

DOSE-EFFECT RELATIONSHIP

The intensity and duration of a drug's effects are a function of the drug dose and drug concentration at the effect site

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Monitoring Dose-Effect

- **Level**
 - **Molecular (e.g, enzyme inhibition)**
 - **Cellular (*in vitro* tissue culture, blood cells)**
 - **Tissue or organ (*in vitro* or *in vivo*)**
 - **Organism**
- **Endpoint used to measure effect may be different at each level**
- **Overall effect = sum of multiple drug effects and physiological response to drug effects**

Dose-Effect Endpoints

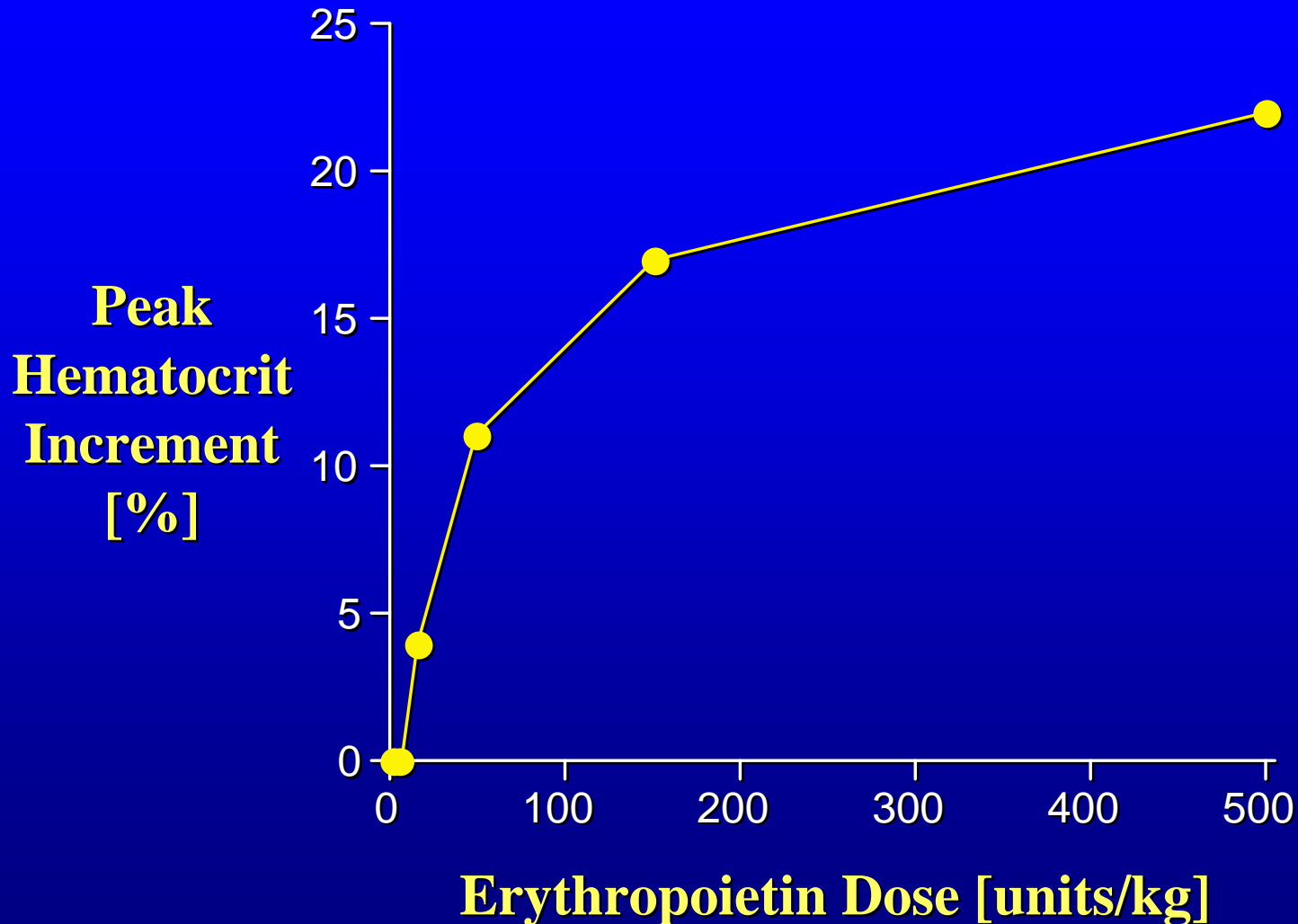
Graded

- Continuous scale (\uparrow dose \rightarrow \uparrow effect)
- Measured in a single biologic unit
- Relates dose to intensity of effect

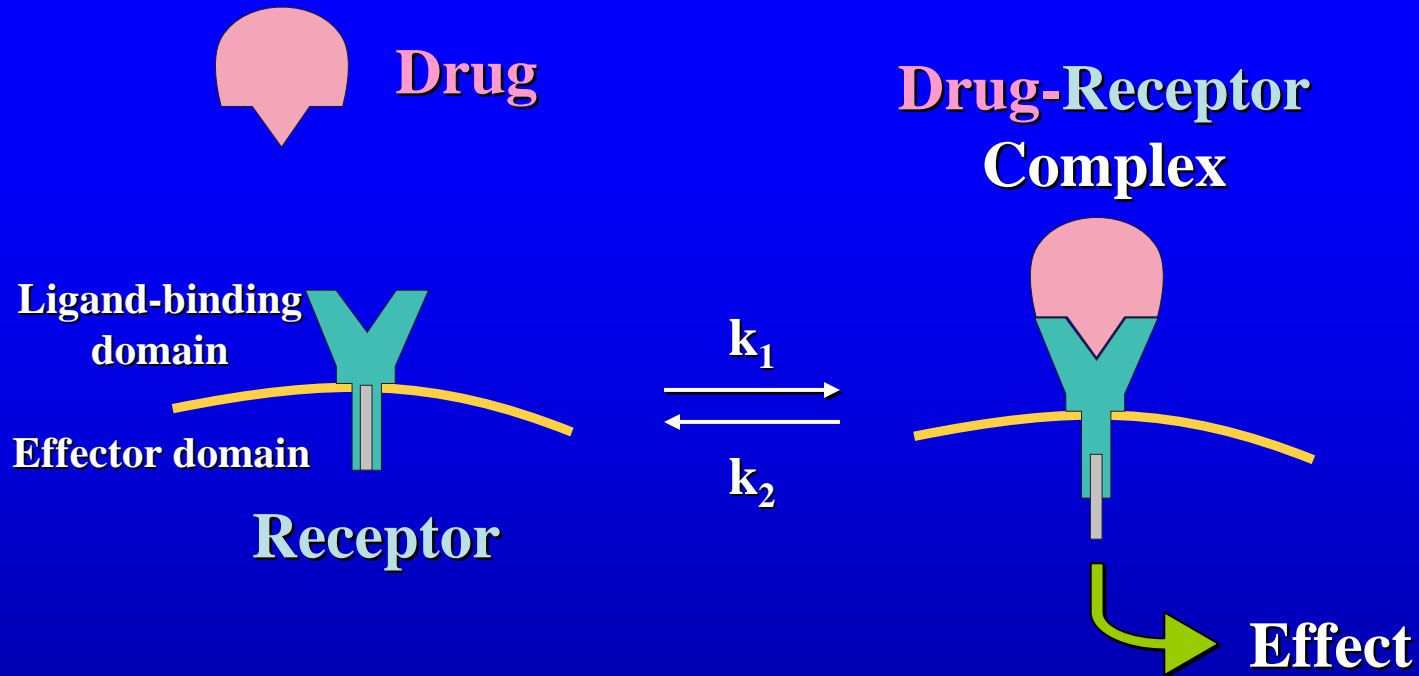
Quantal

- All-or-none pharmacologic effect
- Population studies
- Relates dose to frequency of effect

Erythropoietin and Anemia



Drug-Receptor Interactions



$$\text{Effect} = \frac{\text{Maximal effect} \cdot [\text{Drug}]}{K_D + [\text{Drug}]}$$

$$(K_D = k_2/k_1)$$

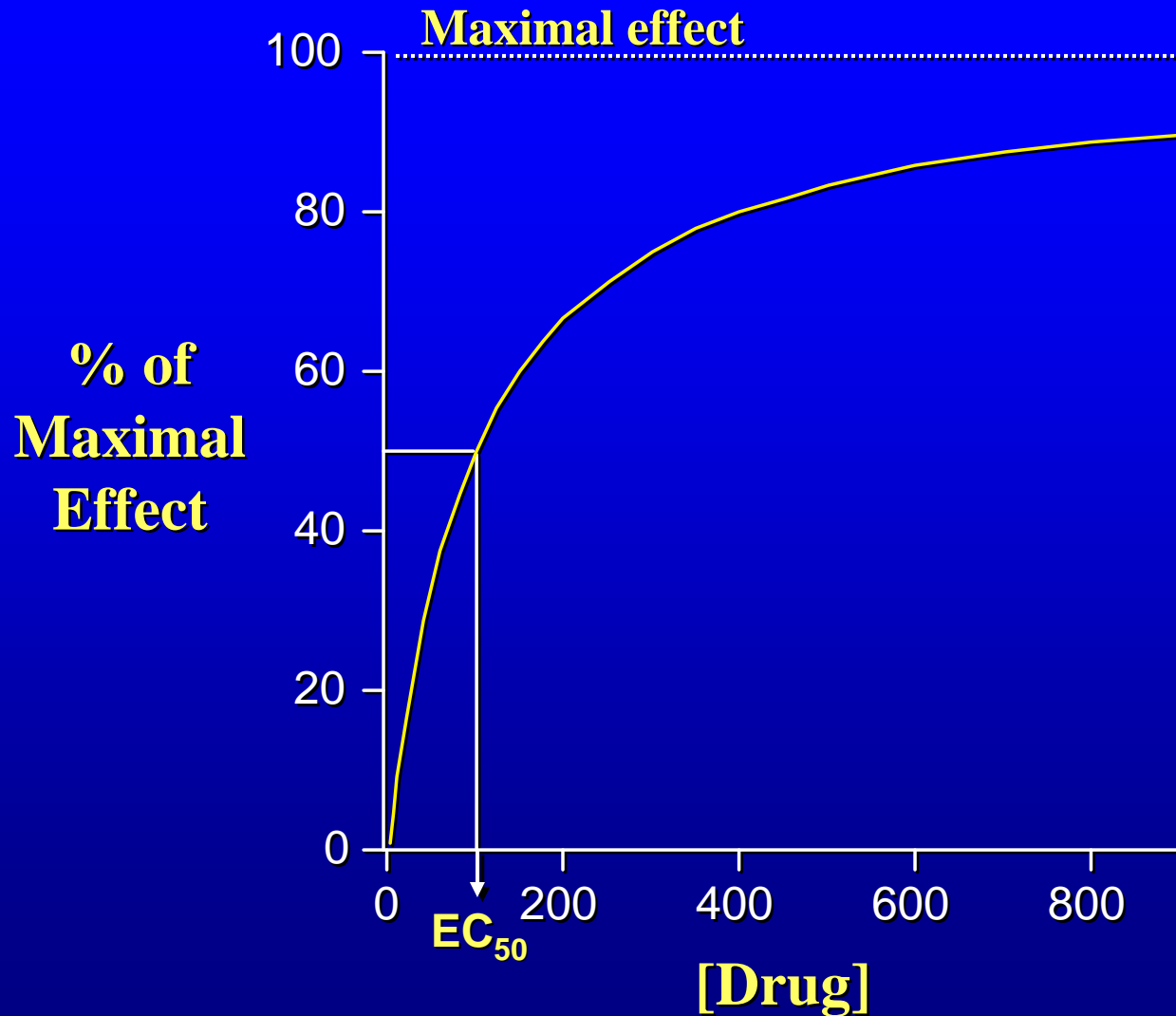
Dose-Effect Relationship

$$\text{Effect} = \frac{\text{Maximal effect} \cdot [\text{Drug}]}{K_D + [\text{Drug}]}$$

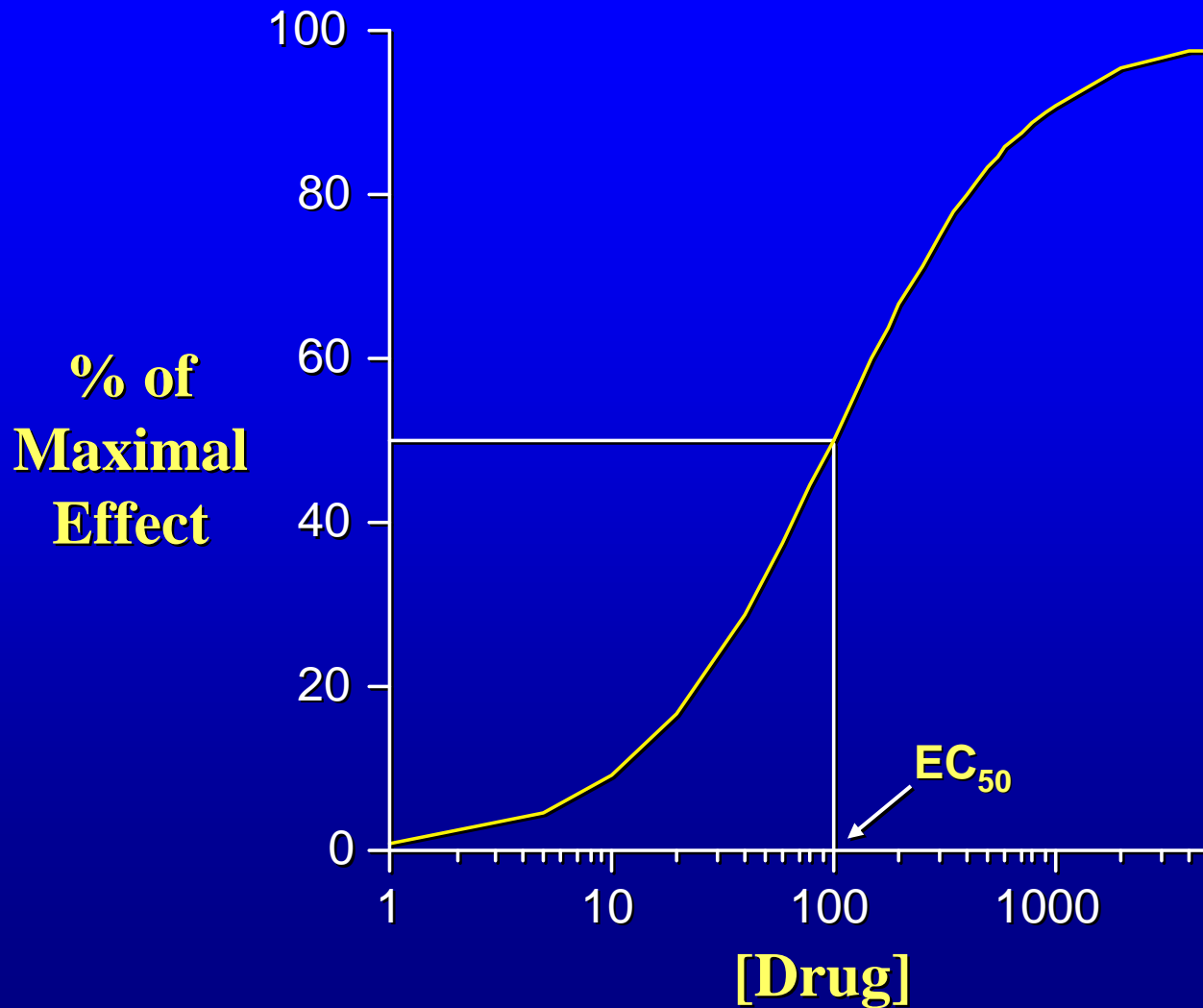
$$\text{Effect} = \text{Maximal effect} \frac{[\text{Drug}]}{K_D + [\text{Drug}]}$$

$$\text{Effect} = \text{Maximal effect} \quad \text{if } [\text{Drug}] \gg K_D$$

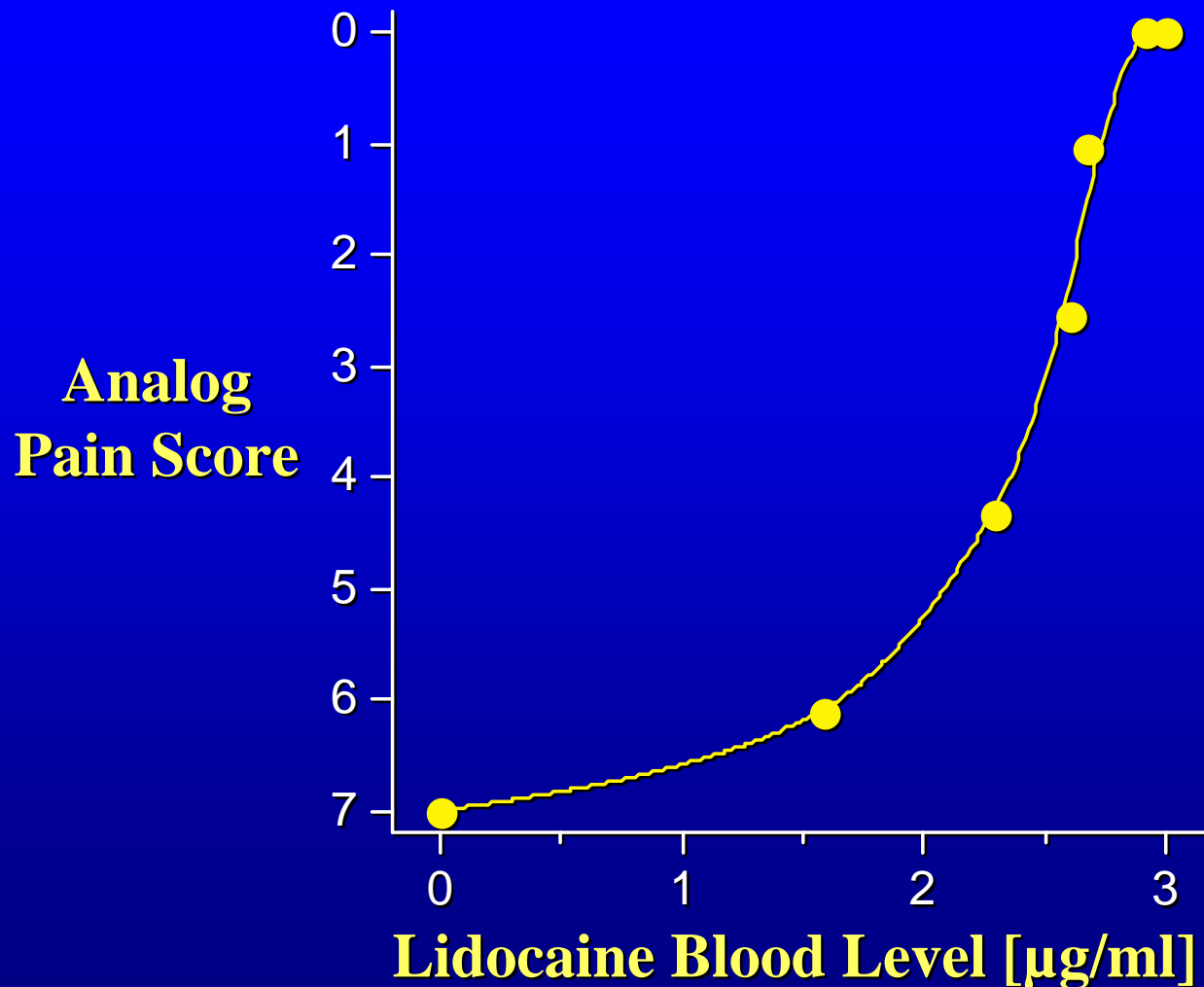
Graded Dose-Effect Curve



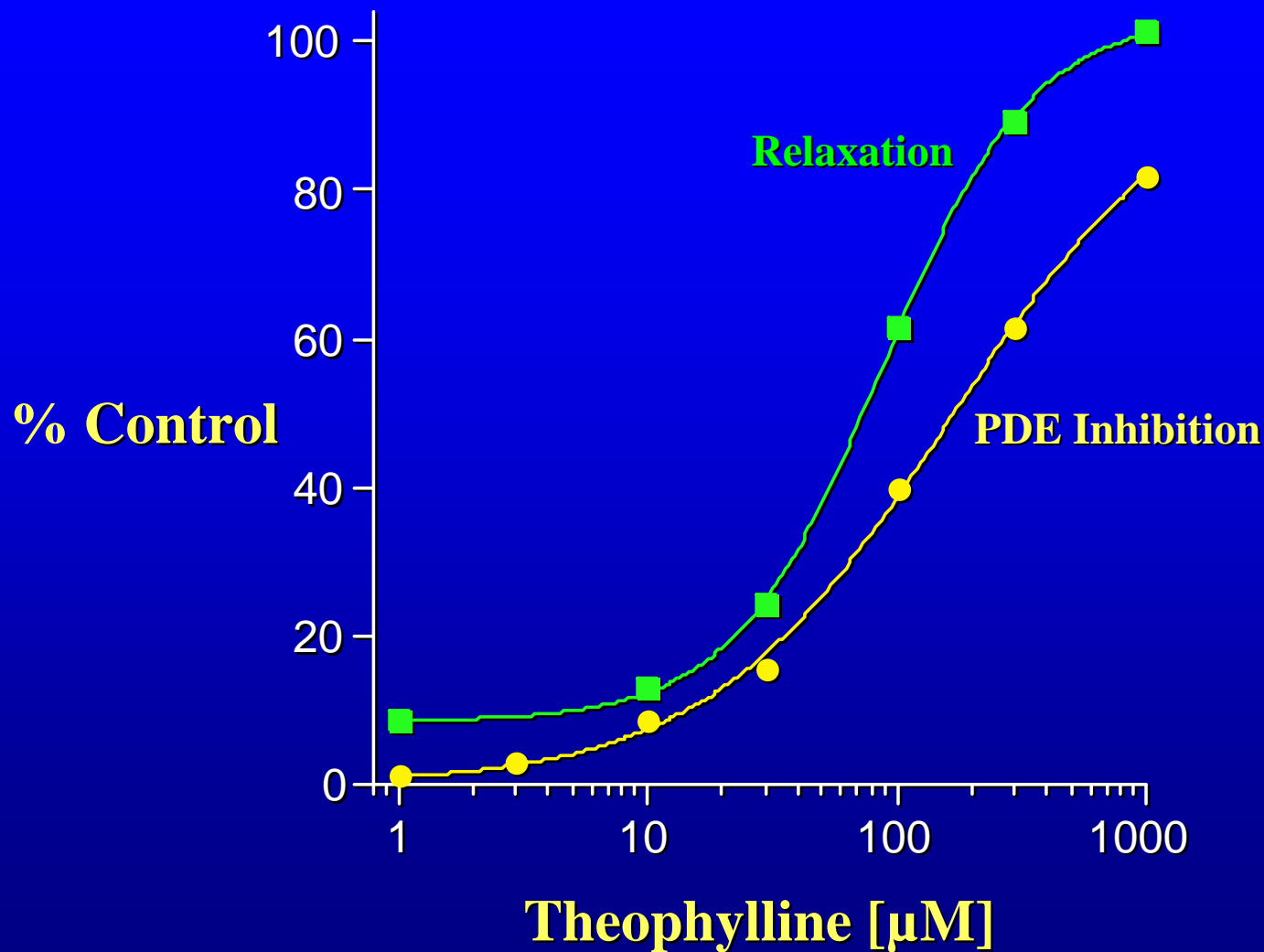
Log Dose-Effect Curve



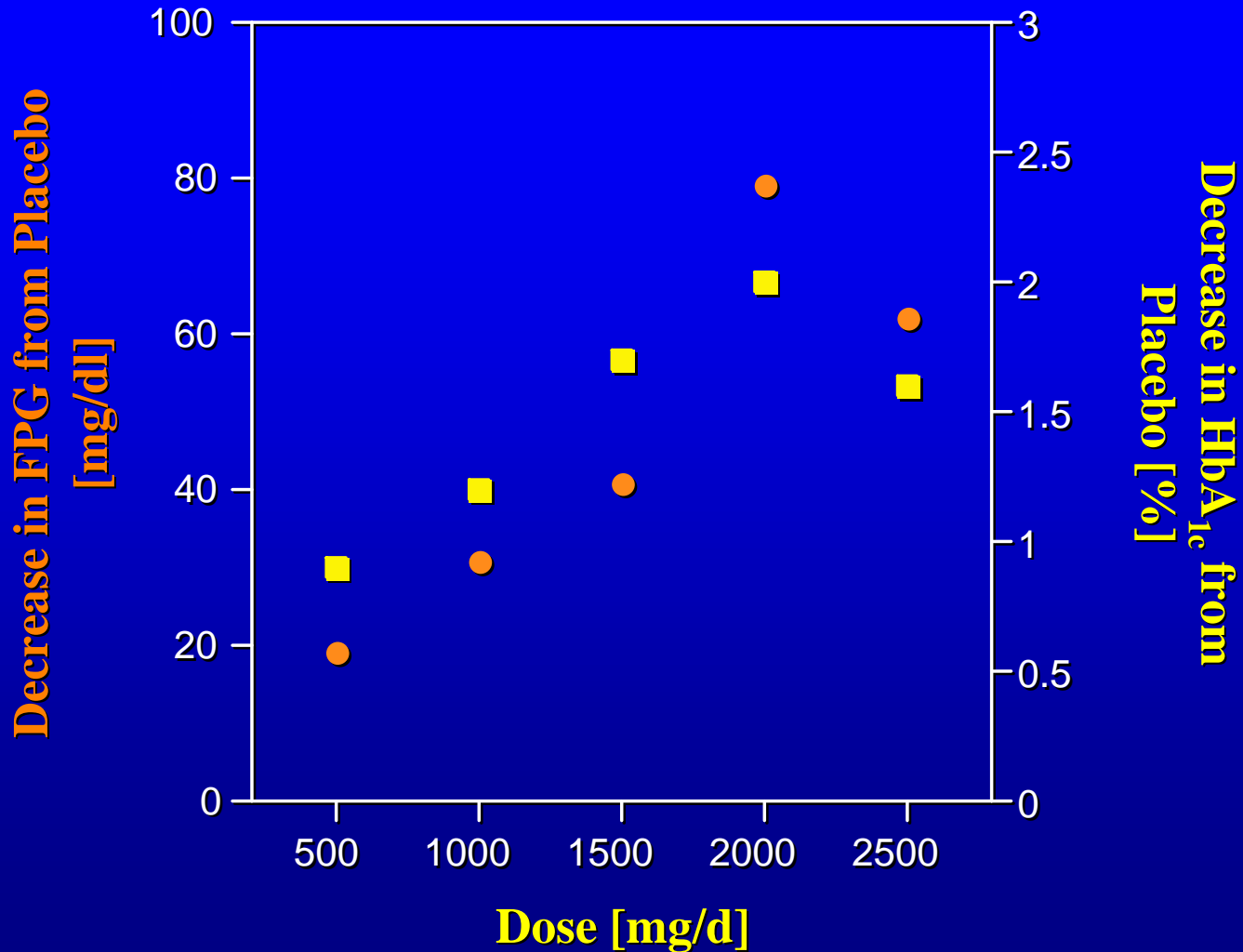
Lidocaine Graded Dose-Effect



Theophylline Dose-Effect



Metformin Dose-Response

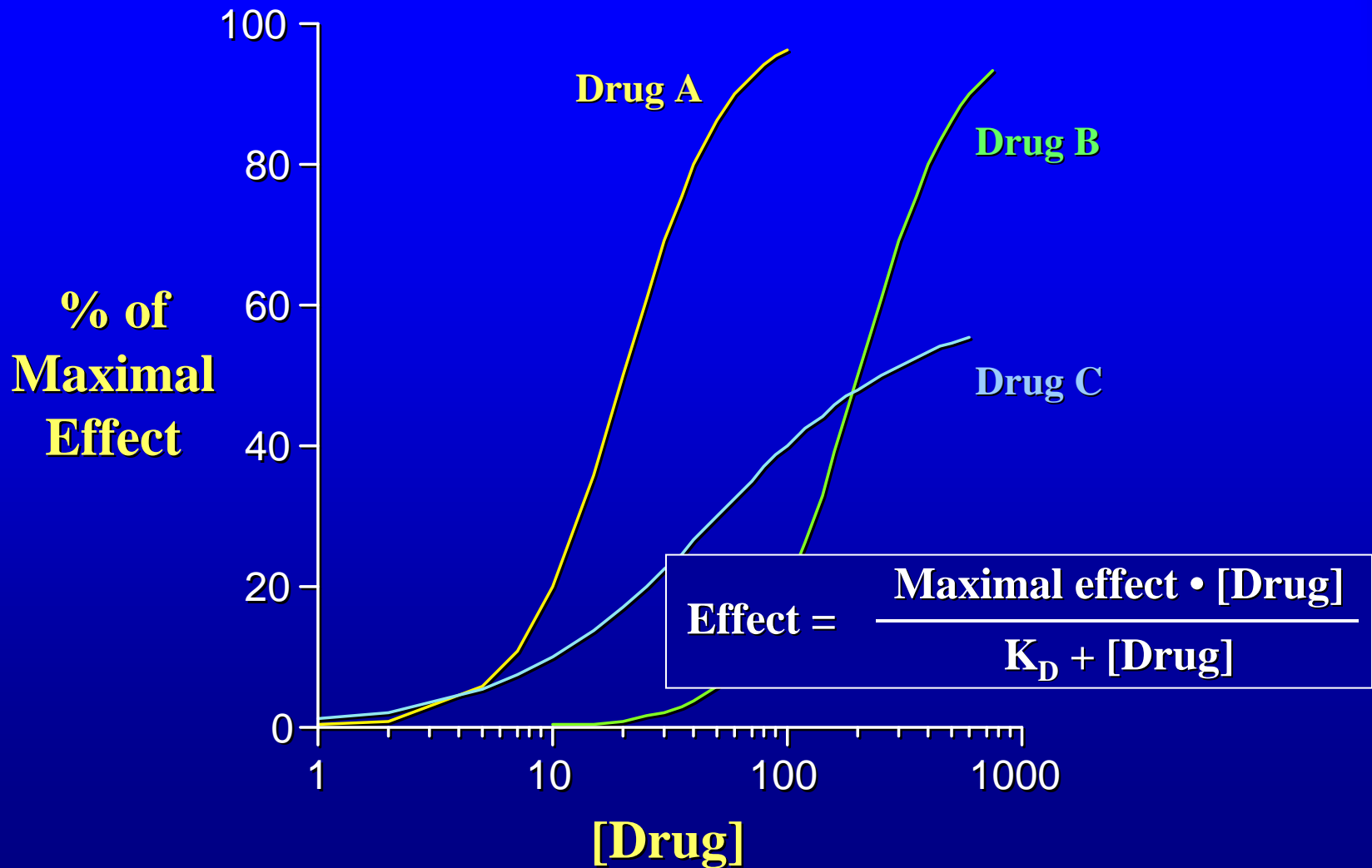


Dose-Effect Parameters

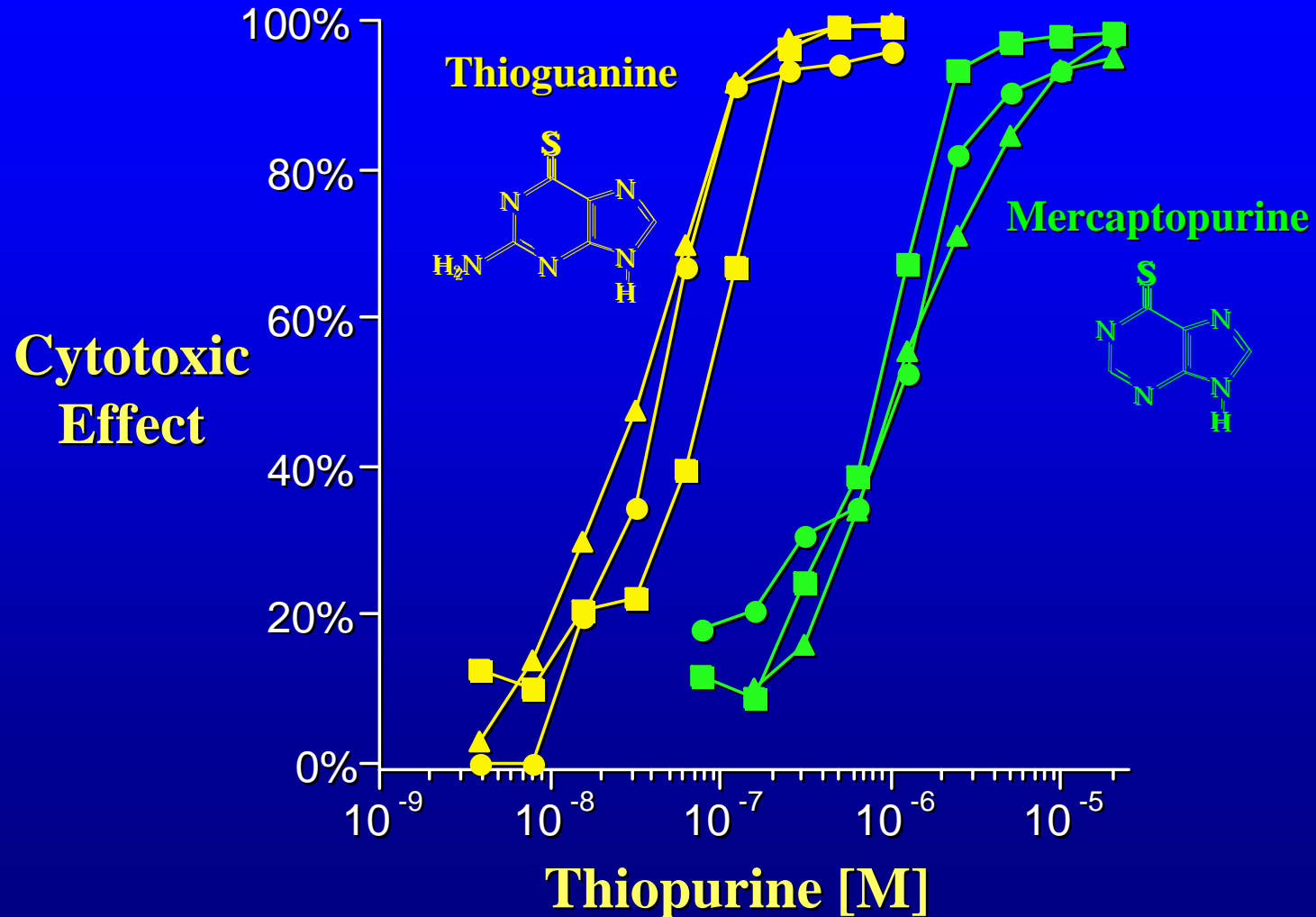
POTENCY: The sensitivity of an organ or tissue to the drug

EFFICACY: The maximum effect

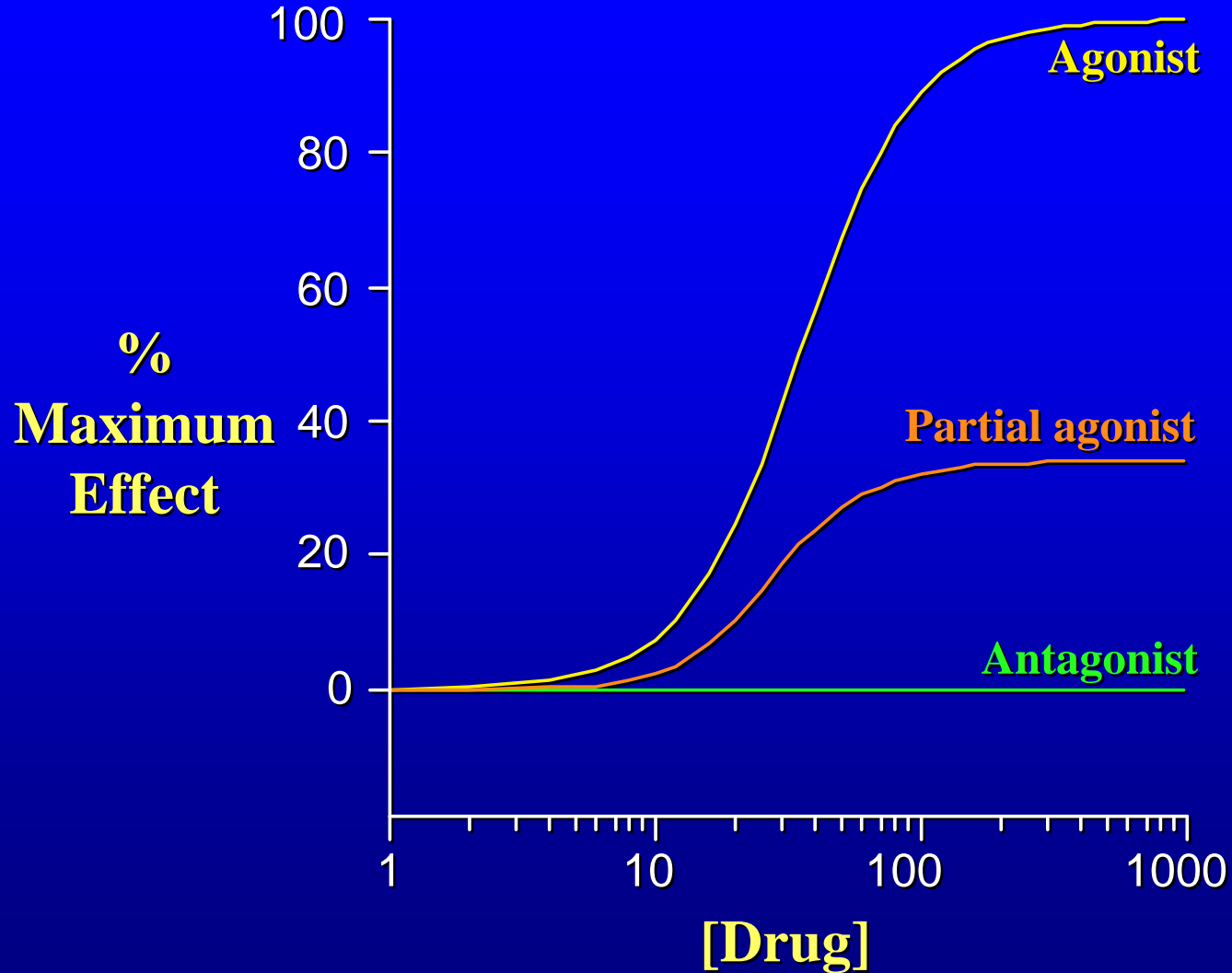
Comparing Dose-Effect Curves



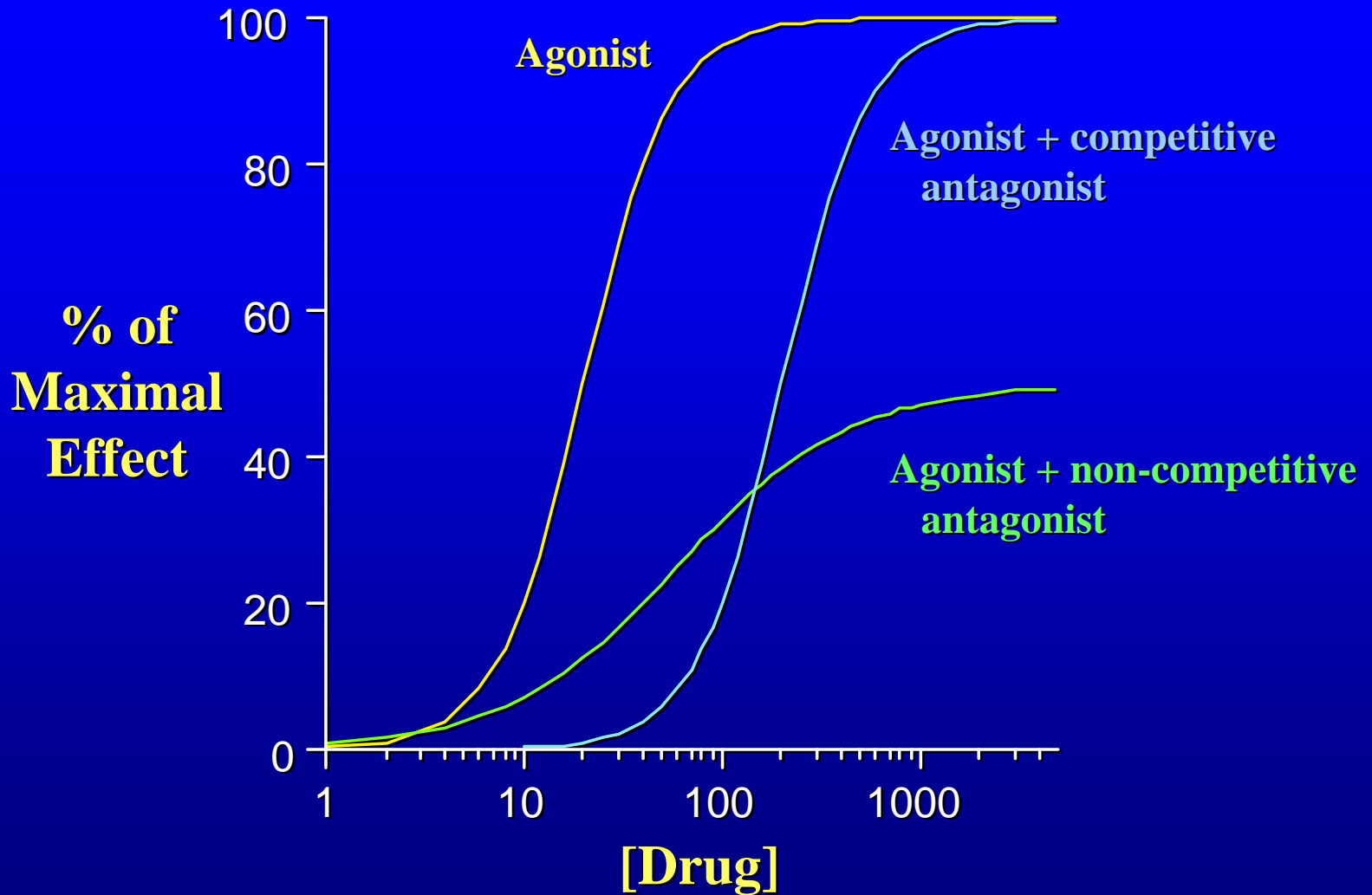
Thiopurine Cytotoxicity



Receptor-Mediated Effects



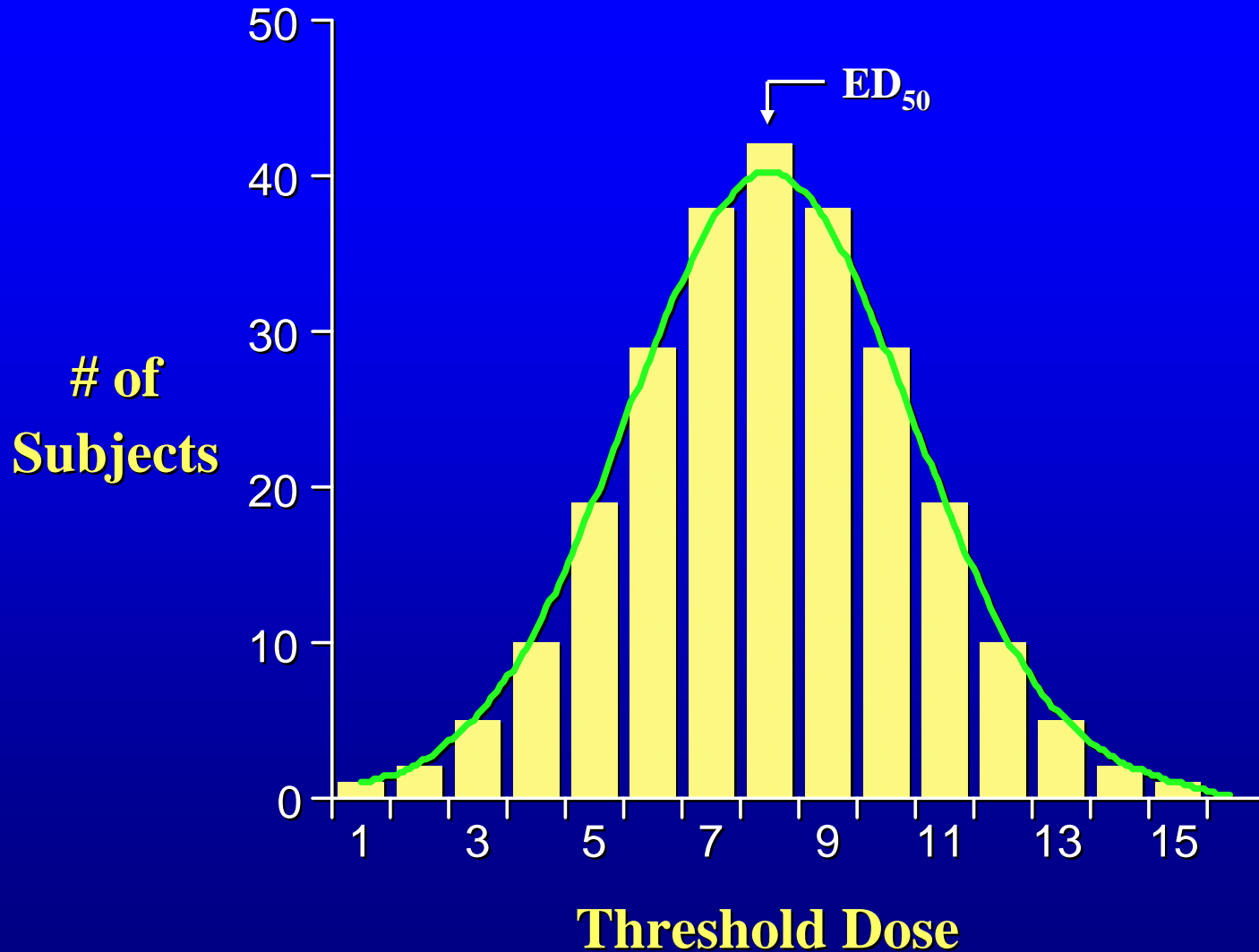
Drug Interactions



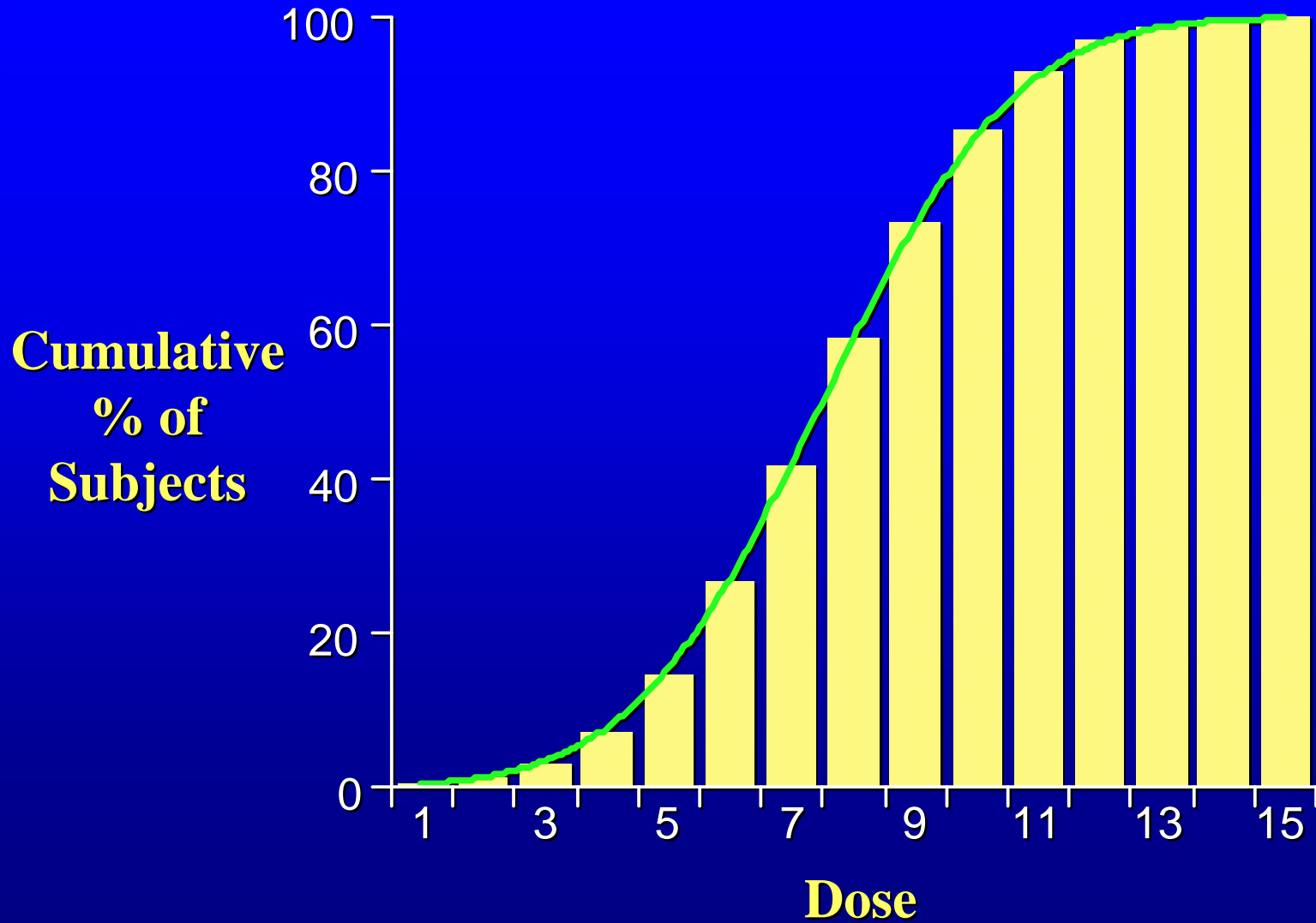
Graded Dose-Effect Analysis

- **Identify the therapeutic dose/concentration**
- **Define site of drug action (receptor)**
- **Classify effect produced by drug-receptor interaction (agonist, antagonist)**
- **Compare the relative potency and efficacy of drugs that produce the same effect**
- **Assess mechanism of drug interactions**

Quantal Dose-Effect Distribution



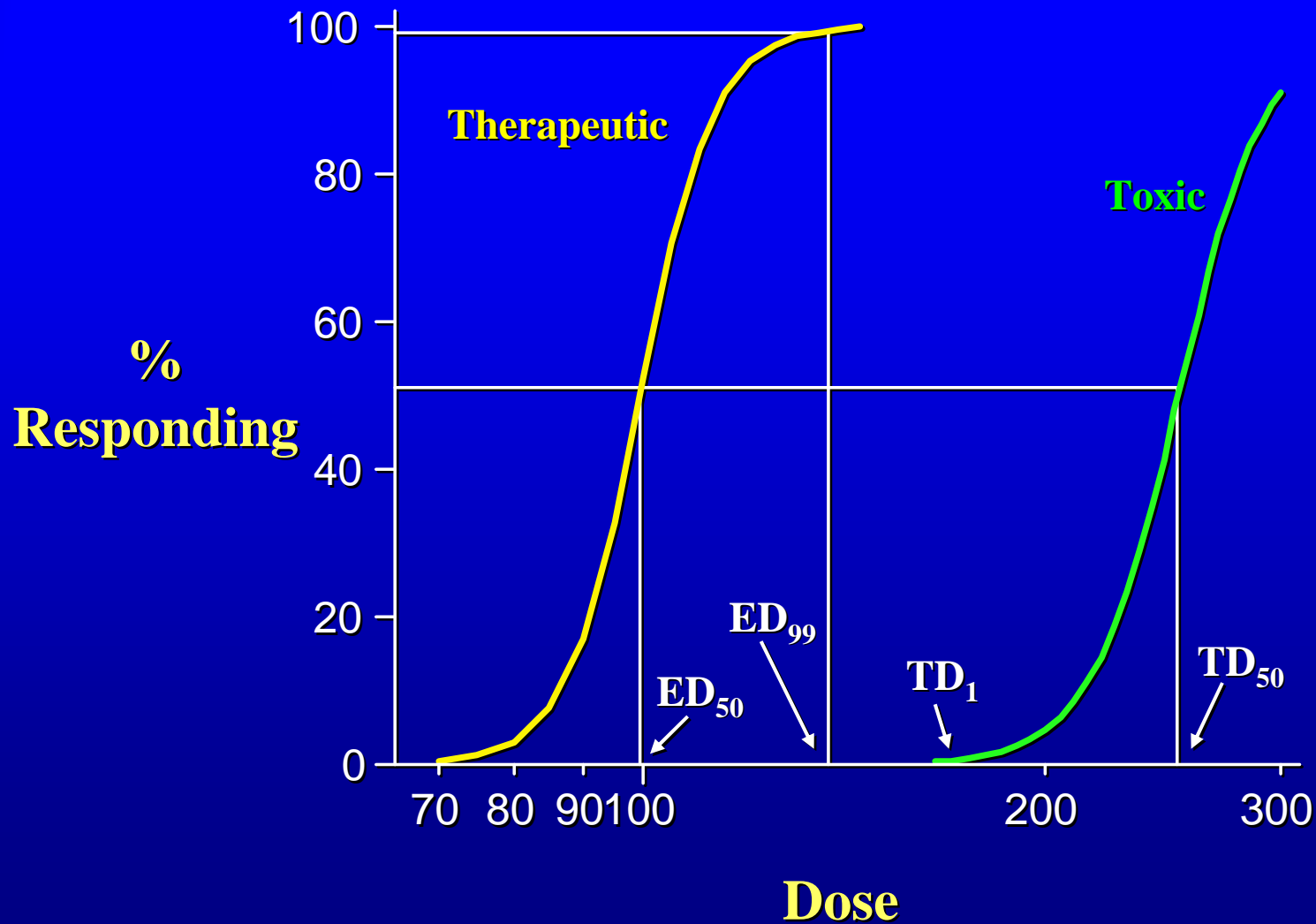
Cumulative Dose-Effect Curve



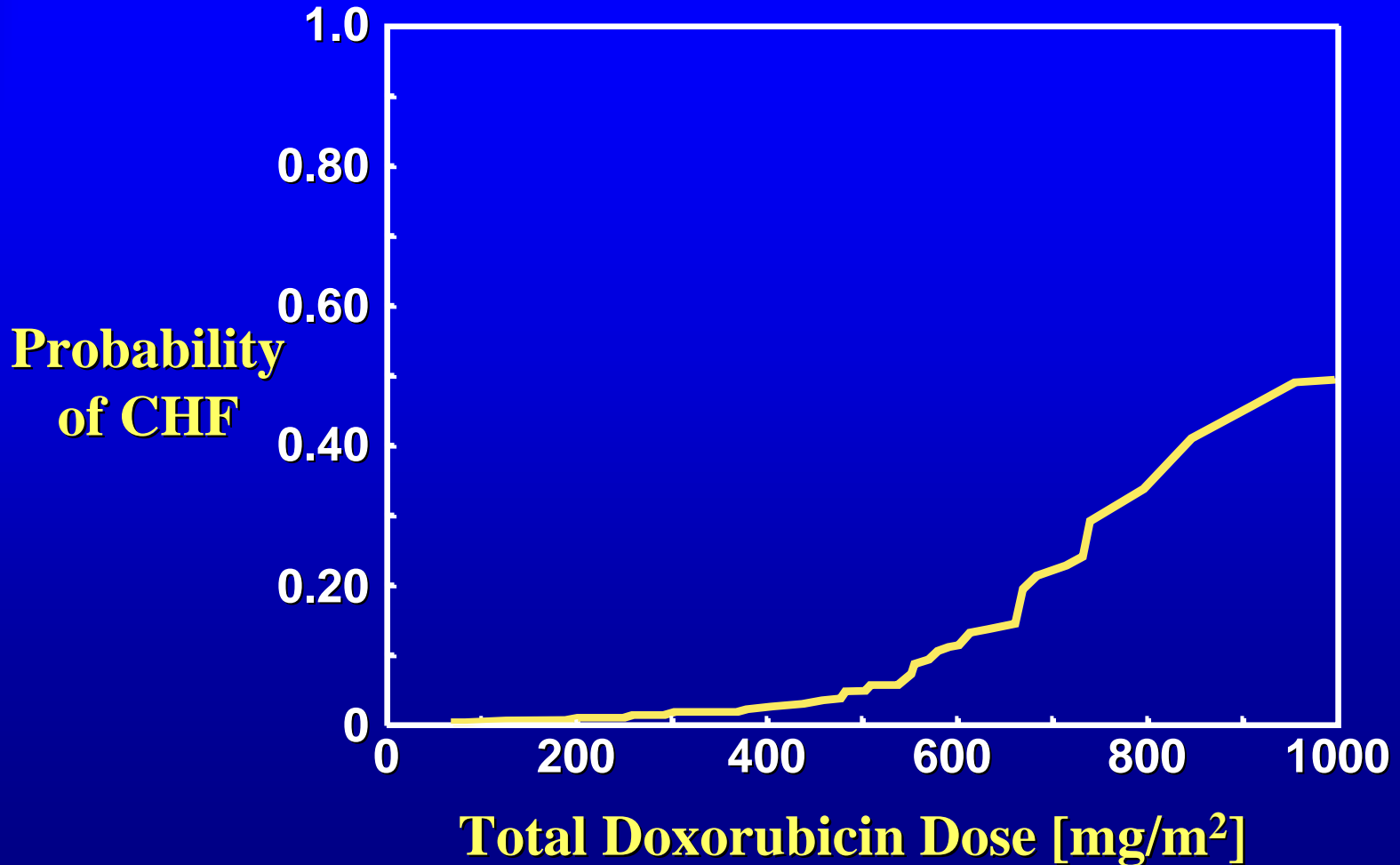
Cumulative Dose-Effect Study

Dose Level	No. of Subjects	No. Responding	% Response
1	10	0	0
2	10	1	10
3	10	3	30
4	10	5	50
5	10	7	70
6	10	8	80
7	10	9	90
8	10	10	100

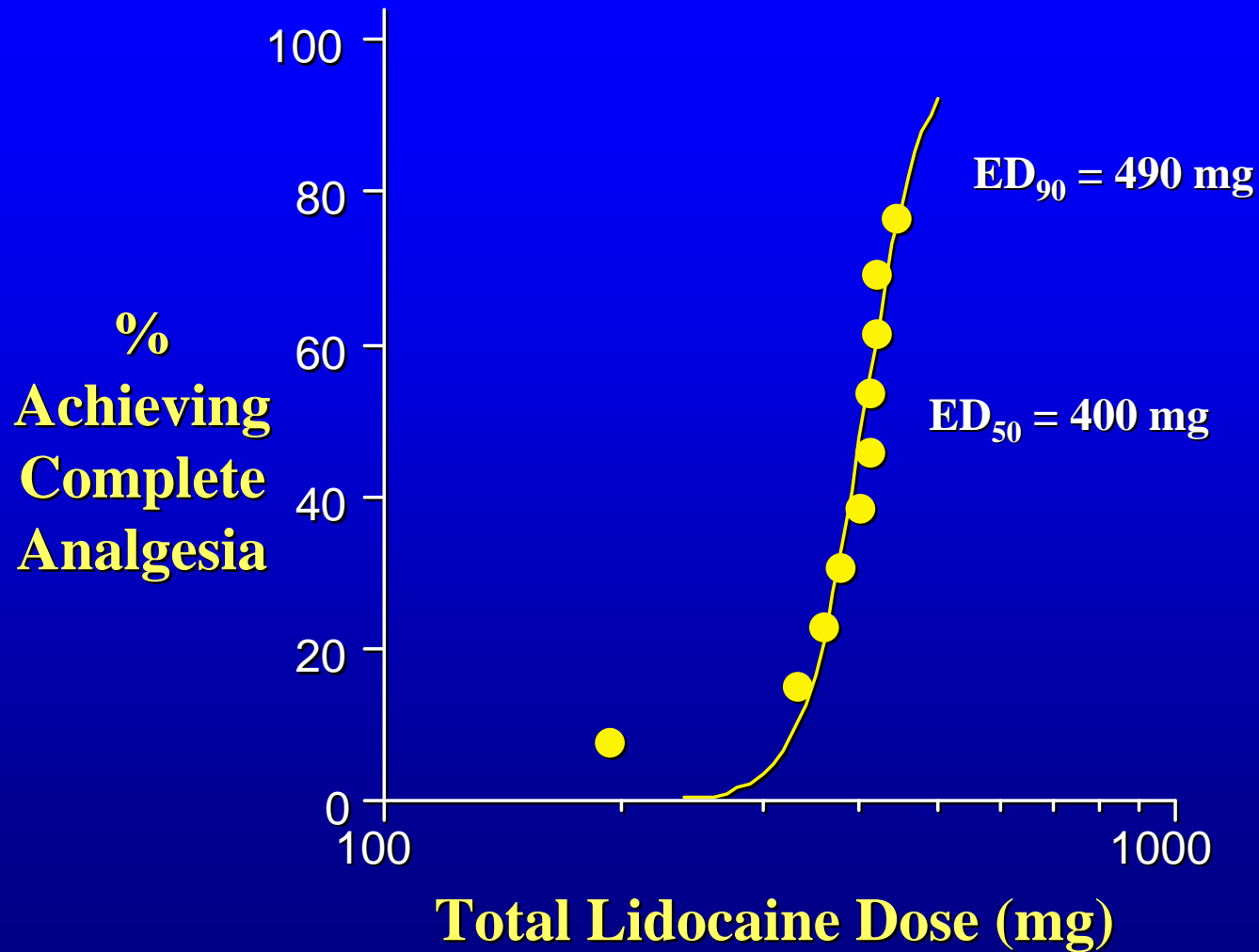
Therapeutic and Toxic Effects



Doxorubicin Cardiotoxicity



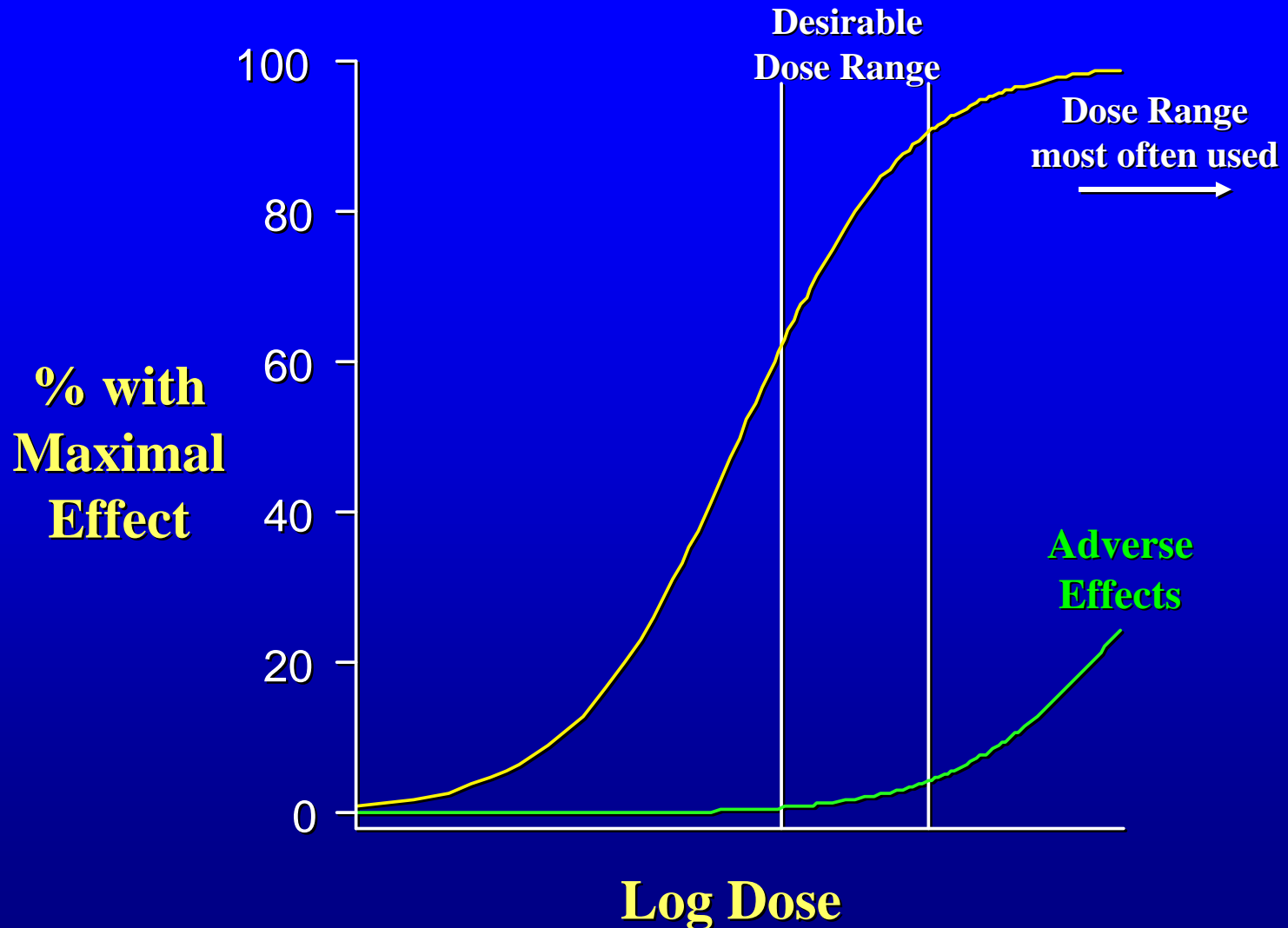
Lidocaine Quantal Dose-Effect



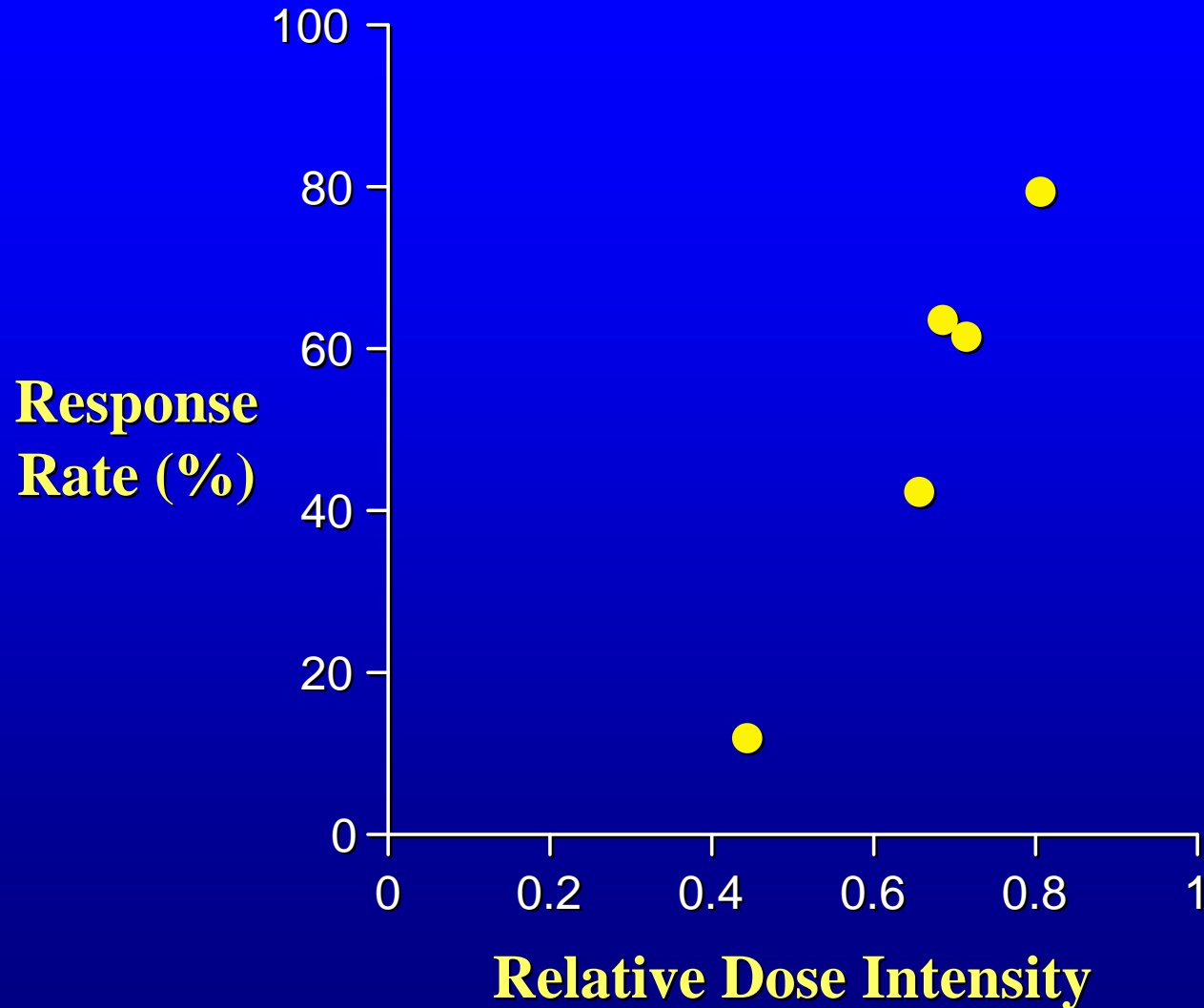
Antihypertensive Dose-Effect

Drug	Dose Range [mg]		Lowest Effective Dose [mg]
	Early Studies	Present Dose	
Propranolol	160-5000	160-320	80
Atenolol	100-2000	50-100	25
Hydrochlorothiazide	50-400	25-50	12.5
Captopril	75-1000	50-150	37.5
Methyldopa	500-6000	500-3000	750

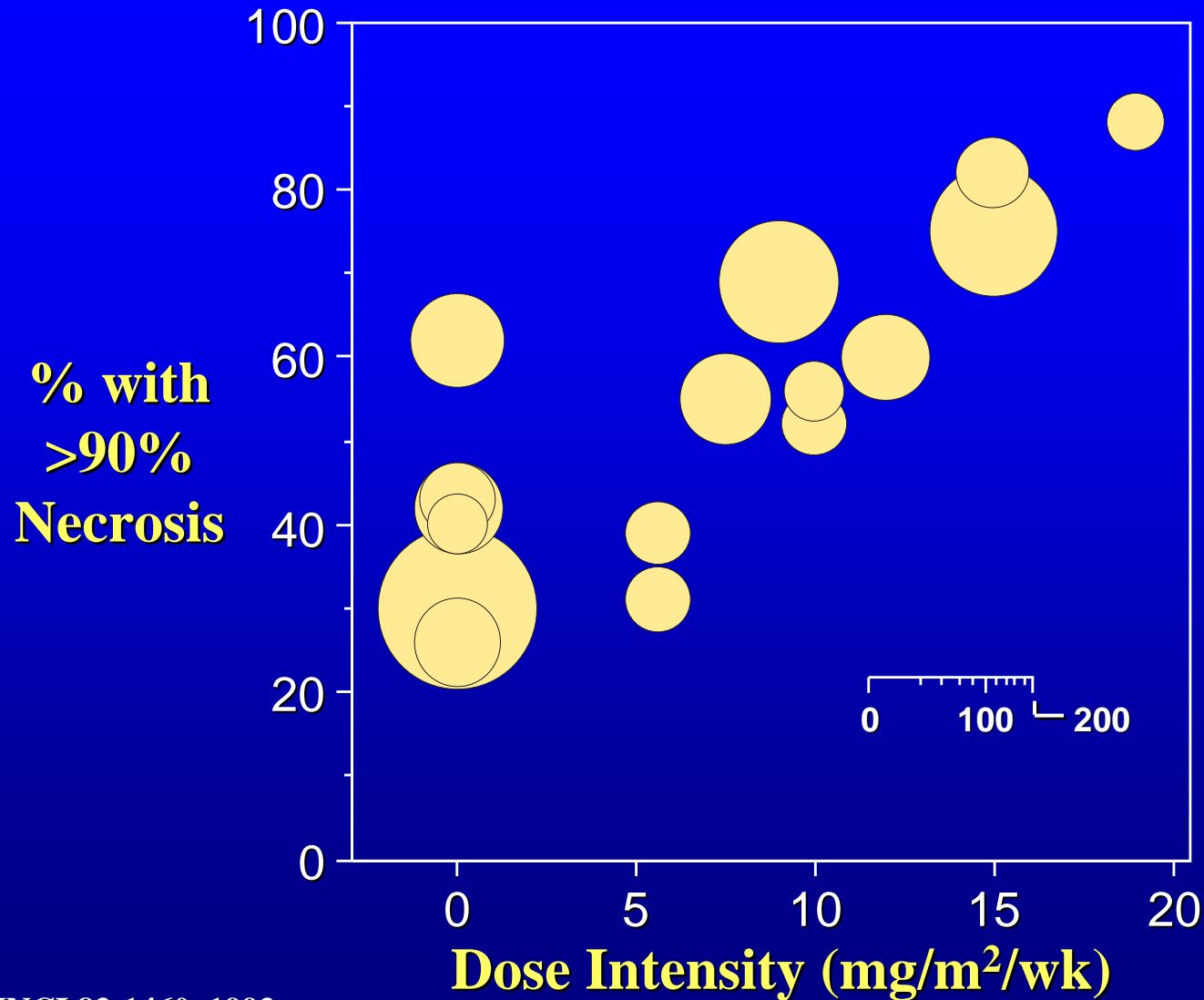
Antihypertensive Drugs



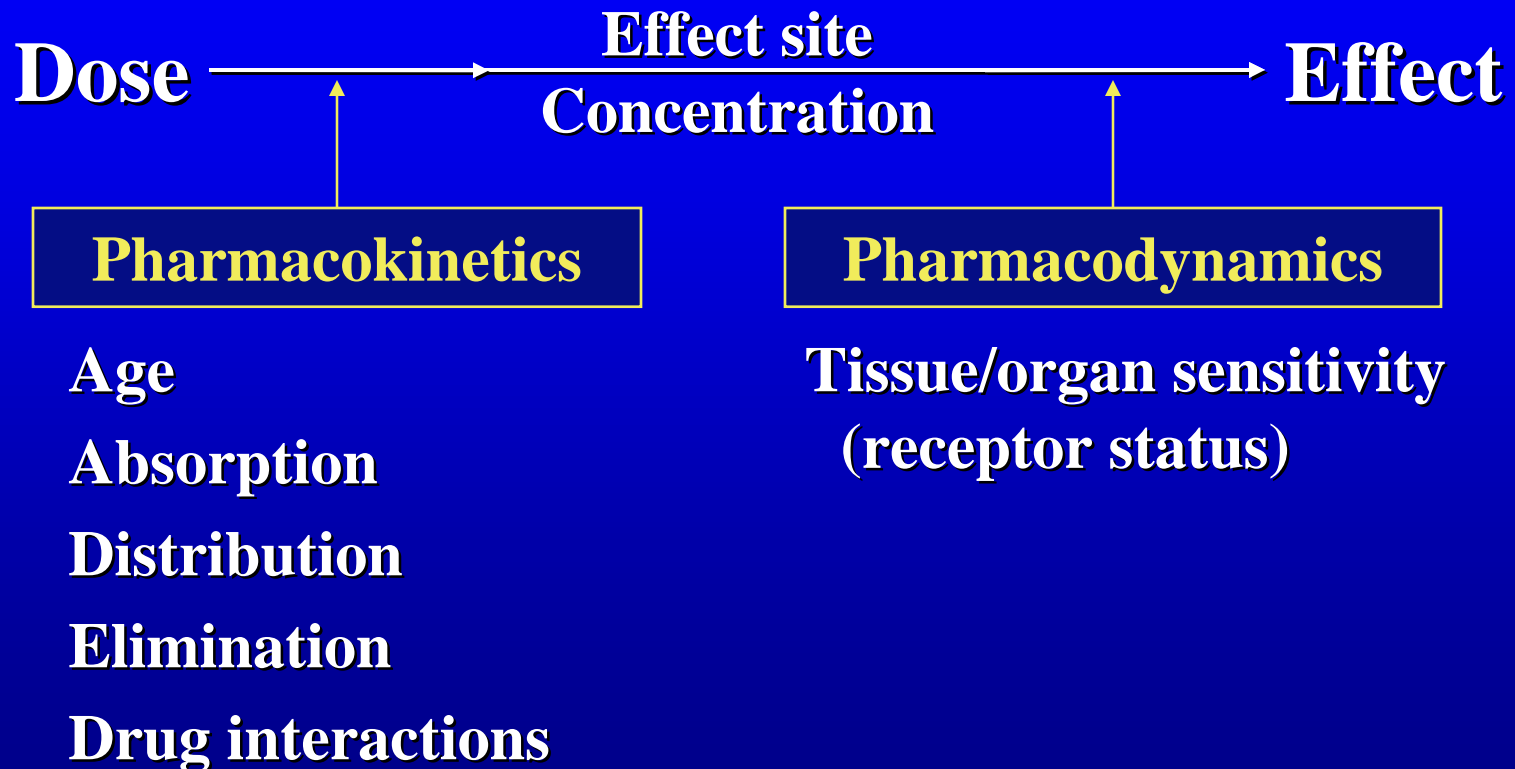
Dose Intensity in Breast Cancer



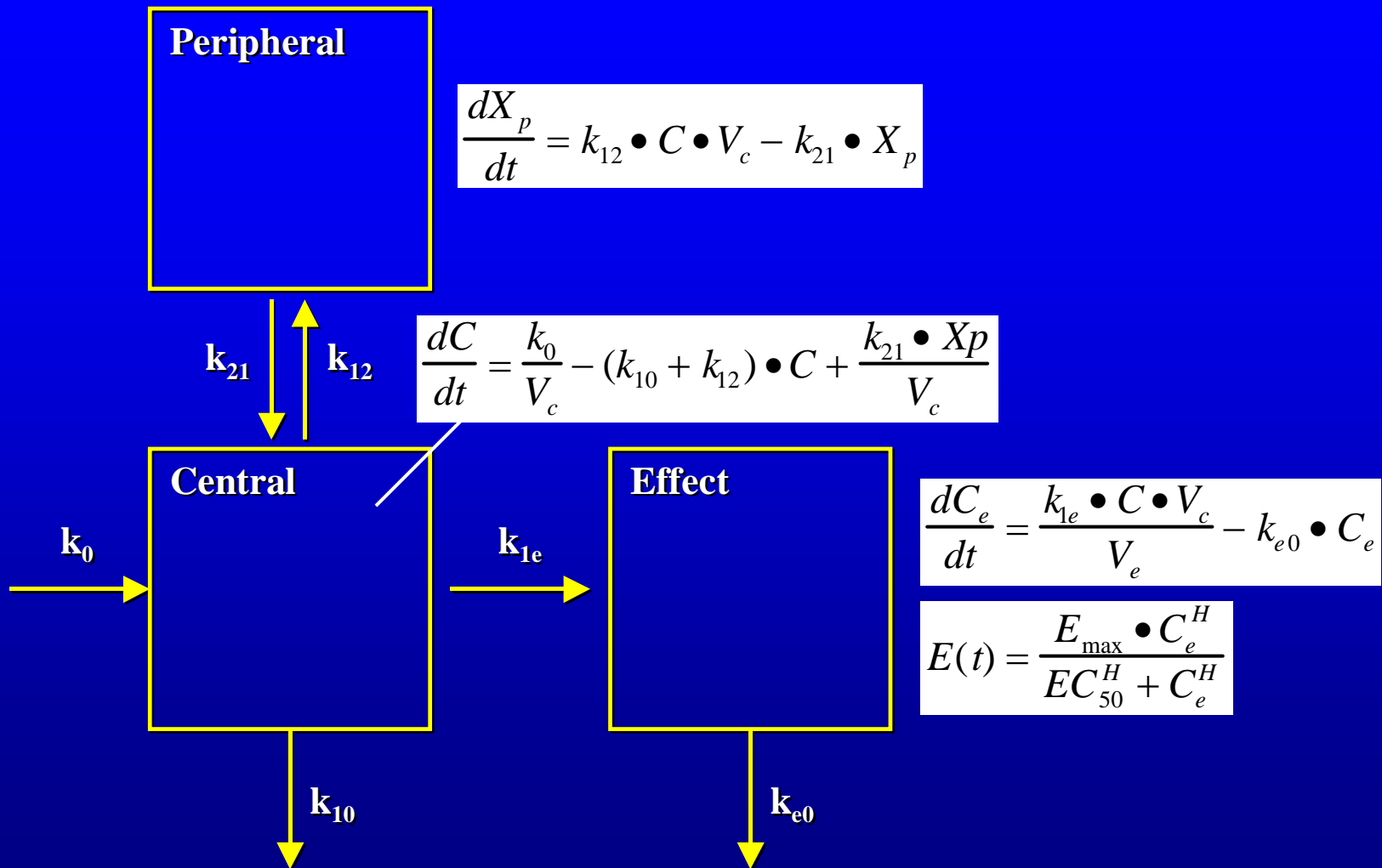
Doxorubicin Dose in Osteosarcoma



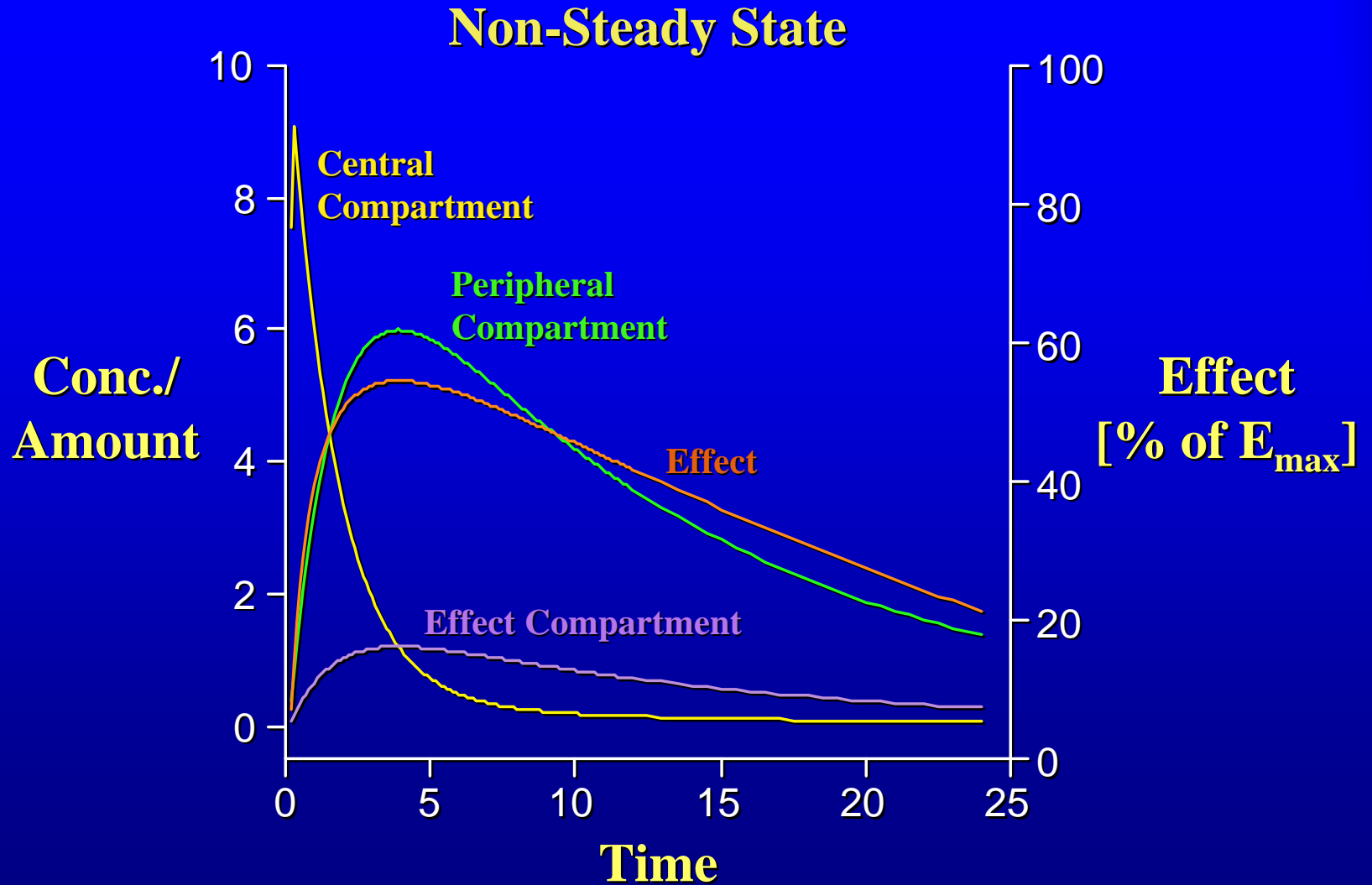
Relating Dose to Effect *In Vivo*



Effect Compartment (PK/PD Model)



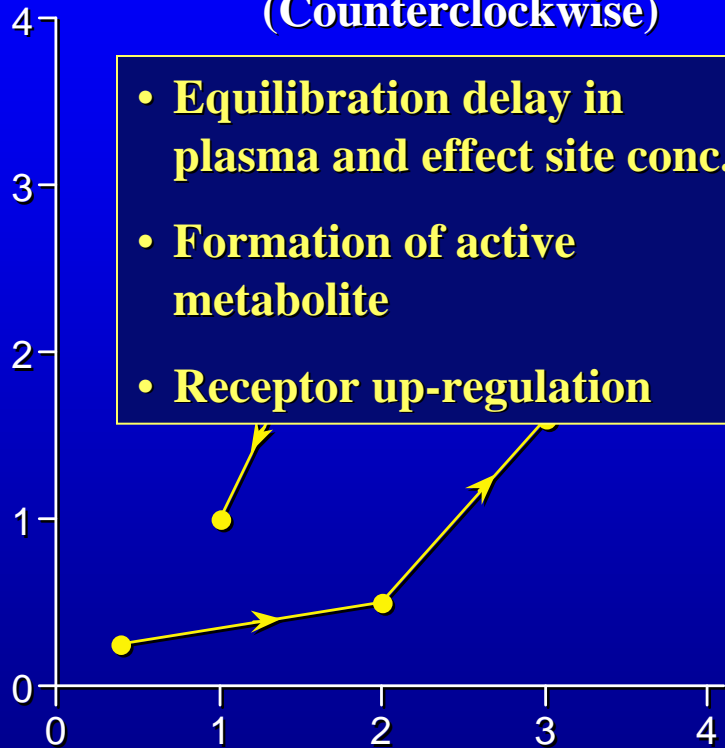
Concentration and Effect vs. Time



Hysteresis and Proteresis Loops

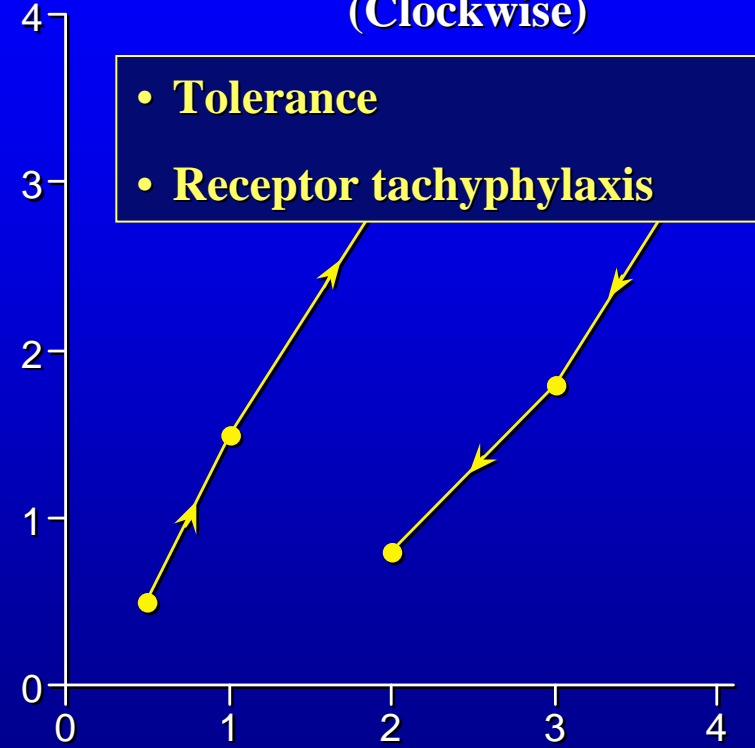
Intensity of Drug Effect

**Hysteresis Loop
(Counterclockwise)**



Intensity of Drug Effect

**Proteresis Loop
(Clockwise)**



Plasma Drug Concentration

Role of Dose-Effect Studies

- **Drug development**
 - **Site of action**
 - **Selection of dose and schedule**
 - **Potency, efficacy and safety**
 - **Drug interactions**
- **Patient management**
 - **Therapeutic drug monitoring**
 - **Risk-benefit (therapeutic indices)**

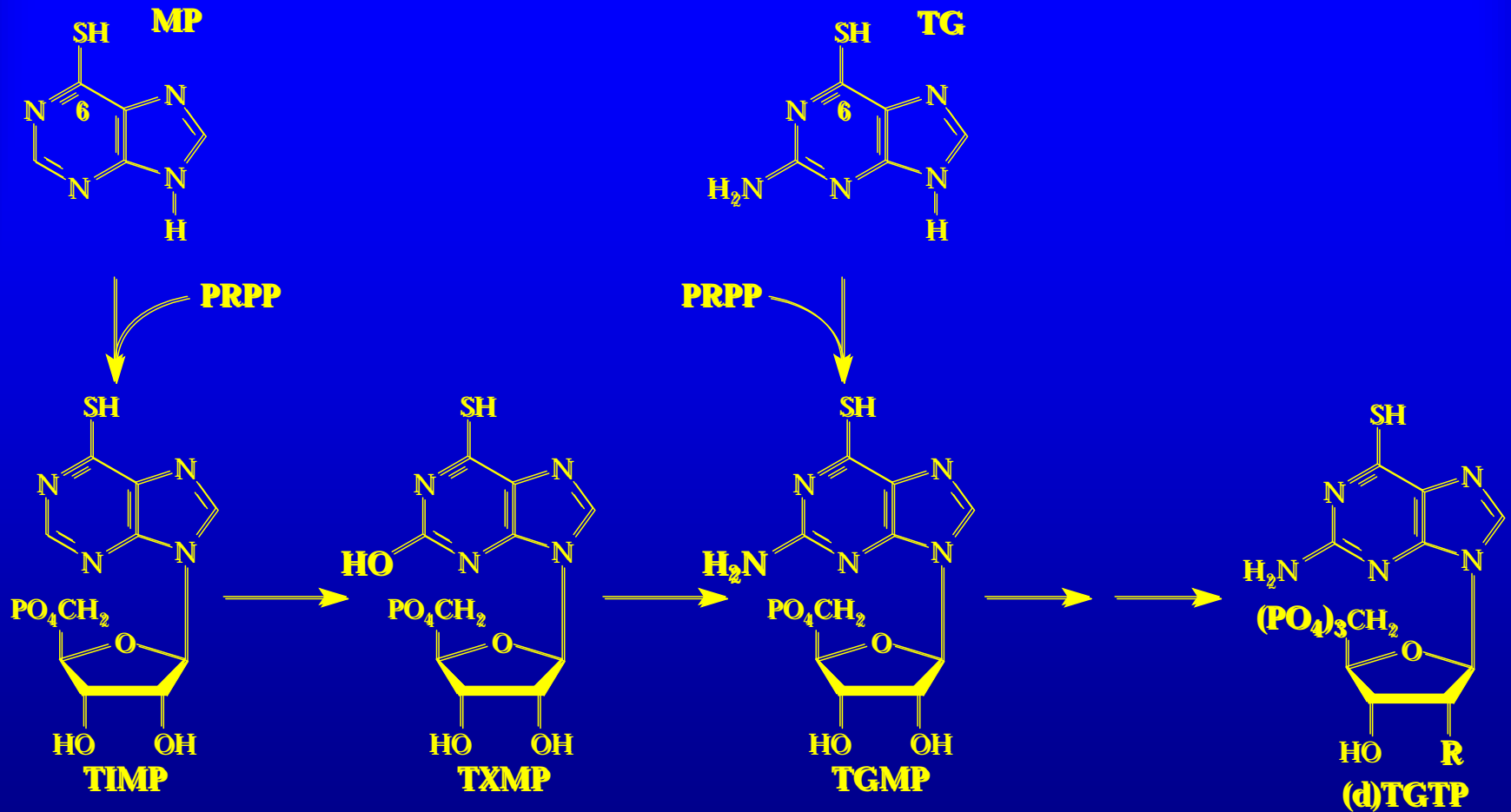
THE END

Endpoints to Monitor Drug Effect

Farnesyltransferase Inhibitors for Cancer

LEVEL	ENDPOINT
Molecular	Farnesyltransferase inhibition
Cellular	Proliferation rate, apoptosis
Tumor	Response (change in tumor size)
Organism	Survival, quality of life

Thiopurine Metabolic Activation



Therapeutic Indices

$$\text{Therapeutic Ratio} = \frac{\text{TD}_{50}}{\text{ED}_{50}} = 2.5$$

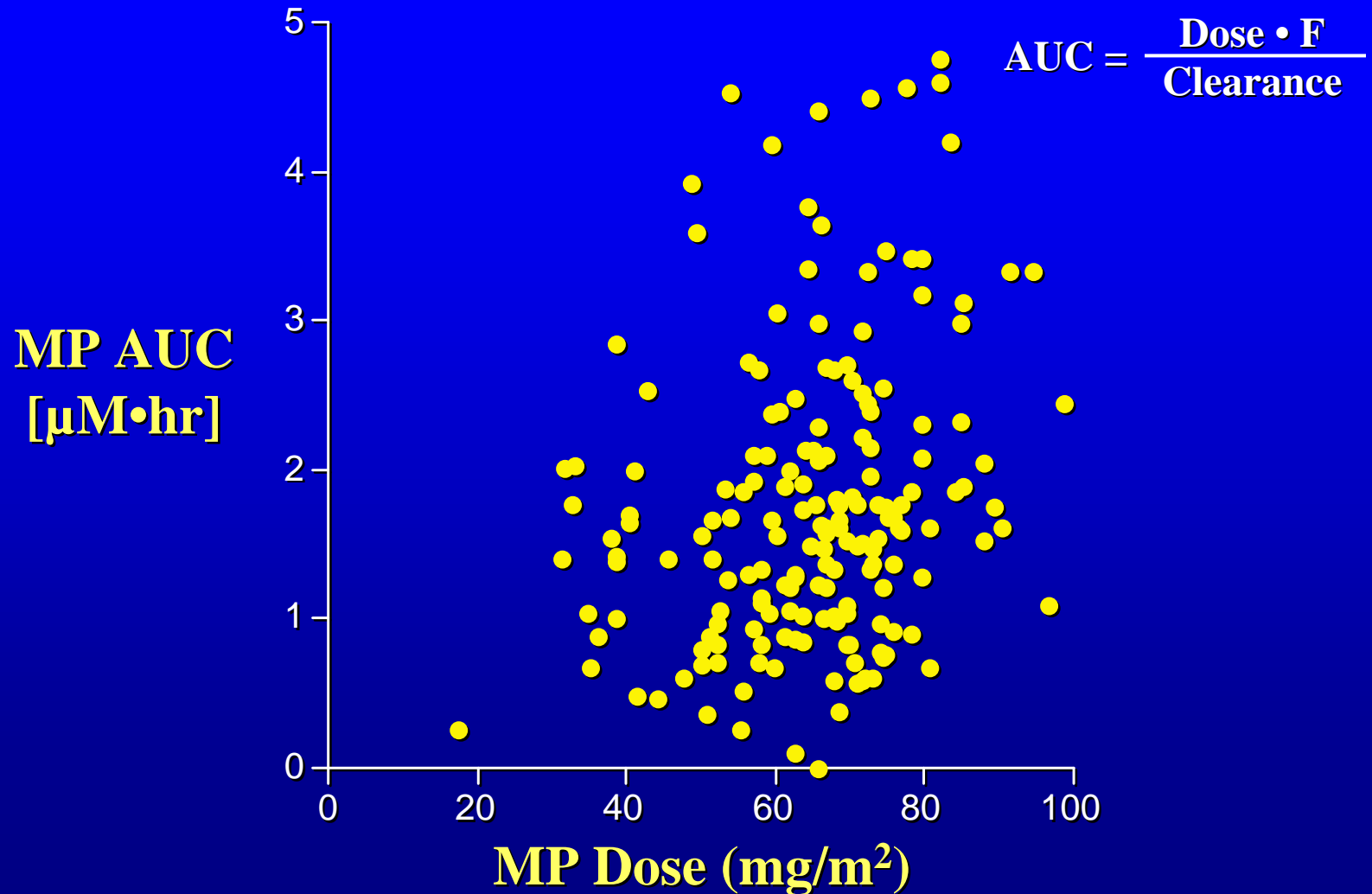
$$\text{Certain Safety Factor} = \frac{\text{TD}_1}{\text{ED}_{99}} = 1.3$$

$$\text{Standard Safety Margin} = \frac{\text{TD}_1 - \text{ED}_{99}}{\text{ED}_{99}} \times 100 = 31\%$$

Relative Dose Intensity

Regimen	Drugs	Dose Rate mg/m ² /wk	R.D.I.	
			Drugs	Regimen
CAF-1	Cyclo	350	1	1
	Doxo	15	1	
	FU	250	1	
CAF-2	Cyclo	125	0.36	0.56
	Doxo	12.5	0.83	
	FU	125	0.50	

Oral Mercaptopurine



Pharmacodynamic Models

- Fixed effect model

- Linear model

$$\text{Effect} = E_0 + S \cdot [\text{Drug}]$$

- Log-linear model

$$\text{Effect} = I + S \cdot \text{Log}([\text{Drug}])$$

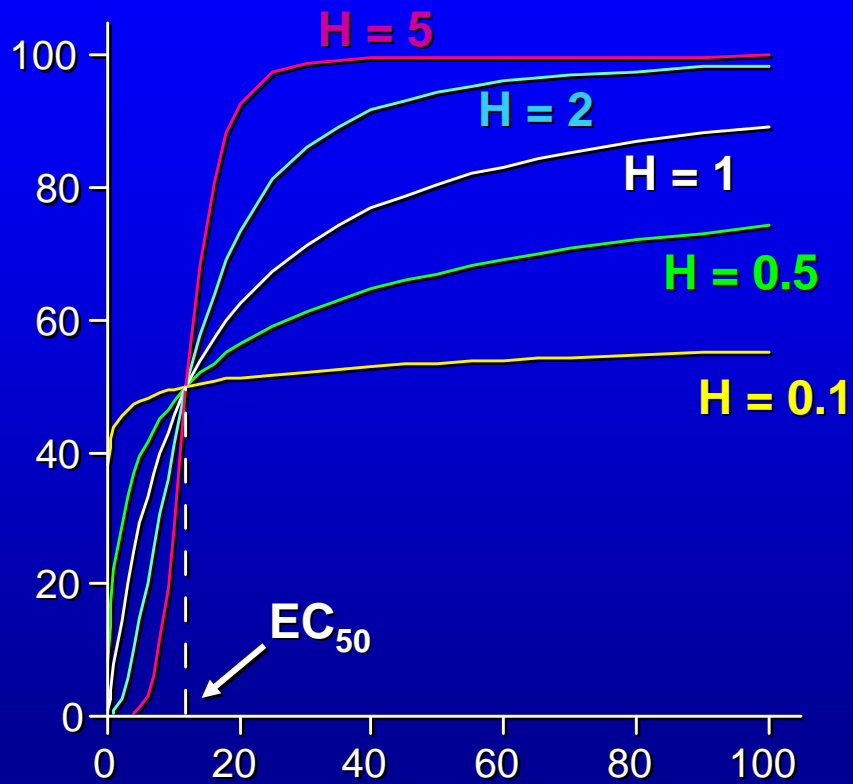
- E_{\max} model

$$\text{Effect} = \frac{E_{\max} \cdot [\text{Drug}]^H}{EC_{50}^H + [\text{Drug}]^H}$$

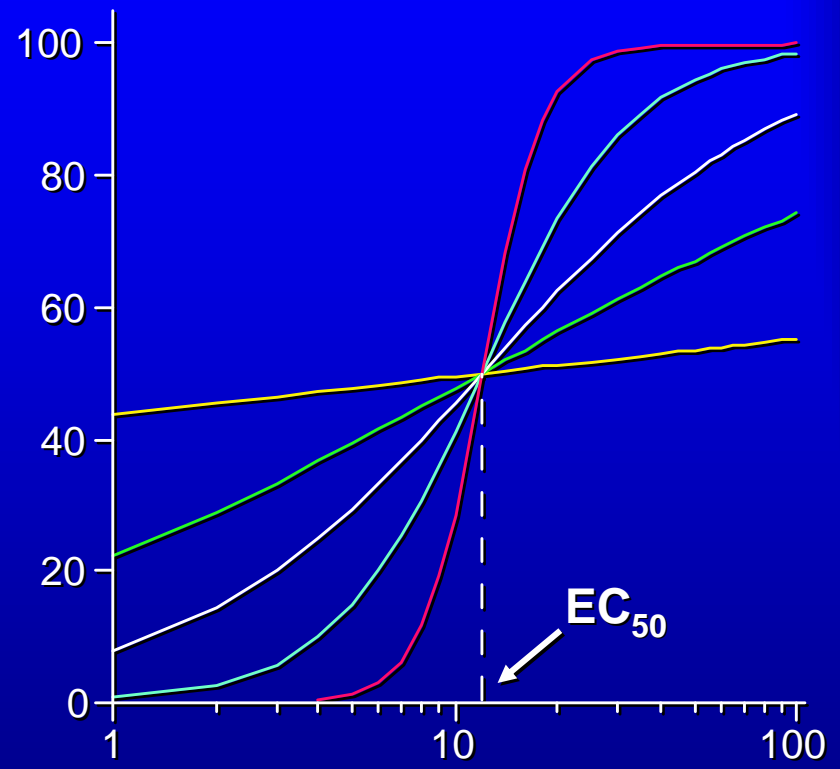
- Sigmoid E_{\max} model

Sigmoid E_{\max} PD Model

Effect (%)

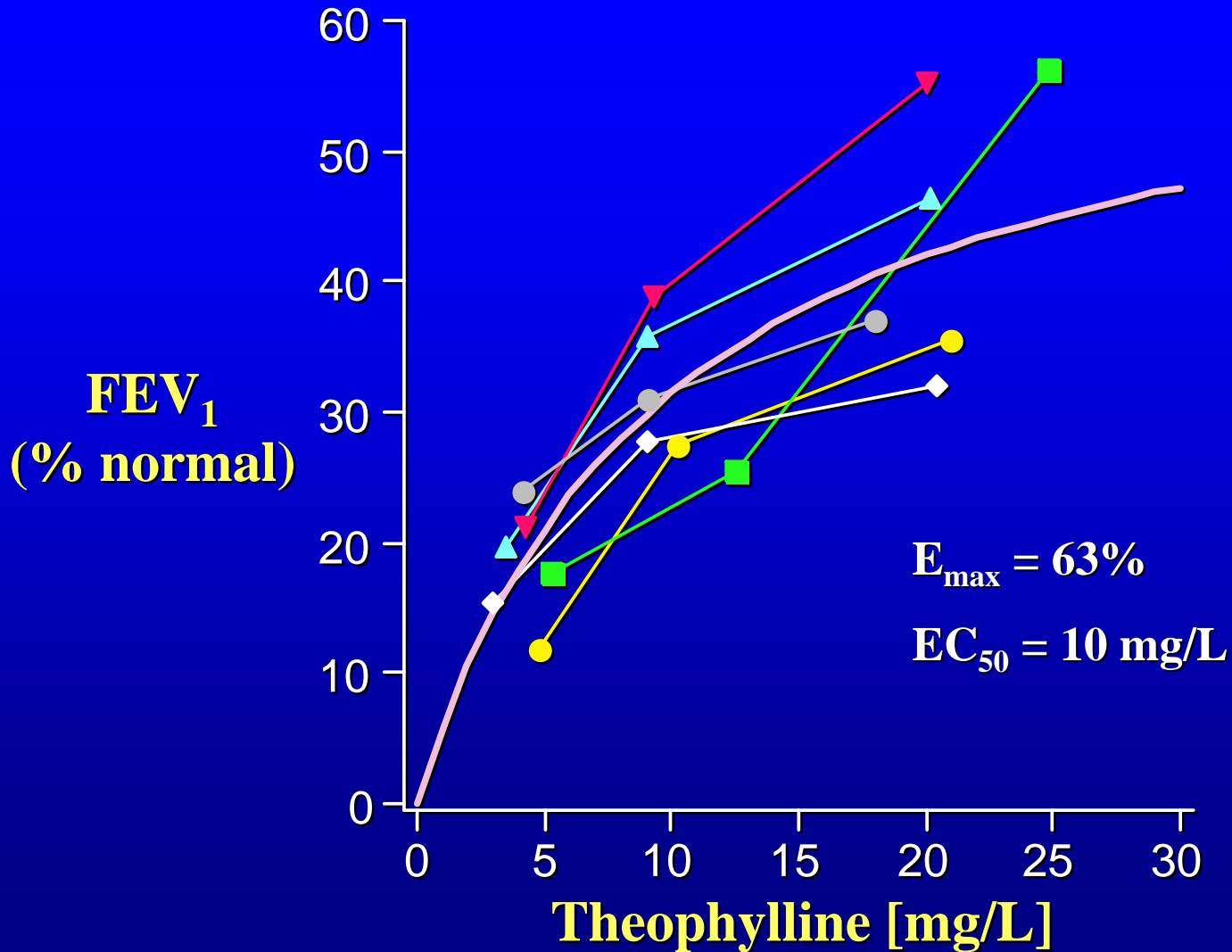


Effect (%)



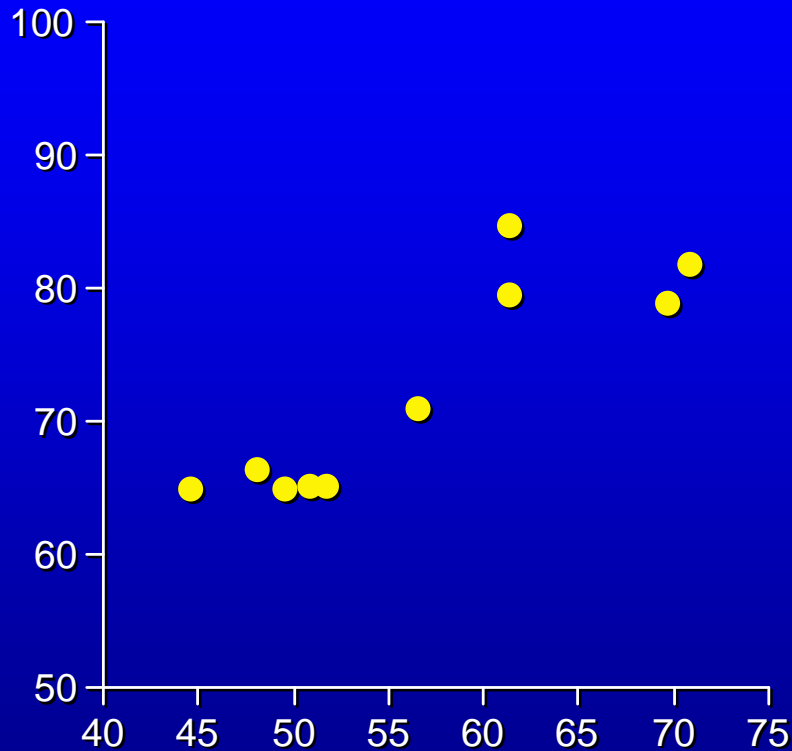
[Drug]

Theophylline Pharmacodynamics

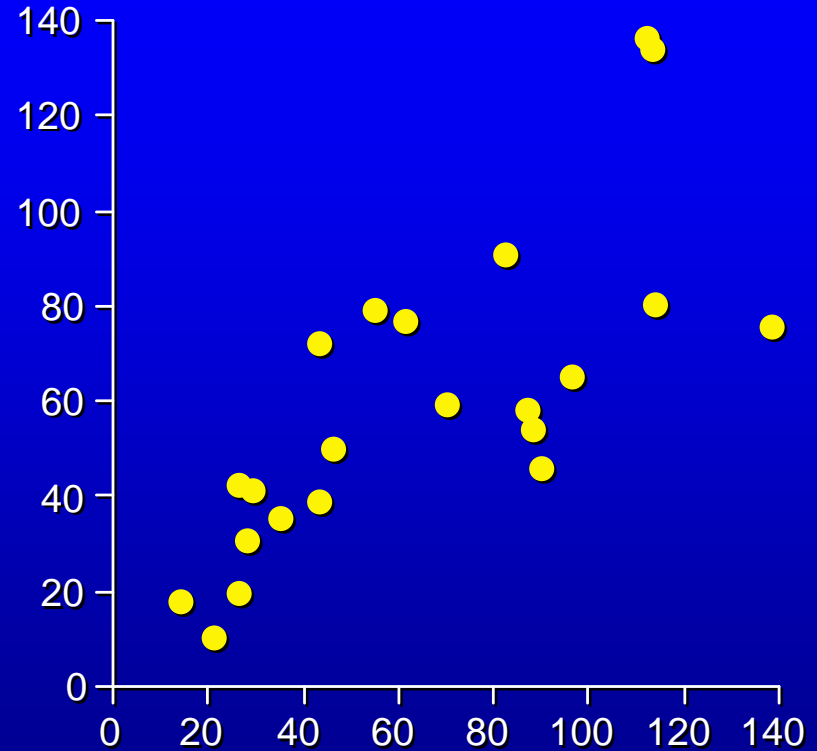


Carboplatin PK/PD

**% Decrease
Platelet**



**Carboplatin
 Cl_{TB} [ml/min]**



**Carboplatin AUC
[$\mu\text{g}\cdot\text{hr}/\text{ml}$]**

**Creatinine Clearance
[ml/min]**

Carboplatin Adaptive Dosing

ADULTS

$$D[\text{mg} / \text{m}^2] = 0.091 \times CL_{CR}[\text{ml} / \text{min} / \text{m}^2] \times \left(\frac{\text{prePlt} - \text{trgtPlt}}{\text{prePlt}} \times 100 - \text{priorRx} \right) + 86$$

$$D[\text{mg}] = \text{trgtAUC}[\text{mg} \cdot \text{min} / \text{ml}] \times (\text{GFR}[\text{ml} / \text{min}] + 25)$$

CHILDREN

$$D[\text{mg} / \text{m}^2] = \text{trgtAUC}[\text{mg} \cdot \text{min} / \text{ml}] \times (0.93 \times \text{GFR}[\text{ml} / \text{min} / \text{m}^2] + 15)$$

$$D[\text{mg}] = \text{trgtAUC}[\text{mg} \cdot \text{min} / \text{ml}] \times (\text{GFR}[\text{ml} / \text{min}] + (0.36 \times \text{BW}[\text{kg}]))$$