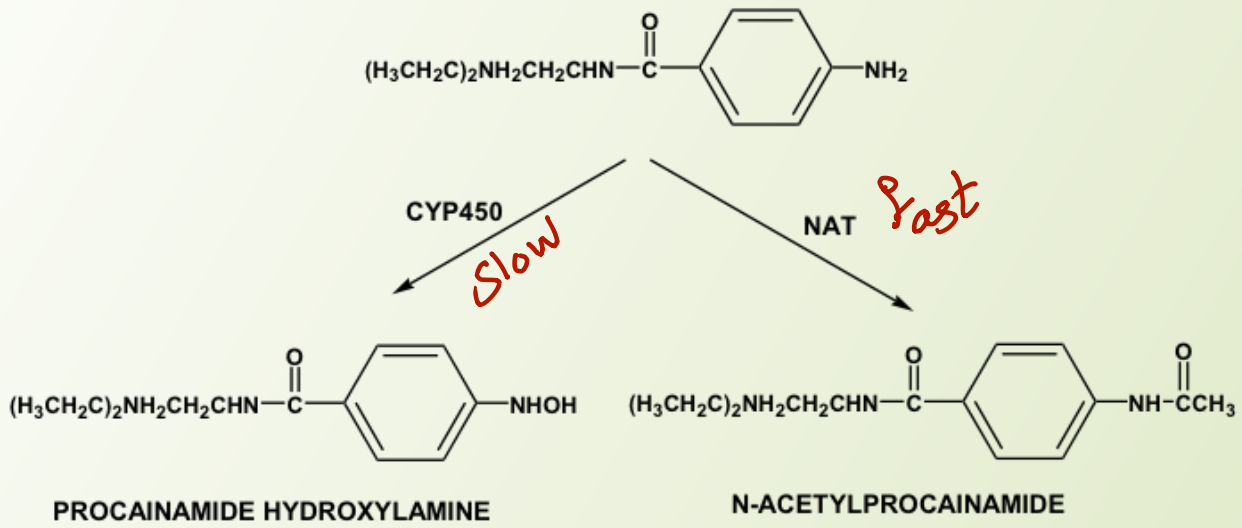
Data from: Das et al. *N Engl J Med* 289:491-495, 1973.

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

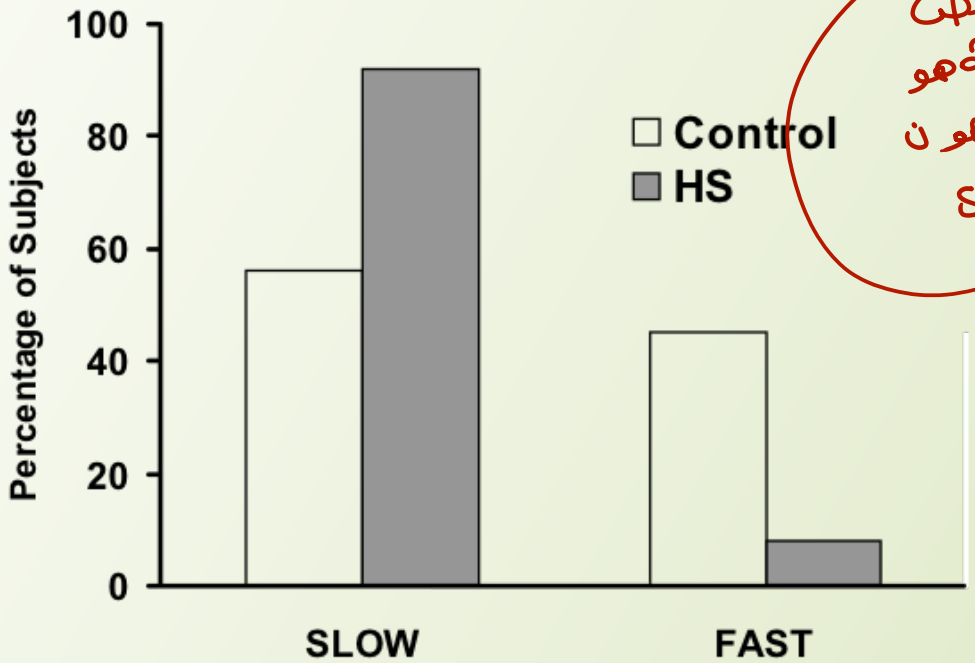


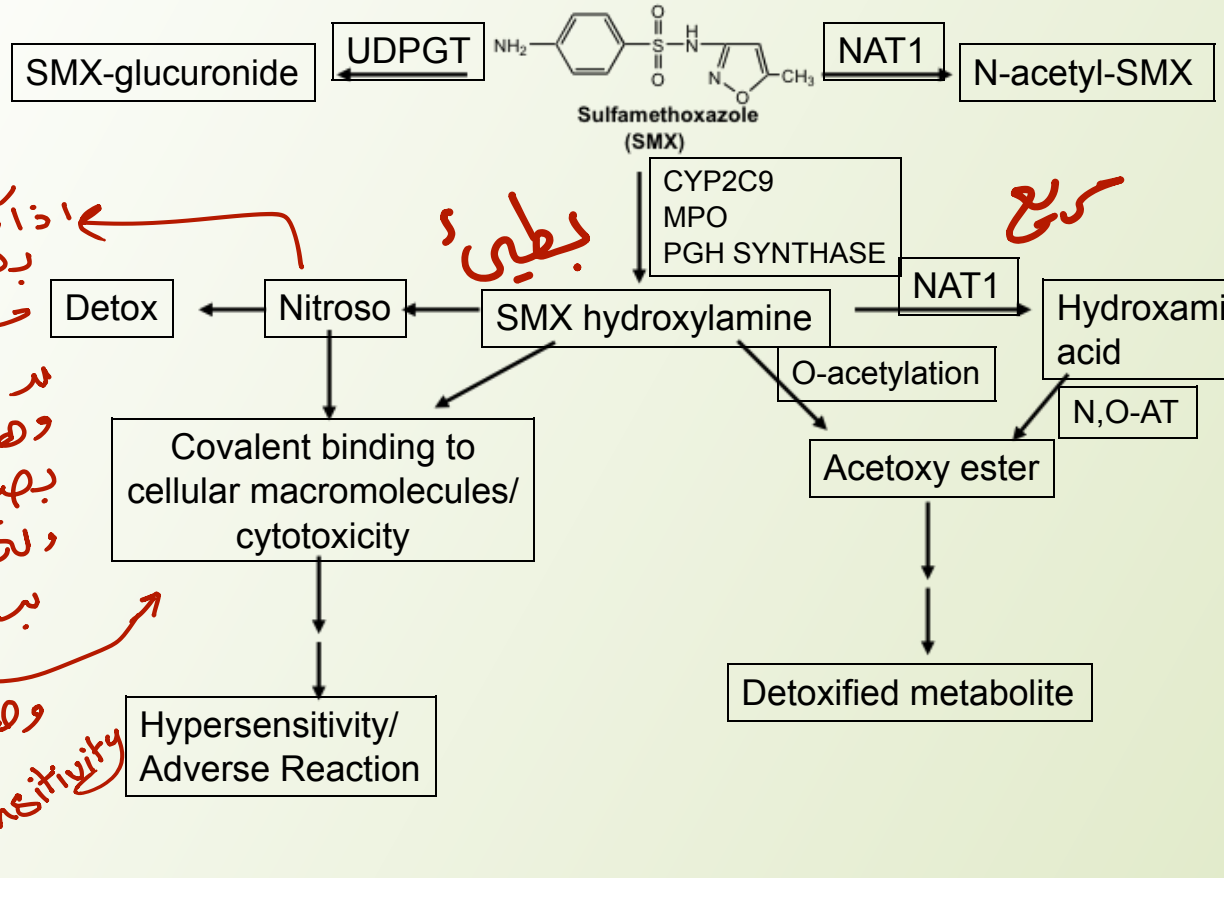
PROCAINAMIDE HYDROXYLAMINE

N-ACETYLPROCAINAMIDE

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