

Session D: Modelling and Simulation in Biomedical Research

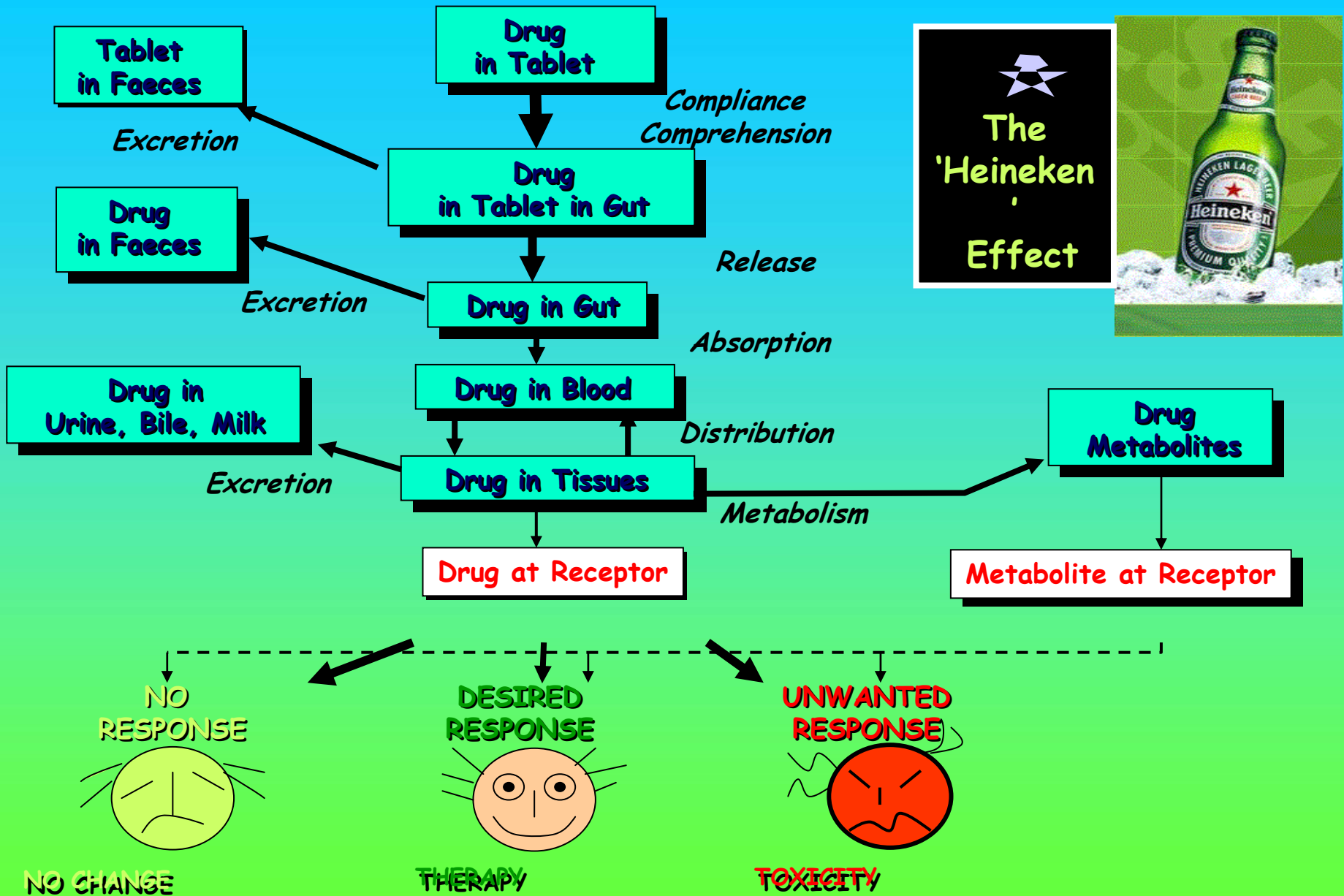
**Modelling ADME in Drug Development and
Linking *in vitro* Data to *in vivo* Outcome:**

**"Integrating Known-Knowns to Assess
Impact of Known-Unknowns"**

Amin Rostami-Hodjegan
University of Sheffield, United Kingdom

a.rostami@sheffield.ac.uk

ADME: The Roadmap to Site of Effect



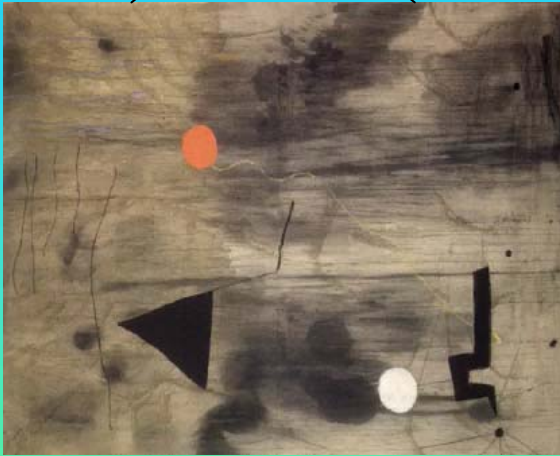


Description & Prediction

Pharmacokinetics

seeks to provide a mathematical basis for the description and prediction of the time course of drug (metabolite) concentrations in relation to dose in the body.
(Quantification of ADME)

A Gallery of Models



M



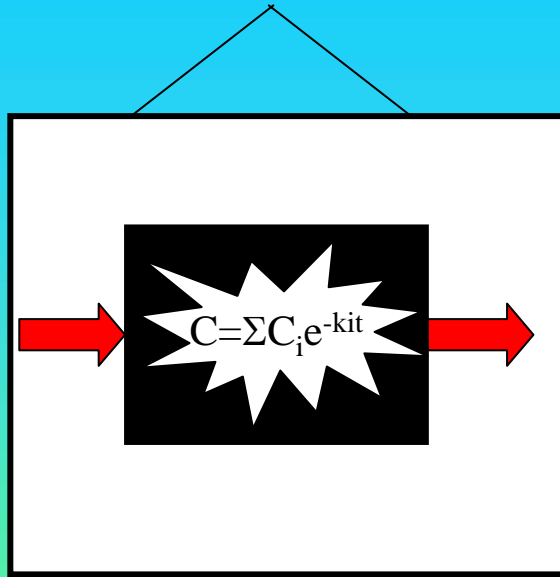
P



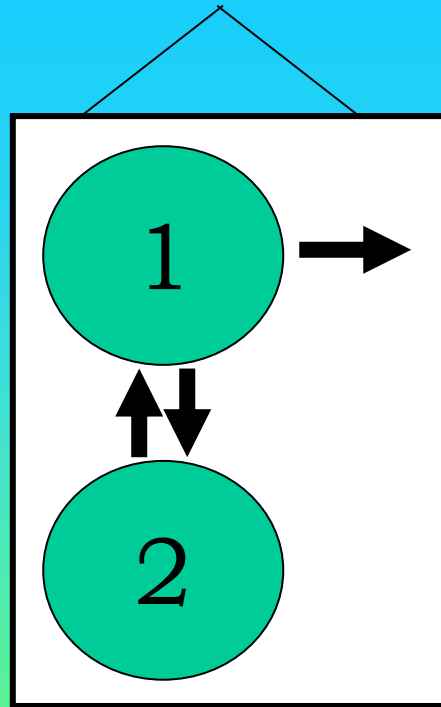
D

Same Object ; Different Views !

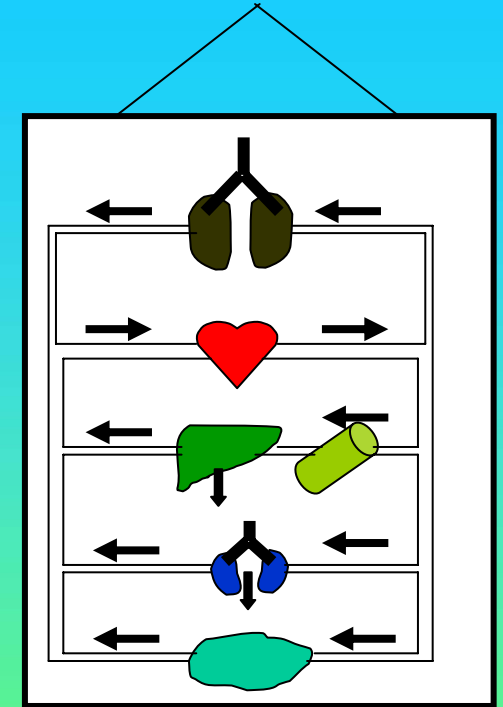
A Gallery of (PK) Models



Empirical



Compartmental



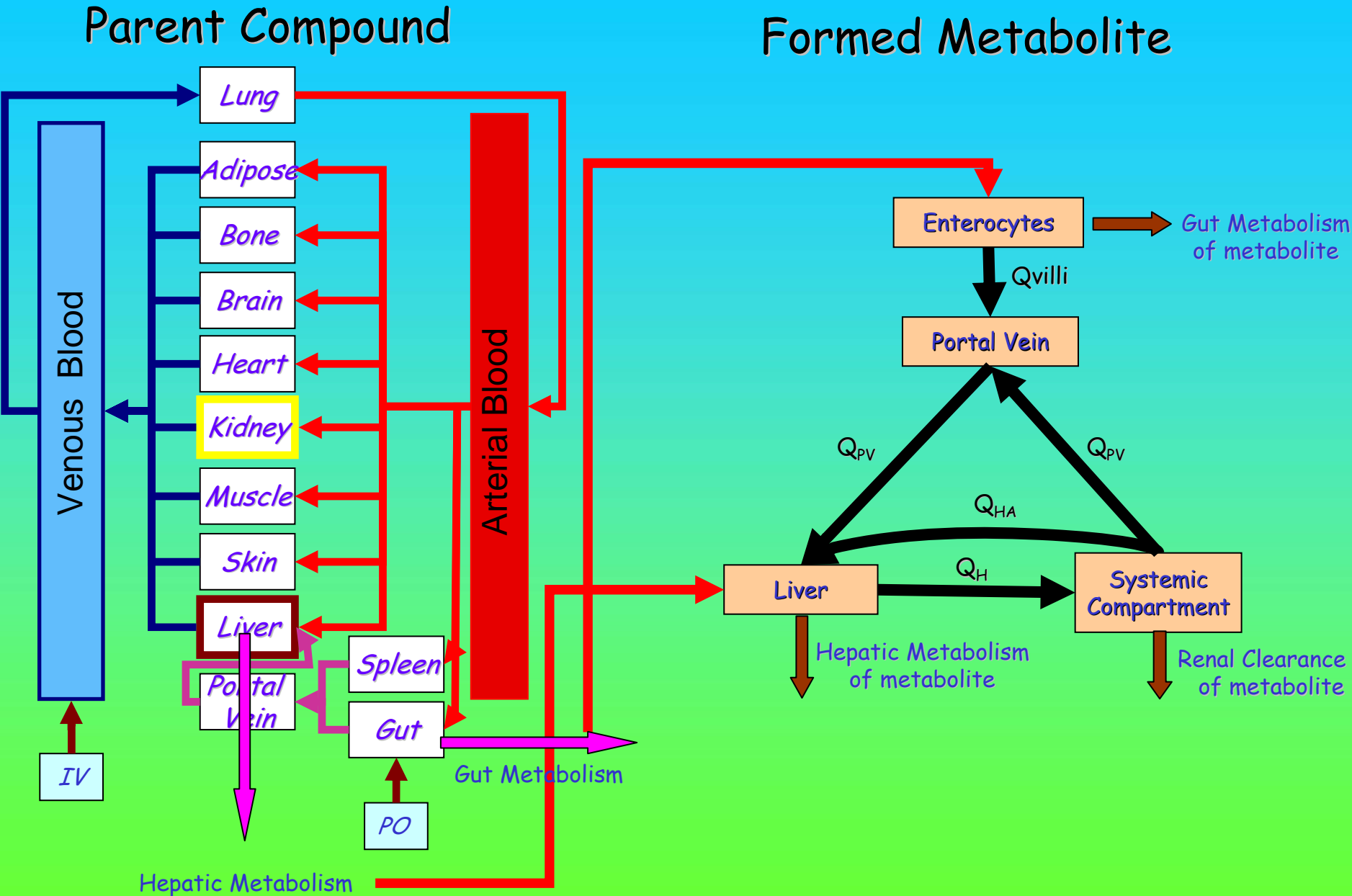
Physiological



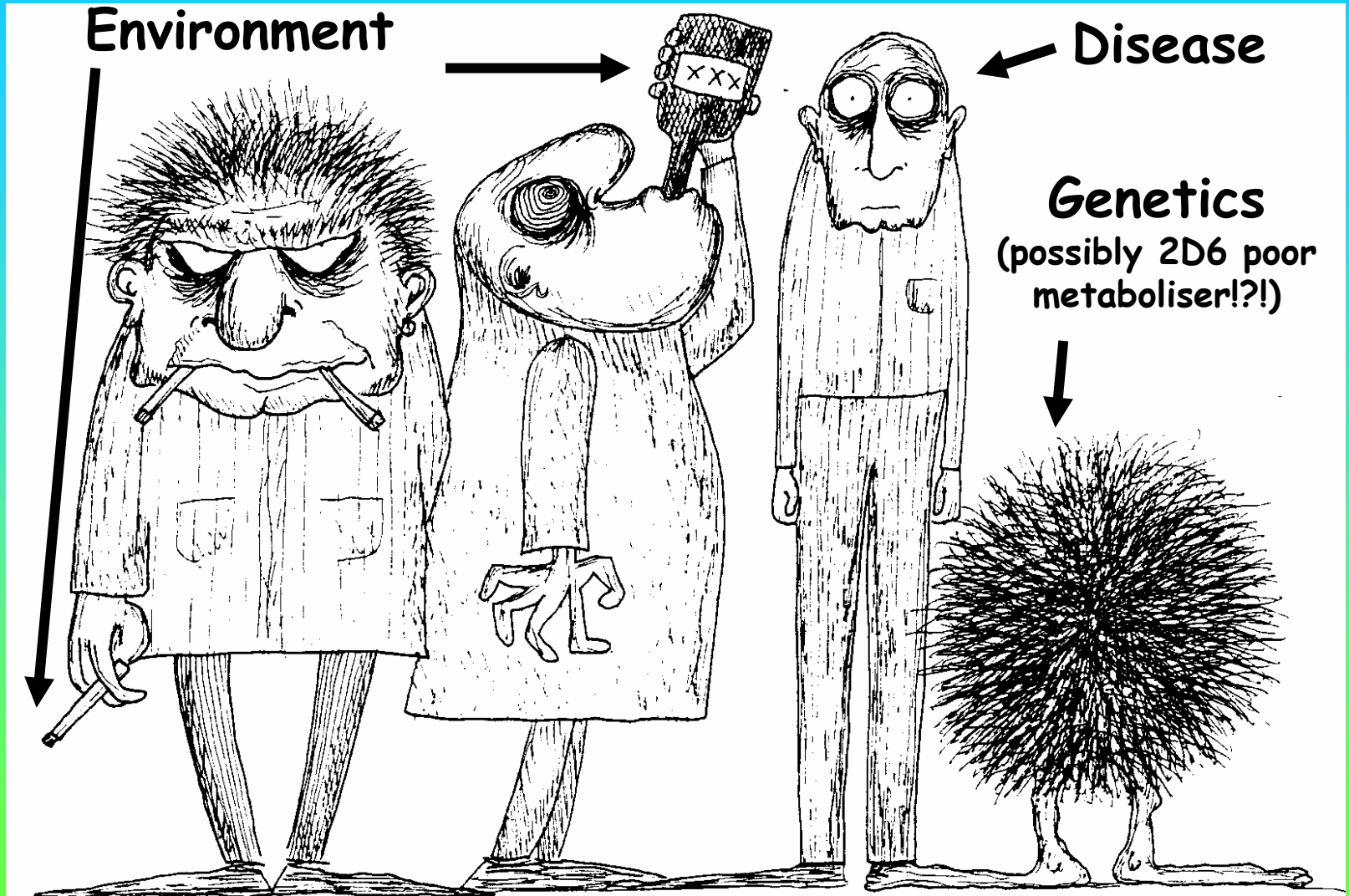
Components:

- fully mechanistic
- pragmatic/minimalistic

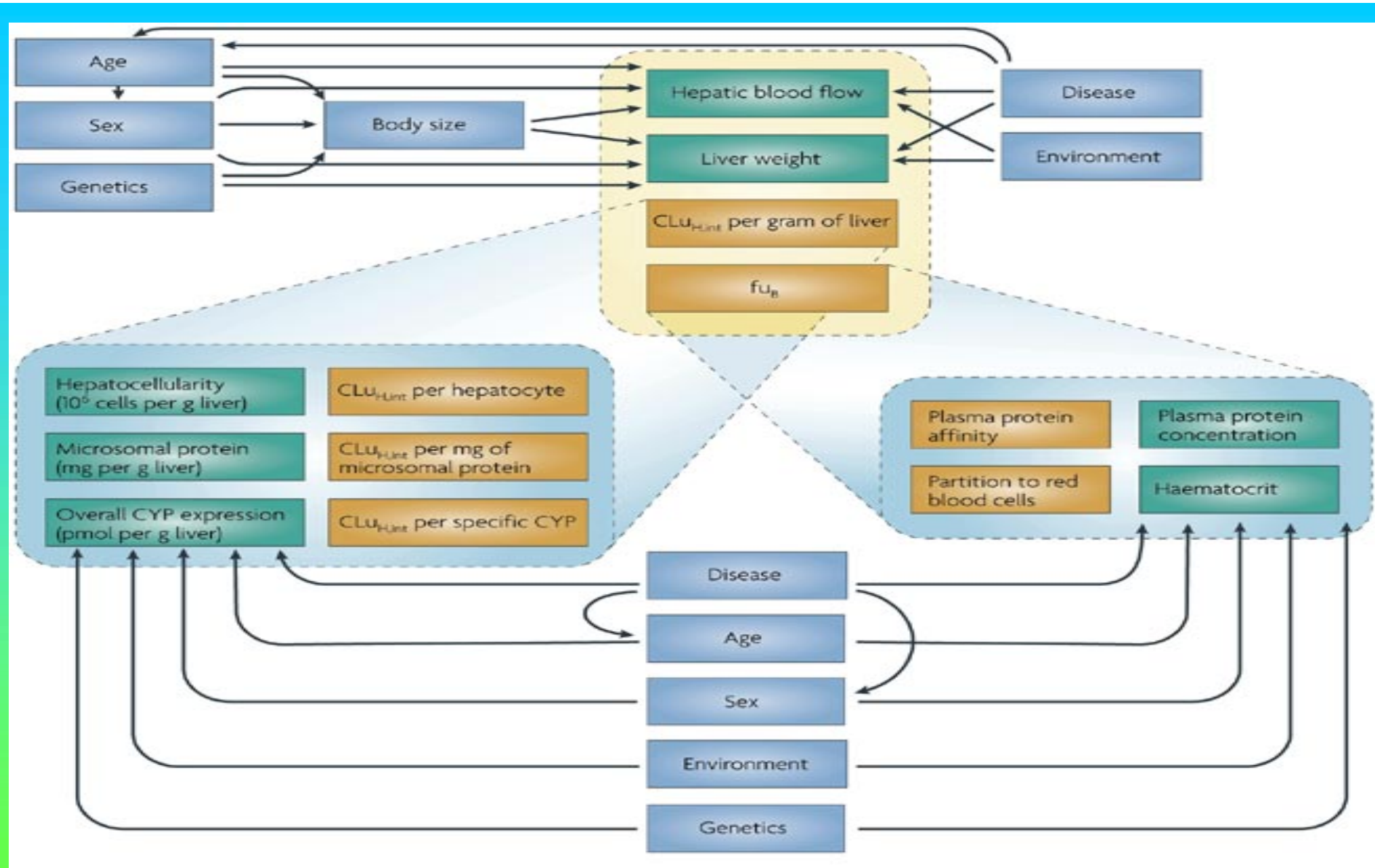
Metabolite formation in the gut and liver



Patients in the Royal Hallamshire Hospital

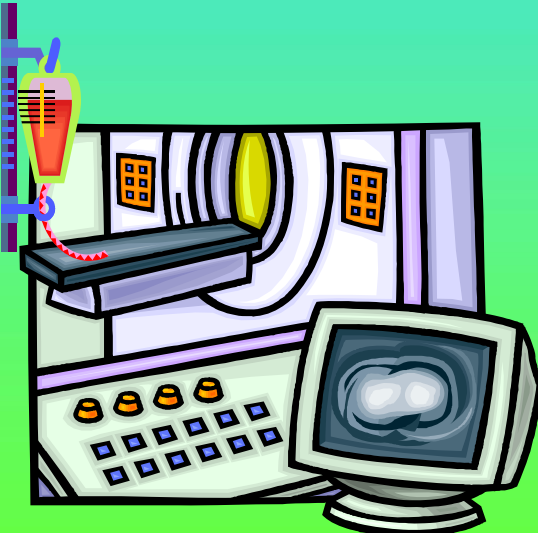
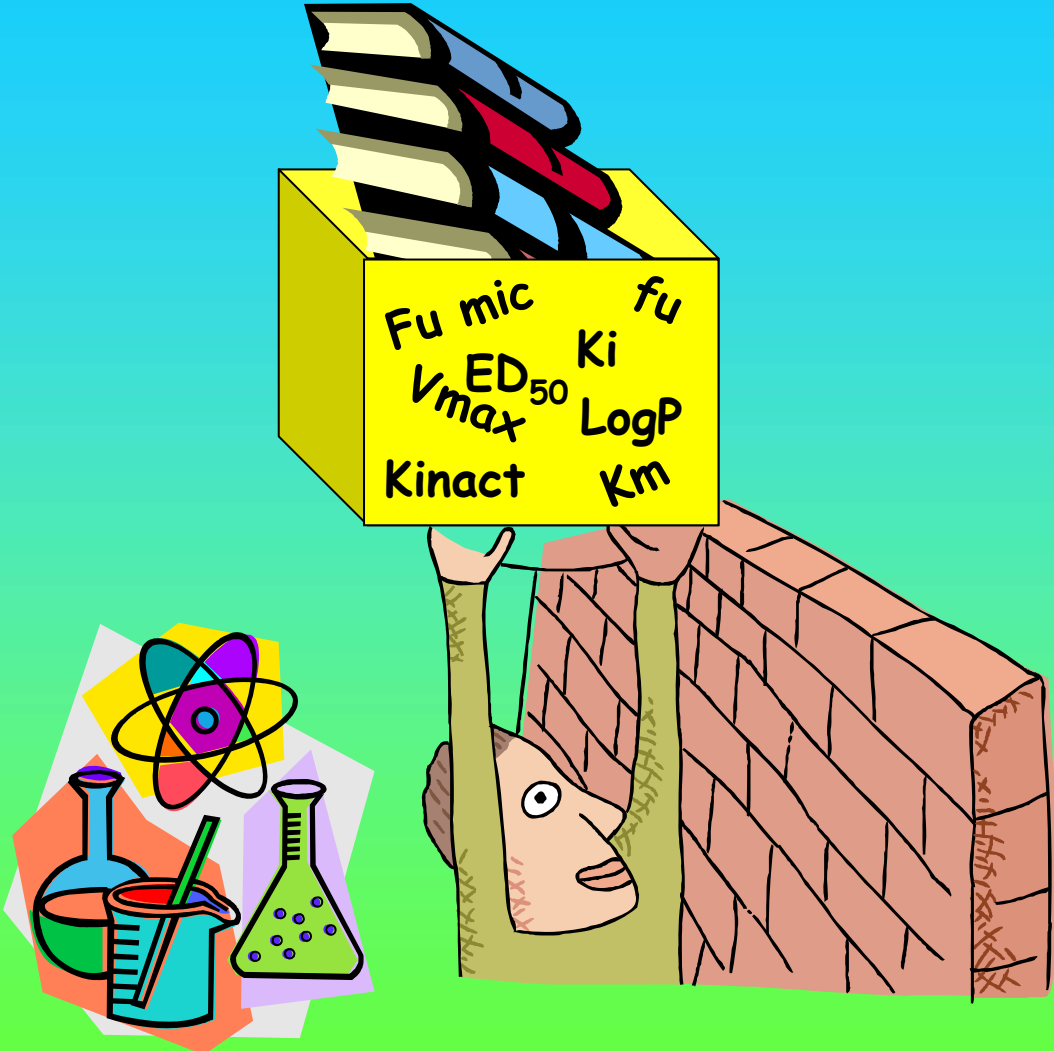


The Complexity of Covariate Effects



PRE-CLINICAL

CLINICAL



Need for Co-operation & Integration

Innovation

Stagnation

**Challenge and Opportunity
on the Critical Path
to New Medical
Products**



**U.S. Department of Health and Human Services
Food and Drug Administration
March 2004**

*Only a concerted effort to apply the new
biomedical science to medical product development will
succeed in modernizing the critical path.*

Co-sponsored by



**Sharing Data and Models to
Improve Clinical Drug Development
and Regulatory Decisions**

January 24-25, 2007 | Washington Marriott Hotel, Washington, DC, USA

Commercial Member Organisations Includes:

Amgen	F Hoffmann-La Roche	Novartis	Sanofi-Aventis
AstraZeneca	GlaxoSmithKline	Novo Nordisk	Servier
Biovitrum	Lundbeck	Nycomed(Altana)	Takeda
Daiichi-Sankyo	Neurocrine	Pfizer	UCB
	Merck & Others		

Associate Regulatory/Governmental Organisations:

MPA - Medical Product Agency (Sweden)

NAM - National Agency for Medicines (Finland)

ECVAM - EU Centre for Validation of Alternative Methods (Italy)

FDA - (USA)

MEB - Medicines Evaluation Board (Holland) [under negotiations]

etc.

Pharmacogenetics and Controversies

Are CYP polymorphisms important for drug PK?

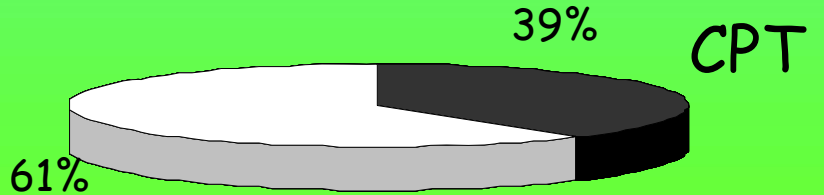
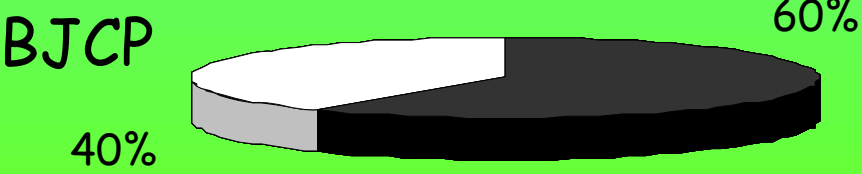
Are CYP polymorphisms important for drug Response?



YES	NO
<i>S</i> -warfarin	<i>S</i> -warfarin
tolbutamide	tolbutamide
rabeprazole	rabeprazole
diclofenac	diclofenac
DEX	

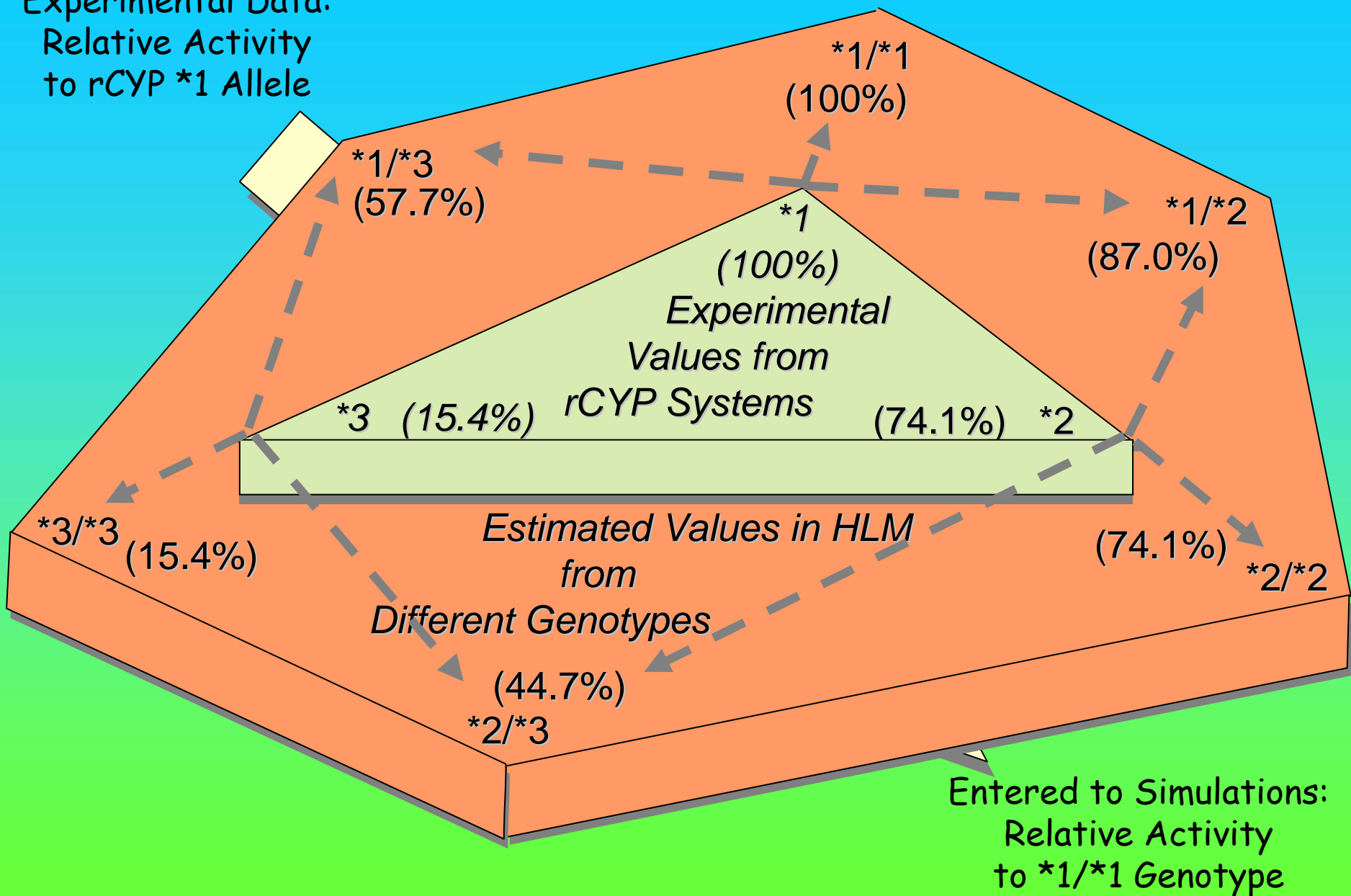
YES	NO
<i>S</i> -warfarin	<i>S</i> -warfarin
tolbutamide	tolbutamide
omeprazole	omeprazole
phenytoin	phenytoin
metoprolol	metoprolol
irbesartan	irbesartan

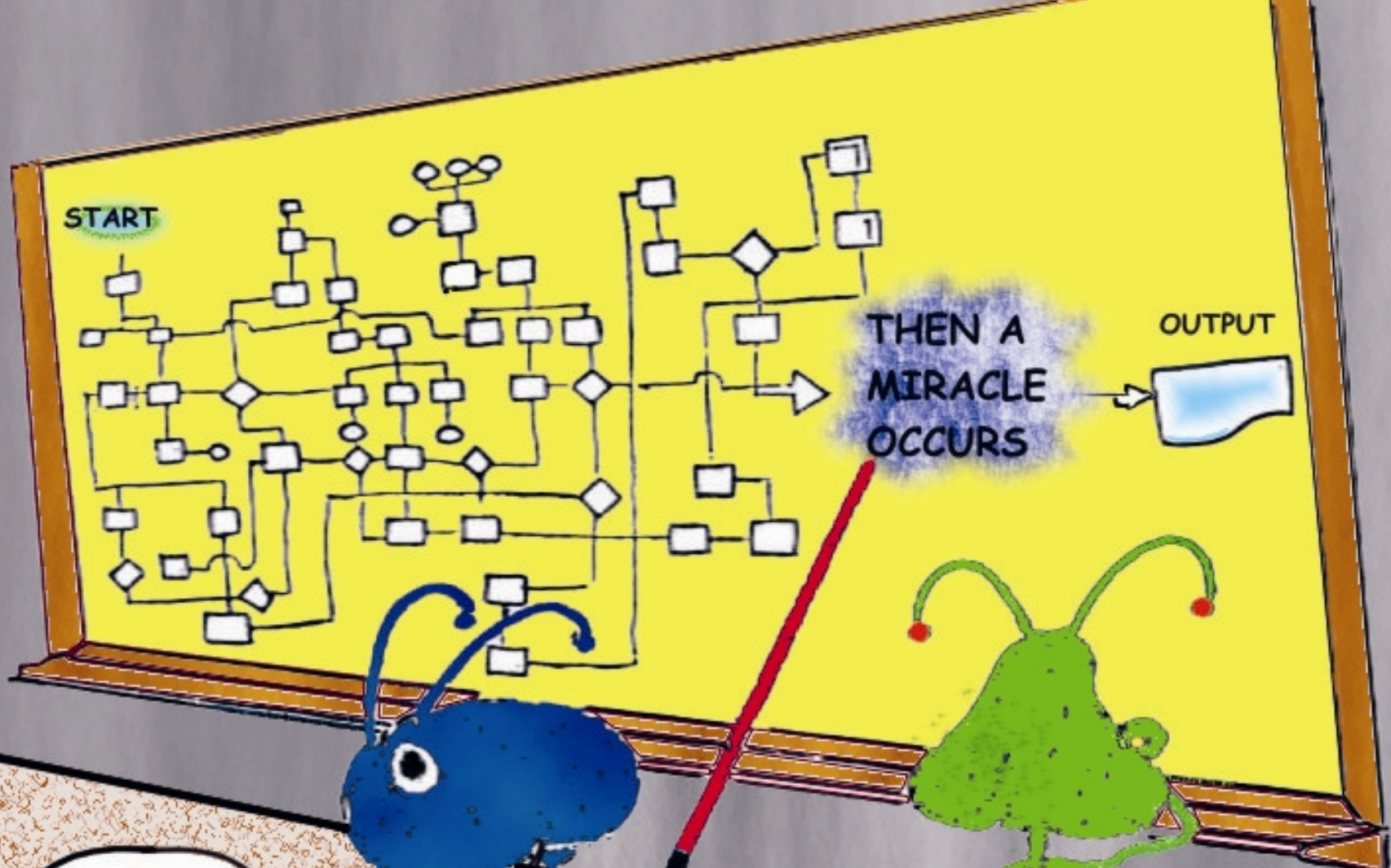
Most of positive associations in Lancet and other High Impact Journals !?!



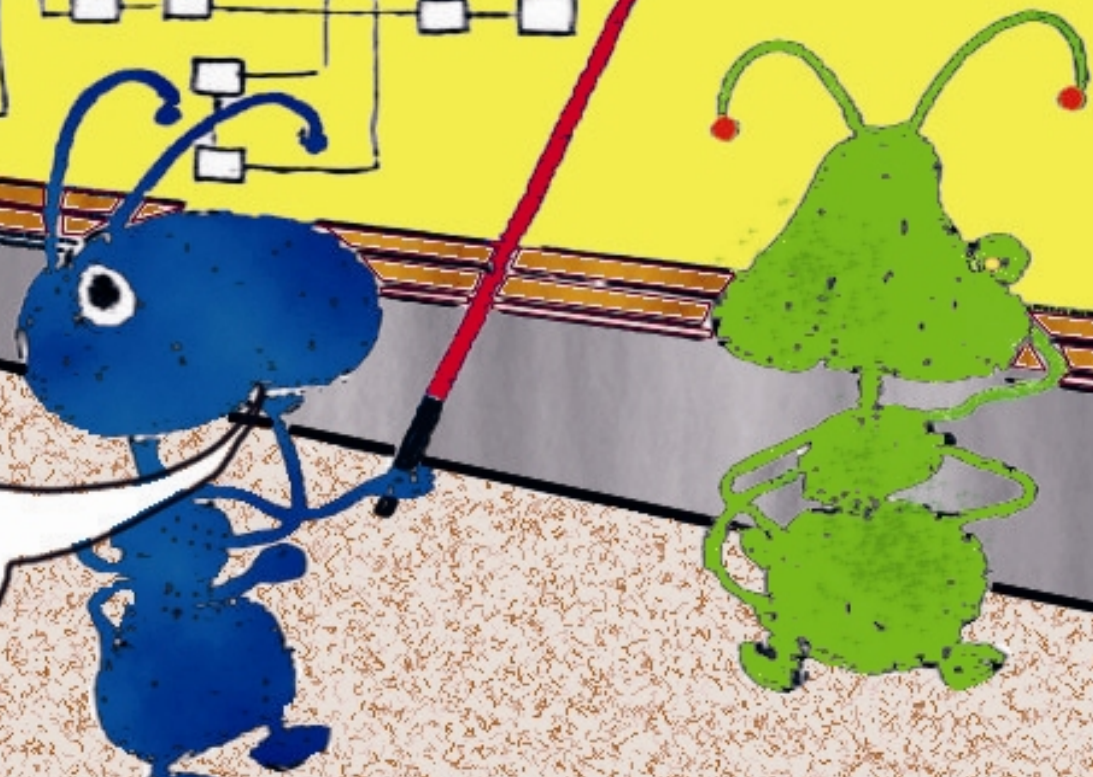
Use of IVIVE to Assess Effects of Genetics

Experimental Data:
Relative Activity
to rCYP *1 Allele





Good work..
but I think we
need just a little
more detail
HERE!



Unselected for CYP2C9 Genotype (not enriched)

Lisa Almond (ISSX Manchester 2006)

Genotype Frequencies

- 14 independent published studies
- Limited to European Caucasian (non Mediterranean)

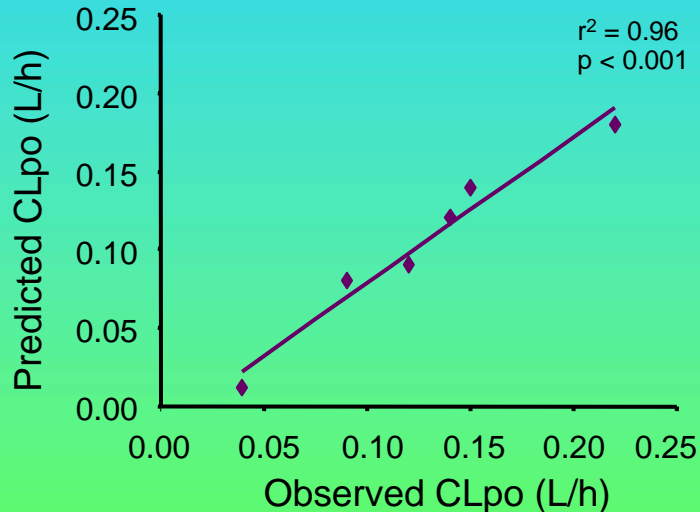
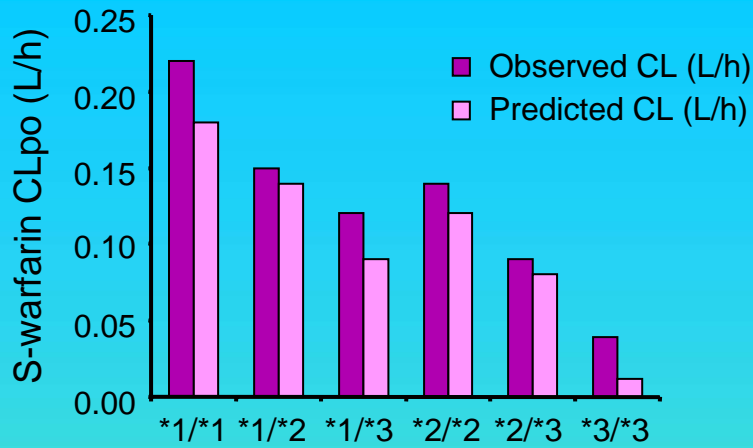
	Genotype Frequency (%)					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
Weighted Mean %	67.2	18.6	11.1	1.1	1.7	0.3
Total n	2297	629	376	37	59	10

Genotype Abundances

- 5 independent sources (published and personal communications)
- Due to paucity of data, intermediate genotypes were combined
- A CV of 60% was arbitrarily set for *3/*3 abundance

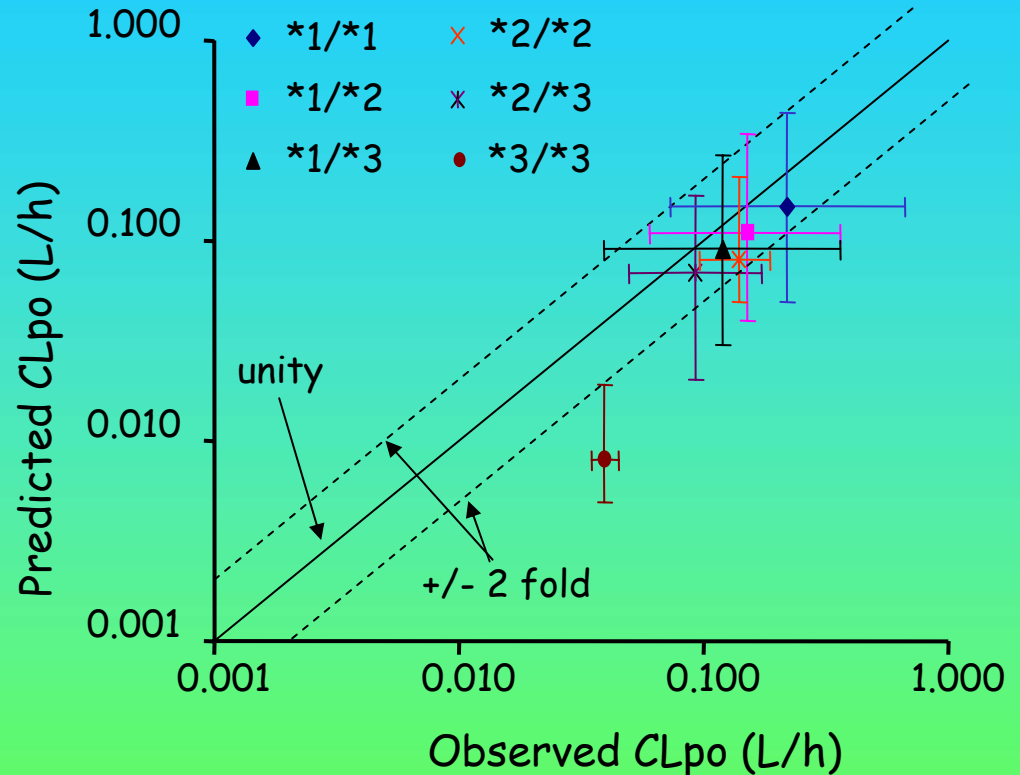
	CYP2C9 pmol/mg	CV	n
*1/*1	83.4	60.5%	65
*1/*2	75.8	63.8%	45
*1/*3			
*2/*2			
*2/*3			
*3/*3	23.0		1

Predicted vs Observed CL_{po}: S-warfarin



Lisa Almond (ISSX Manchester 2006)

Not just central tendency (mean or median)
but also variability:



The Propagation of Genetic Polymorphism in CYP2C9 into Tolbutamide Pharmacokinetics:
Assessment Using an Integrated Model

Dickinson et al. (ISSX Manchester 2006)

Could we predict the outcome?

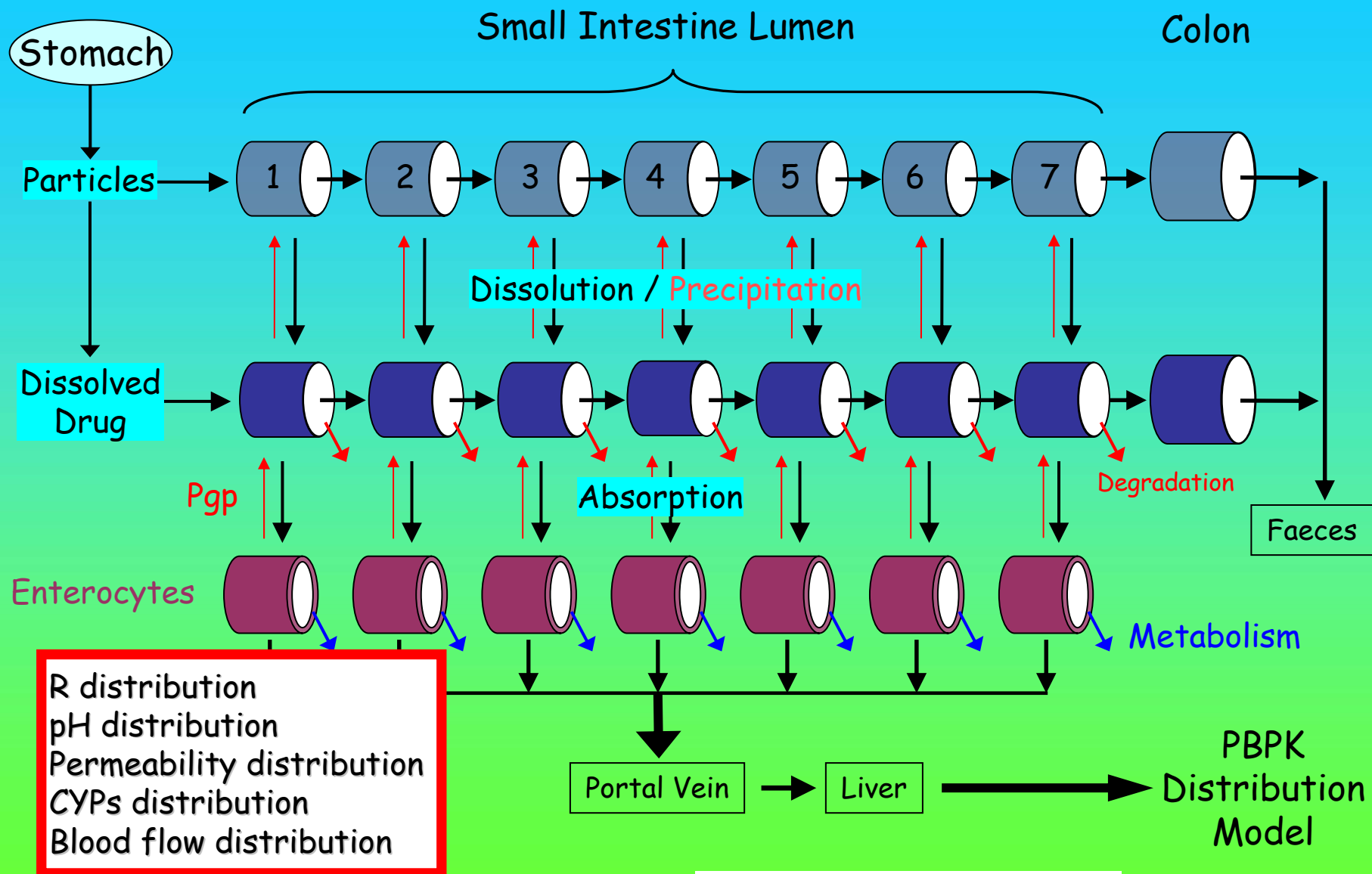
Table 6

The outcomes of reported studies of the pharmacokinetics (PK) and/or pharmacodynamics (PD) of warfarin with respect to CYP2C9 genotype

Reference	Type of study	Outcome measure	n	Significant difference between *1/*1 and											
				*1/*2	*2/*2	*1/*3	*2/*3	*3/*3	Combo						
Takahashi <i>et al.</i> 2003 [10]	PK	Unbound oral clearance	47	<u>×</u>	<u>25</u>	<u>×</u>	0	<u>×</u>	48	<u>×</u>	20	<u>×</u>	0		
Scordo <i>et al.</i> 2002 [8]	PK	Unbound oral clearance	93	<u>×</u>	<u>20</u>	<u>×</u>	0	×	82	✓	44	✓	10		
Kamali <i>et al.</i> 2004 [9]	PK	Plasma (S)-warfarin concentration	121	✓	<u>20</u>	<u>×</u>	0	×	92	<u>×</u>	48	<u>×</u>	12		
Loebstein <i>et al.</i> 2001 [11]	PK	Plasma clearance	156	<u>×</u>	<u>18</u>	<u>×</u>	0	✓	94	×	52	<u>×</u>	16		
Takahashi <i>et al.</i> 2003 [10]	PD	Weight normalized maintenance dose	47	<u>×</u>	<u>15</u>	<u>×</u>	0	<u>×</u>	48	<u>×</u>	15	<u>×</u>	0		
Khan <i>et al.</i> 2004 [13]	PD	Maintenance dose	53	<u>×</u>	<u>16</u>	<u>×</u>	0	✓	50	<u>×</u>	16	<u>×</u>	0		
Joffe <i>et al.</i> 2004 [15]	PD	Maintenance dose/bleeding rate	73	<u>×</u>	<u>12</u>	<u>×</u>	0	×	64	<u>×</u>	26	<u>×</u>	4	✓	42
Scordo <i>et al.</i> 2002 [8]	PD	Maintenance dose	93	<u>×</u>	<u>10</u>	<u>×</u>	0	✓	76	✓	45	✓	10		
Kamali <i>et al.</i> 2004 [9]	PD	Maintenance dose	121	<u>×</u>	<u>10</u>	<u>×</u>	2	✓	82	<u>×</u>	45	<u>×</u>	12		
Sigaret <i>et al.</i> 2004 [23]	PD	Maintenance dose	126	<u>×</u>	<u>11</u>	<u>×</u>	2	×	82	<u>×</u>	45	<u>×</u>	13		
Loebstein <i>et al.</i> 2001 [11]	PD	Maintenance dose	156	✓	<u>12</u>	<u>×</u>	3	✓	86	<u>×</u>	45	<u>×</u>	16		
Tabrizi <i>et al.</i> 2002 [24]	PD	Maintenance dose	153	✓	<u>12</u>	<u>×</u>	3	✓	86	<u>×</u>	45	<u>×</u>	17		
King <i>et al.</i> 2004 [21]	PD	Maintenance dose	159	<u>×</u>	<u>12</u>	<u>×</u>	3	✓	88	<u>×</u>	45	<u>×</u>	18		
Peyvandi <i>et al.</i> 2004 [14]	PD	Mean maintenance dose	175	<u>×</u>	<u>12</u>	<u>×</u>	3	✓	88	<u>×</u>	45	<u>×</u>	20	✓	60
Maragaglione <i>et al.</i> 2002 [18]	PD	Mean maintenance dose	180	✓	<u>12</u>	<u>×</u>	3	✓	88	<u>×</u>	45	<u>×</u>	20		
Higashi <i>et al.</i> 2002 [17]	PD	Maintenance dose/bleeding rate	185	<u>×</u>	<u>12</u>	<u>×</u>	3	×	90	<u>×</u>	45	<u>×</u>	21	✓	62
Lindh <i>et al.</i> 2005 [12]	PD	INR > 3	219	<u>×</u>	<u>14</u>	<u>×</u>	4	×	92	<u>×</u>	45	<u>×</u>	26	✓	68
Sconce <i>et al.</i> 2005 [22]	PD	Maintenance dose	297	✓	<u>20</u>	✓	8	✓	94	<u>×</u>	50	<u>×</u>	32	✓	78
Aquilante <i>et al.</i> 2006 [43]	PD	Maintenance dose	350	×	<u>24</u>	<u>×</u>	12	×	94	<u>×</u>	54	<u>×</u>	35	✓	80

'Combo' signifies comparison between wild type vs. the combination of all other genotypes. Crosses (×) indicate failure of the study to show a statistically significant difference between the corresponding genotype and wild type. Ticks (✓) indicate success of the study in showing a statistically significant difference between the corresponding genotype and wild type. All observations that were consistent with simulated results are underlined (i.e. × for true negative and ✓ for true positive).

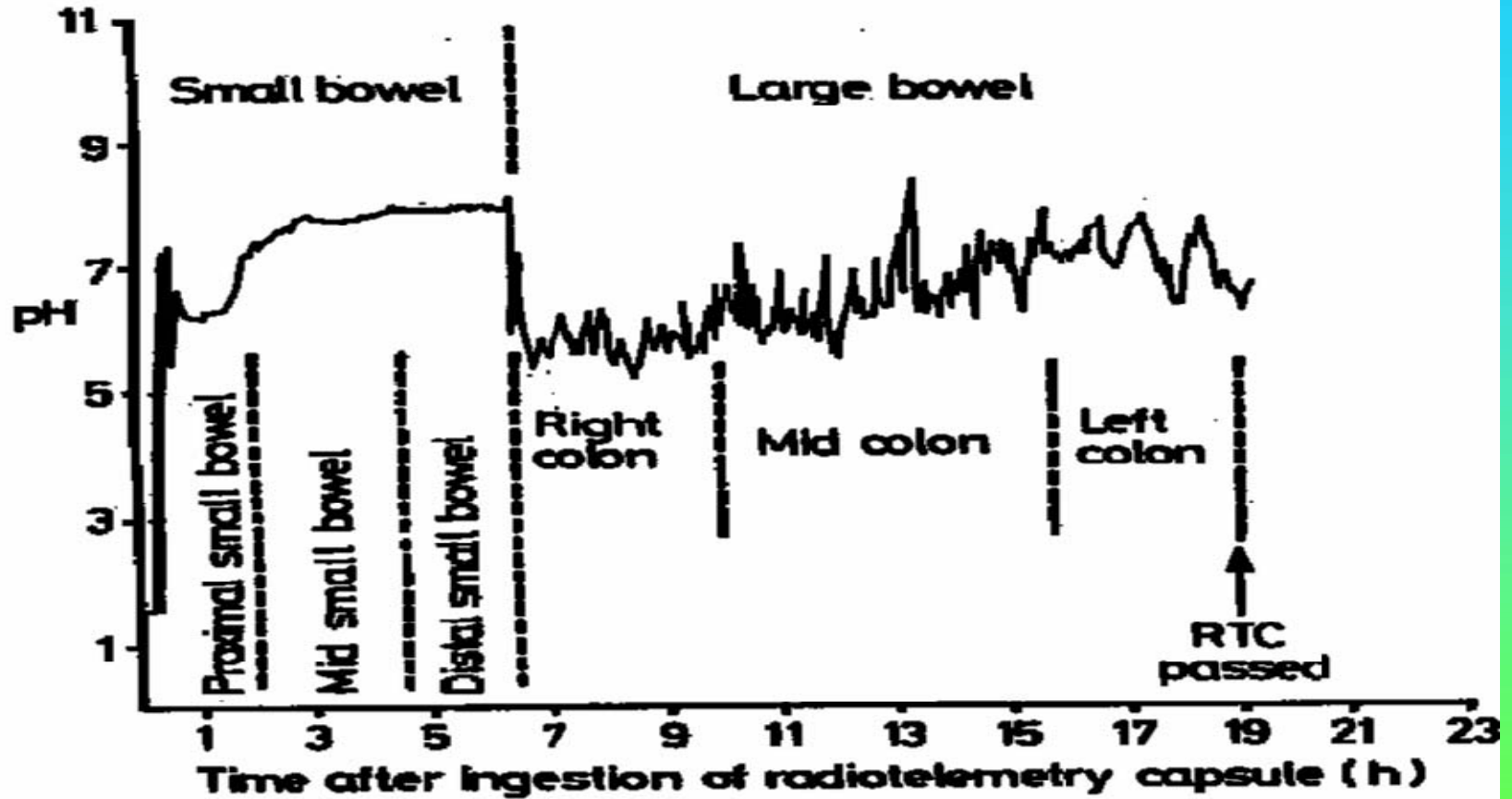
ADAM Model



*after Agoram et al. 2001

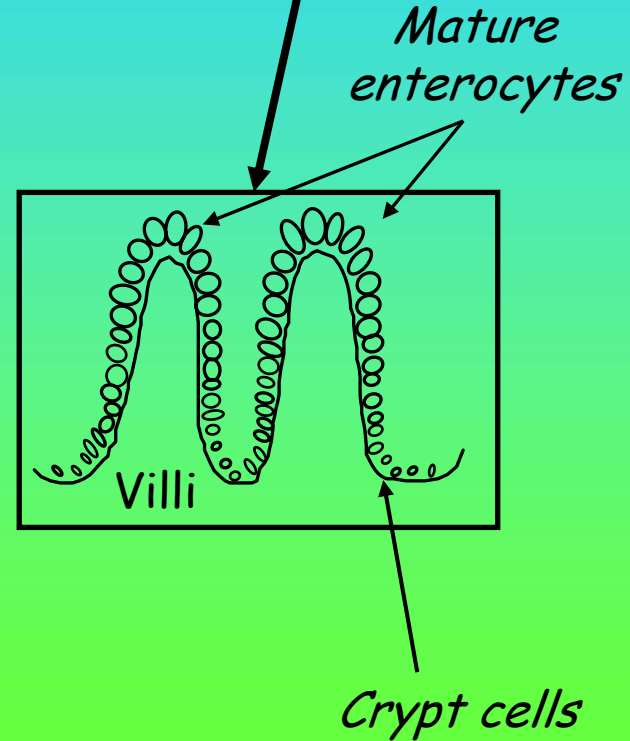
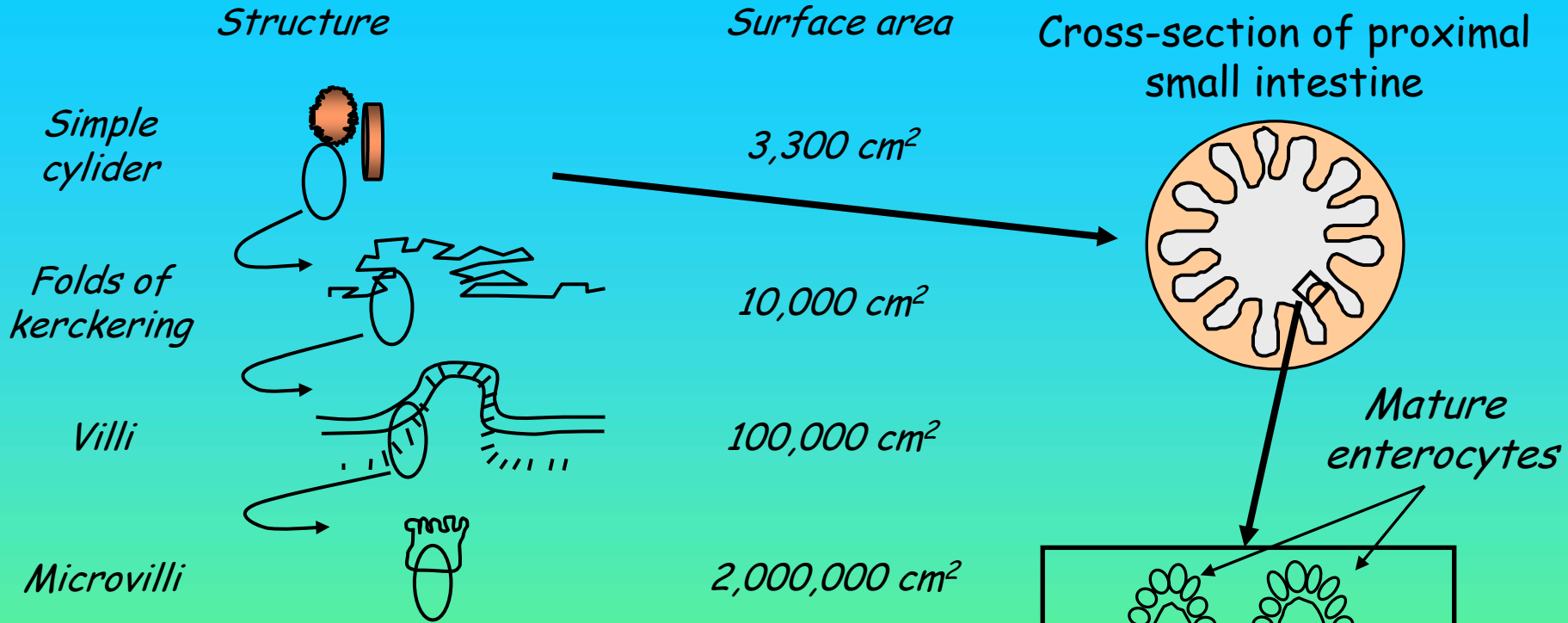
pH Profile in the GI Tract

FASTED pH PROFILE IN MAN

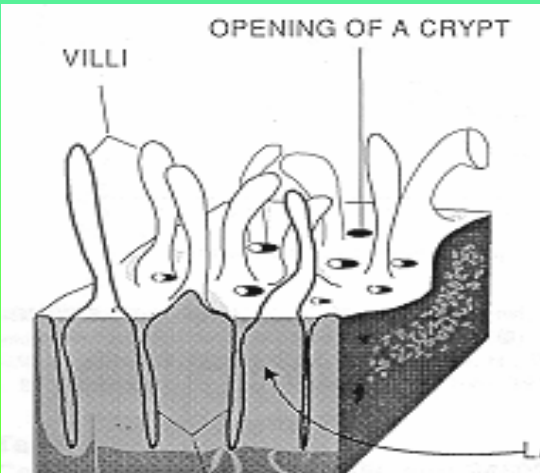


Wilding et al. (Presented at PKUK 2004)

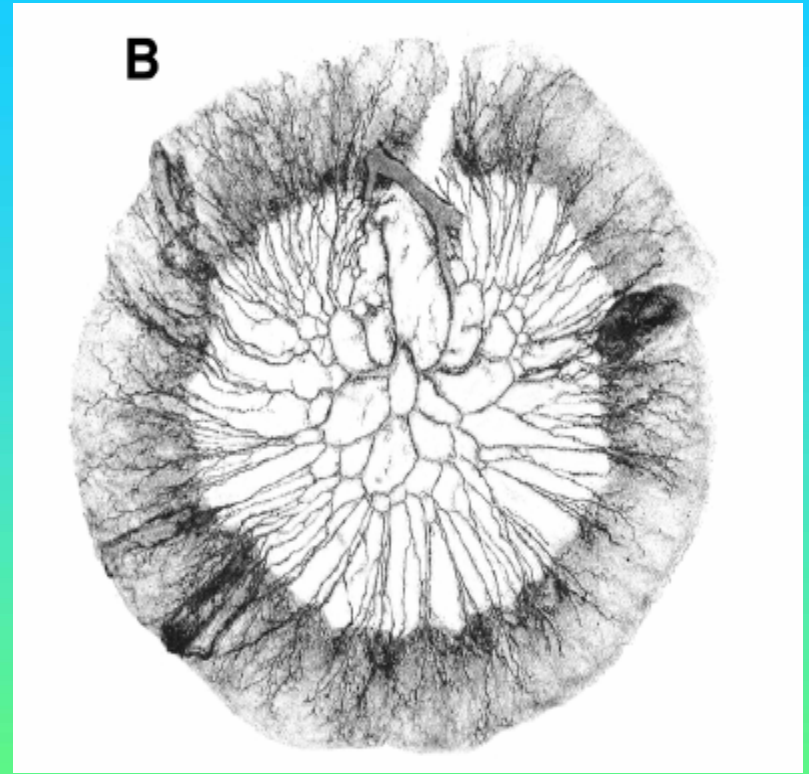
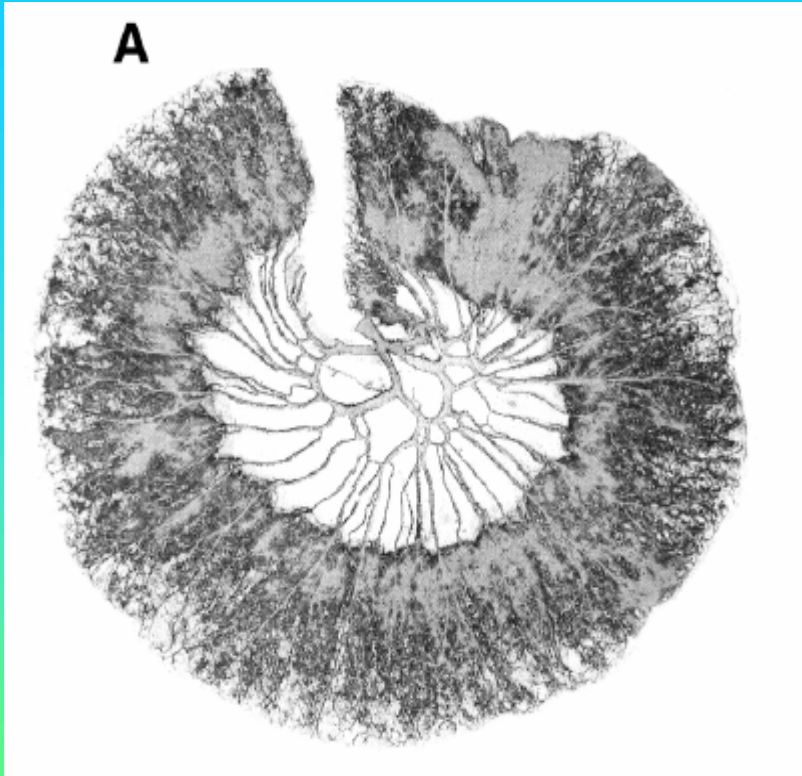
Morphology of Gut & Assigning Correct Blood Flow



Blood Flows:
 Mucosal ?? ml/min
 Submucosal ?? ml/min
 etc



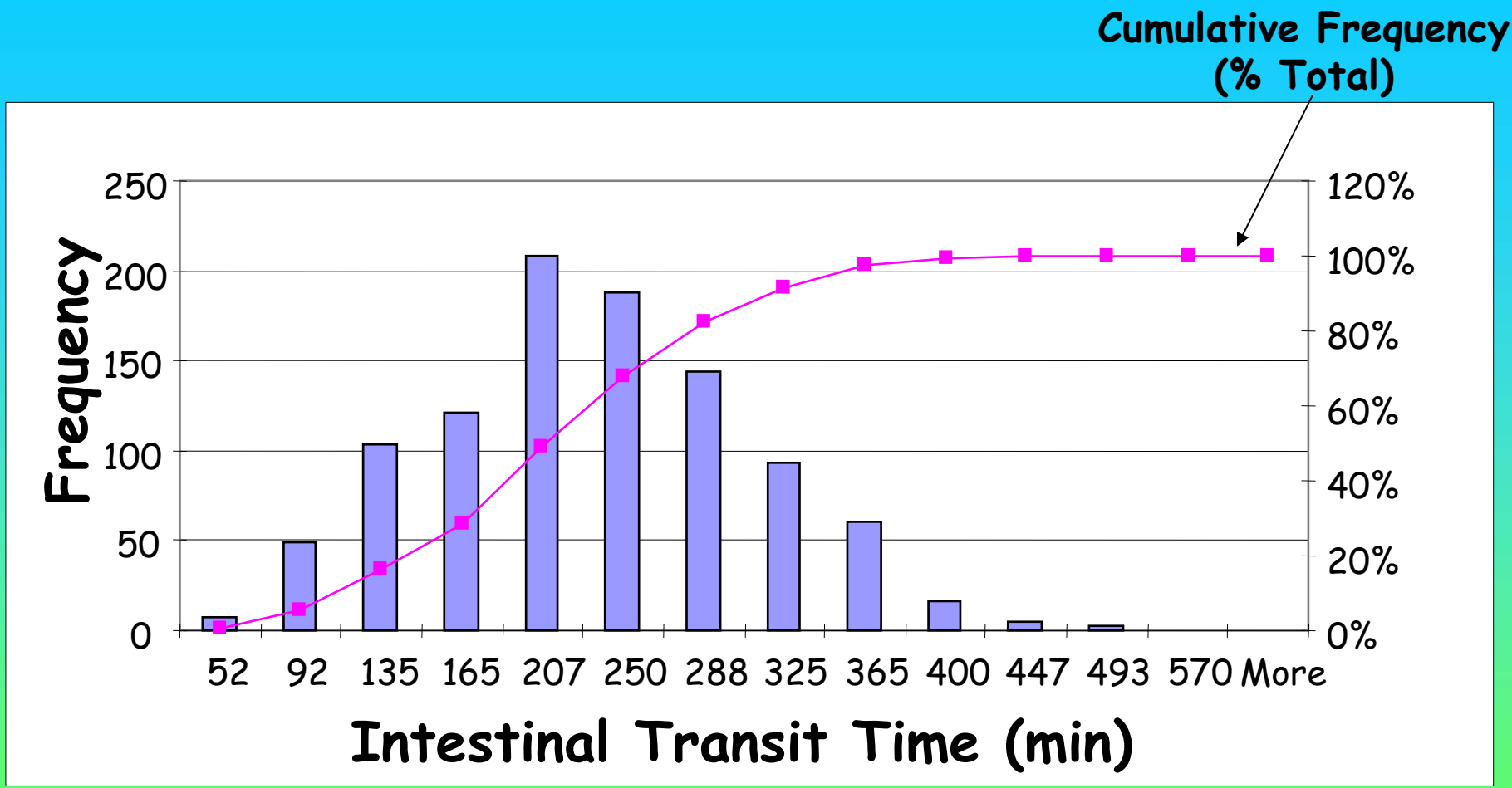
Blood Supply in the Human Small Intestine



Blood supply (vascularity) in the human jejunum (A) and ileum (B)

(DeSesso *et al*, 2001)

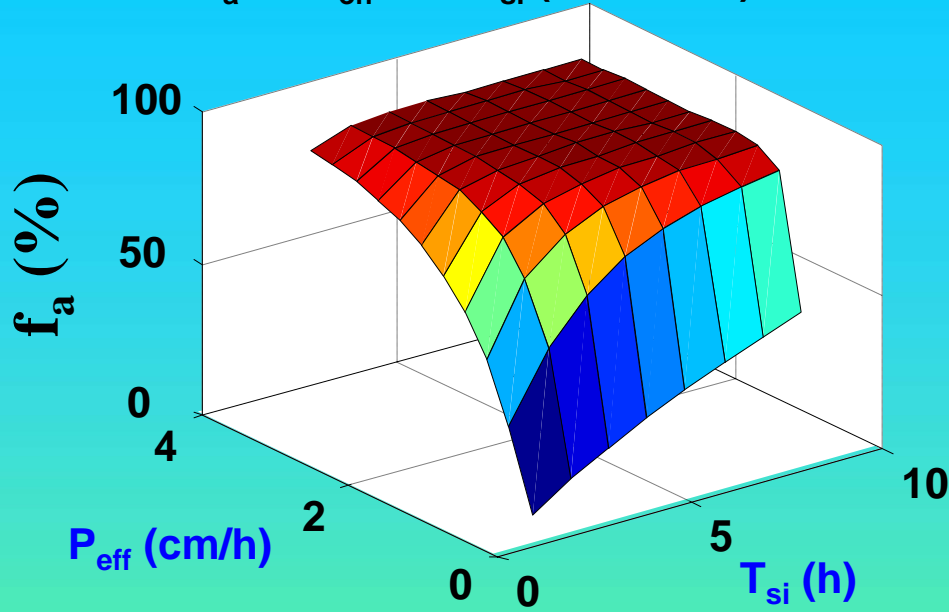
Small Intestinal Transit Time



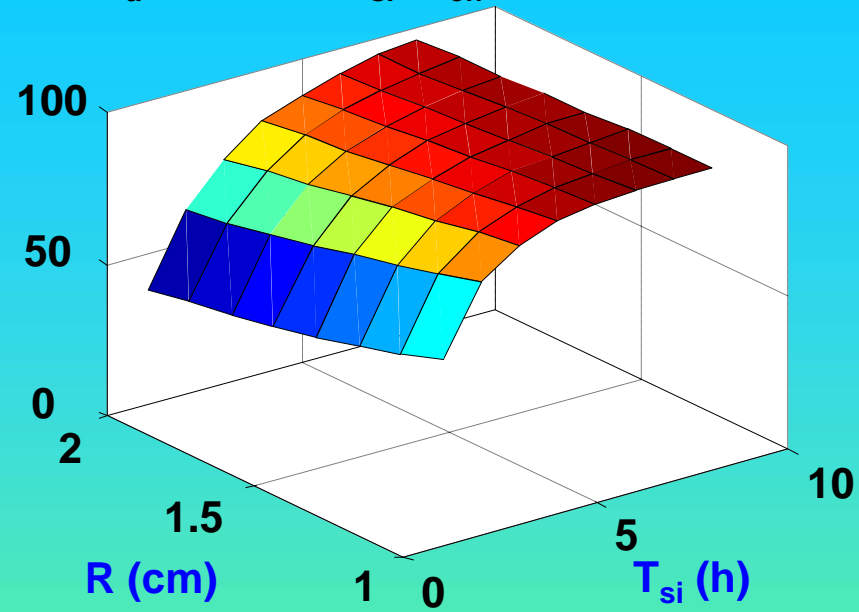
Yu et al. (1998)

Inter-individual Variability & fa

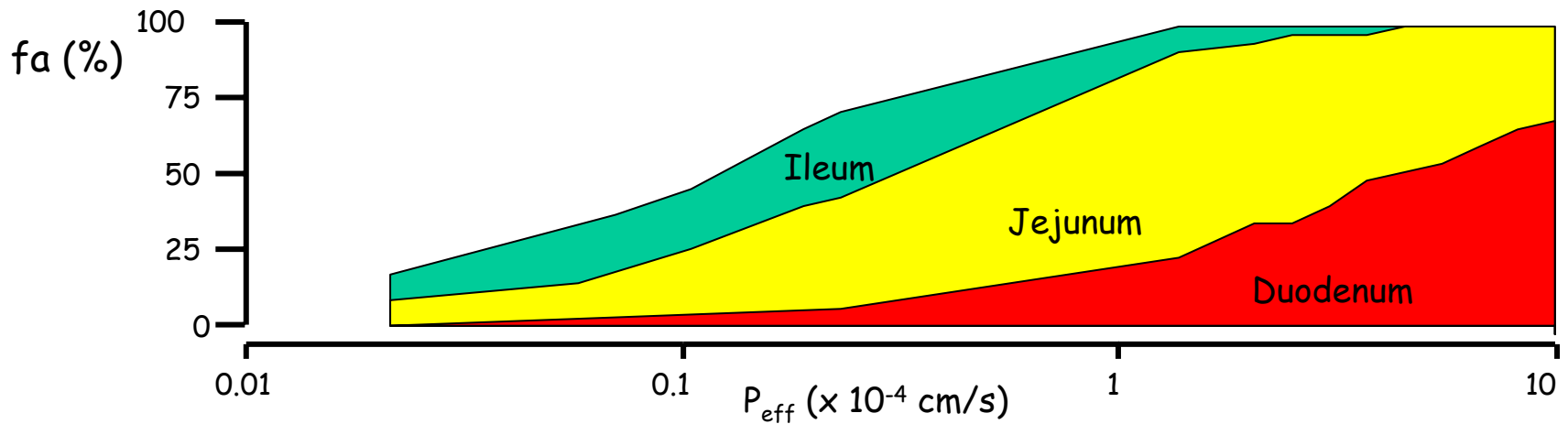
f_a vs P_{eff} and T_{si} ($R=1.7$ cm)



f_a vs R and T_{si} ($P_{eff}=0.5$ cm/h)



M Jamei *et al*, LogP 2004, Switzerland



Variability in Metabolism

Genetics & Ethnicity

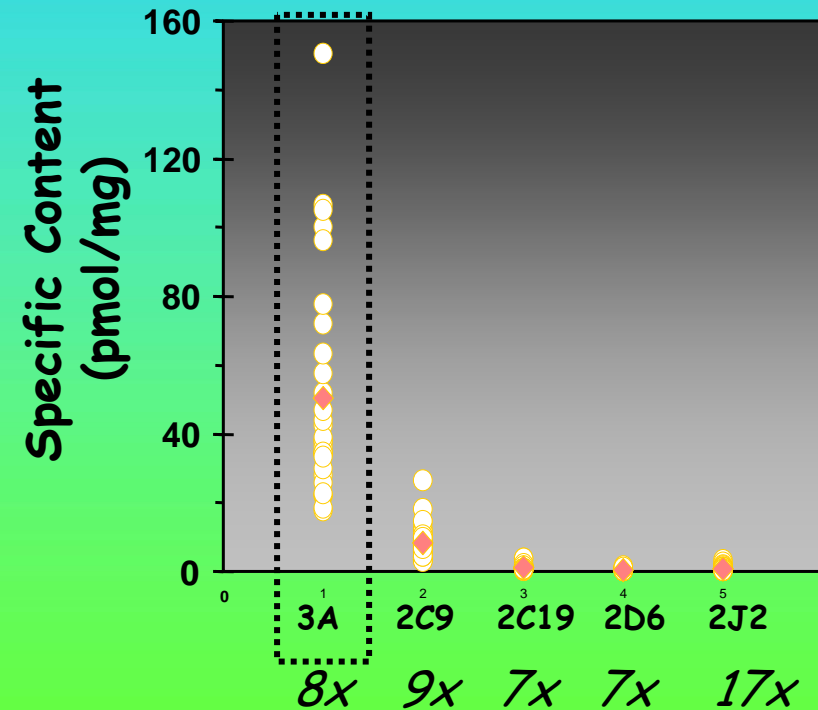
(3A5*1 vs 3A5*3 population frequency in Black vs Caucasians)

Environment & Food

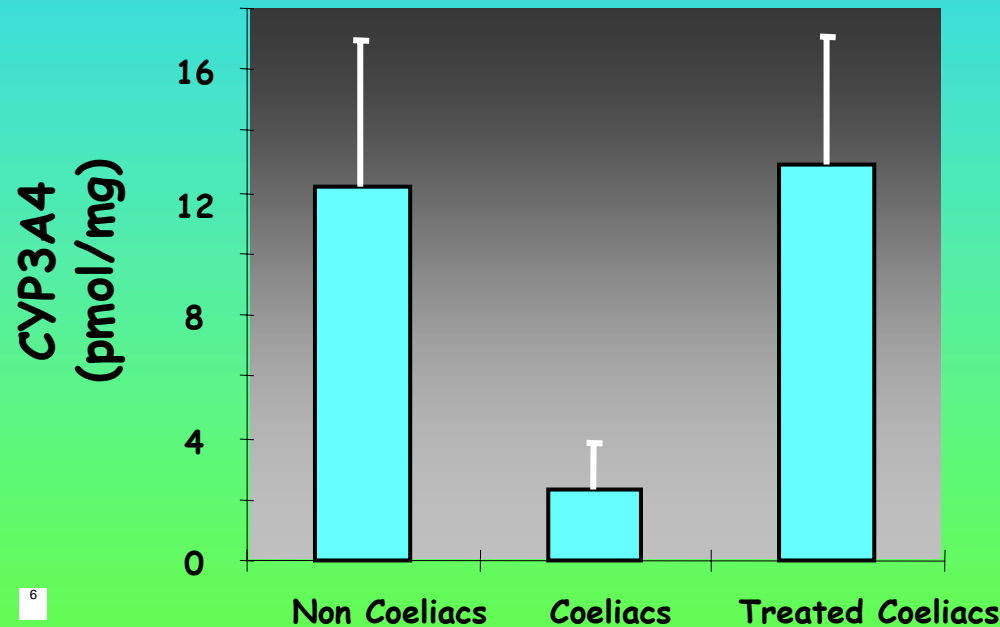
(Grapefruit juice, cruciferous vegetables, St. John's wort ...)

Disease and Concomitant Drug Intake

(Coeliac, ketoconazole, rifampicine, ...)



Paine et al. (2006) DMD 34:880-6



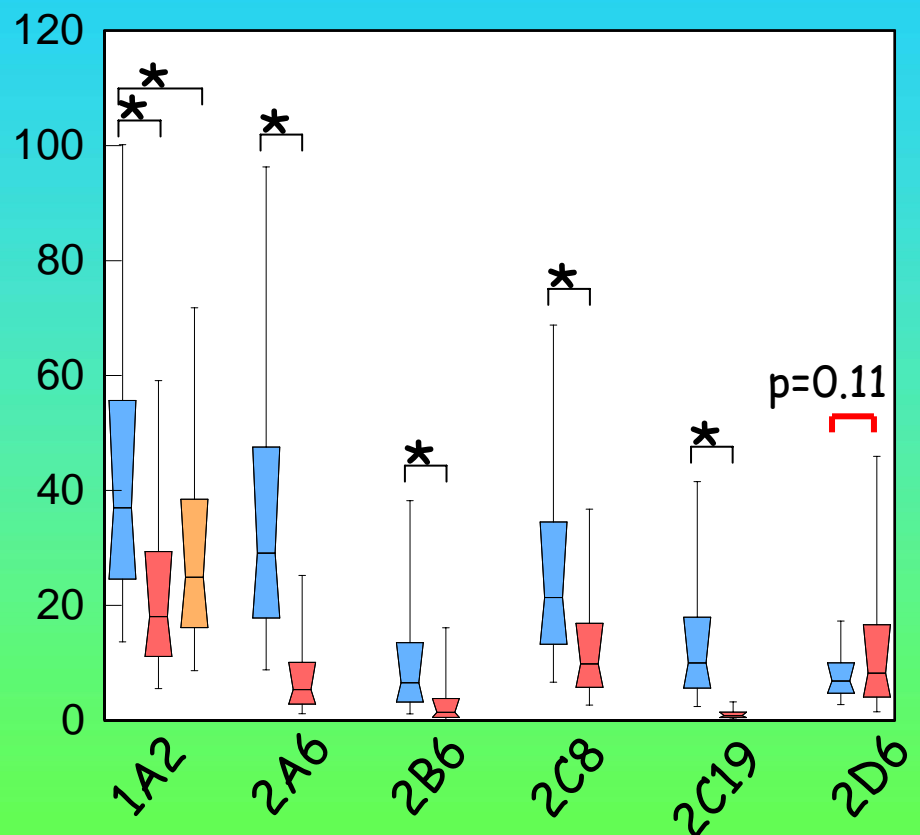
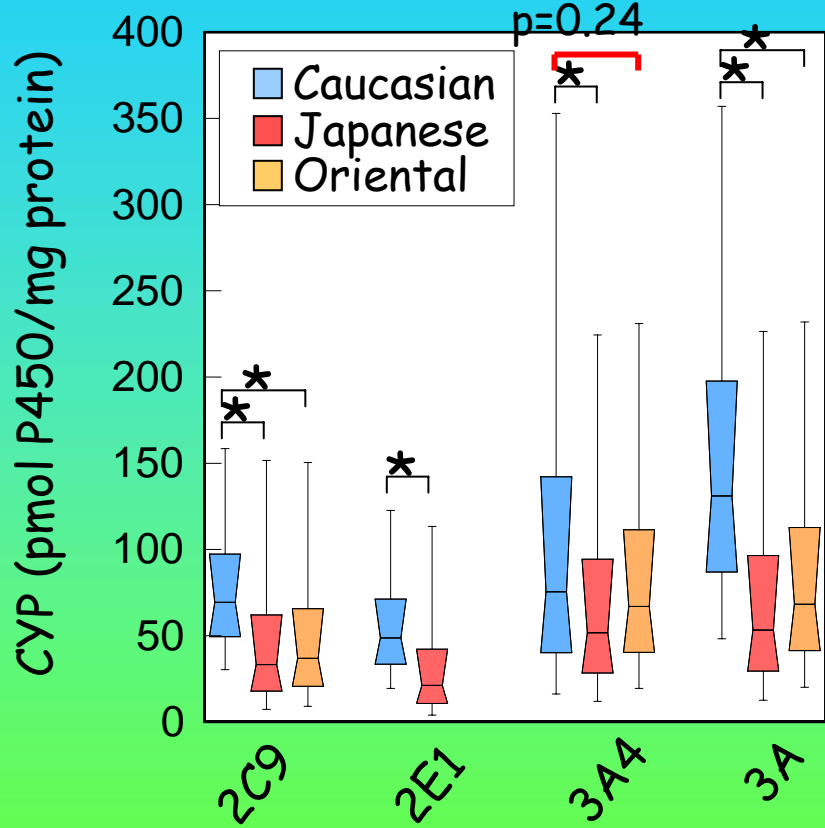
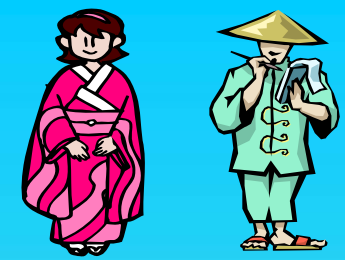
Johnson et al. (2001) BJCP 51: 451-60

Ethnic Differences in Abundance and Frequency

Americans/Europeans

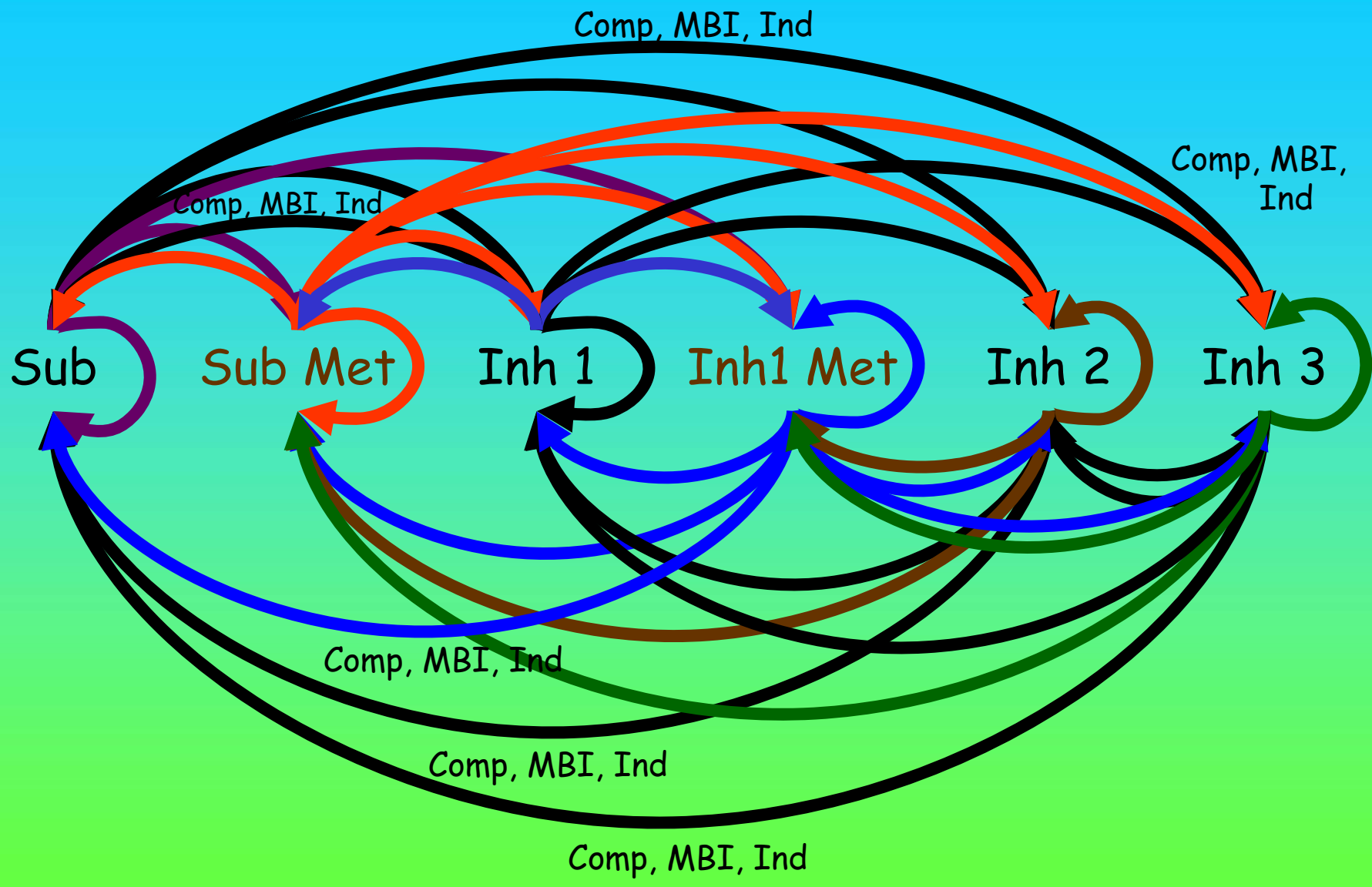


Japanese/Chinese



Numbers of livers: Caucasian: 42-241, Japanese: 31-132
 Oriental (JP+Chinese) Only 1A2, 2C9, 3A4, 3A: 108-174

Interactions between Concomitantly Used Compounds



Inhibitors acting on the same enzymes

DEX + Quinidine (CYP2D6)

$$R_{ss}=2.4$$

DEX + Terbinafine (CYP2D6)

$$R_{ss}=2.0$$

DEX + Quinidine + Terbinafine

$$R_{ss}=2.4$$

Inhibitors acting on different enzymes

DEX + Quinidine (CYP2D6)

$$R_{ss}=2.4$$

DEX + Sulfaphenazole (CYP2C9 + CYP2C19)

$$R_{ss}=1.3$$

DEX + Quinidine + Sulfaphenazole

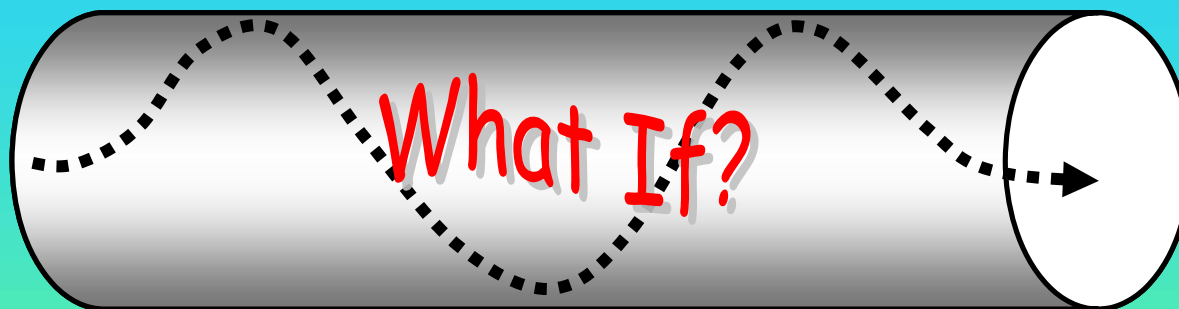
$$R_{ss}=4.9$$

Useful Simulations vs Accurate Predictions

Accumulation of Information on Compound (as Substrate)

fm <i>via</i> each route in average subject	→	Population distribution of fm
Estimates of microsomal/plasma binding	→	Actual f_u and $f_{u_{mic}}$
Estimates of gut absorption (e.g. Caco-2)	→	f_a from Phase I
Estimate of CL_R	→	CL_R from mass balance
Estimate of $CL_{u_{int}}$	→	K_m and V_{max}

Simulation



Prediction

Assumptions for Inputs

Confidence in Outputs

Single concn simulations	→	Full concn profile
Possible effects on transporters	→	Characterised effects on transporters
Likely mechanism of inhibition	→	Confirmed mechanism of inhibition
Estimate of inhibitory potency (IC_{50})	→	K_i

Accumulation of Information on Compound (as Inhibitor)

“...there are known knowns; there are things we know we know ...

... We also know there are known unknowns; that is to say we know there are some things we do not know..

... But there are also unknown unknowns - the ones we don't know we don't know.”



From Known Knowns

to Known Unknowns

& to Unknown Unknowns!

New Safe Medicines Faster

Science Team

(Univ Sheffield & Simcyp Ltd)

Involved in the Presented Research:

Masoud Jamei
Jiansong Yang
David Turner
Zoe Barter
Lisa Almond
Gemma Dickinson

Visiting Scientists

Liu Xiadong
Saeed Rezaee
Mahmut Özdemir

Shin-Ichi Inoue
Ali Sabzghabae
Hege Christensen

Geoff Tucker (Chairman)
Amin Rostami-H (D R&D)
Karen Rowland-Yeo
Trevor Johnson
Masoud Jamei
Jiansong Yang
David Turner
Mark Baker
Kim Crewe
Lisa Almond
Helen Perrett
Sebastian Polak
Gemma Dickinson
Fatemah Ghanbari
Sibylle Neuhoff
Helen Musther
Zoe Barter
Linh Van
Amir Heydari

EUFEPS 2004, NSMF