DOSE –RESONSE CURVE

1. **Graded dose-response curve**

2. Quantal (all or none) curve

Graded Dose-response Curve

1. Response is continuous and gradual.
2. Curve is usually sigmoid in shape (Log dose or concentration).
3. used to calculate
   - ED50
   - Potency
   - Efficacy

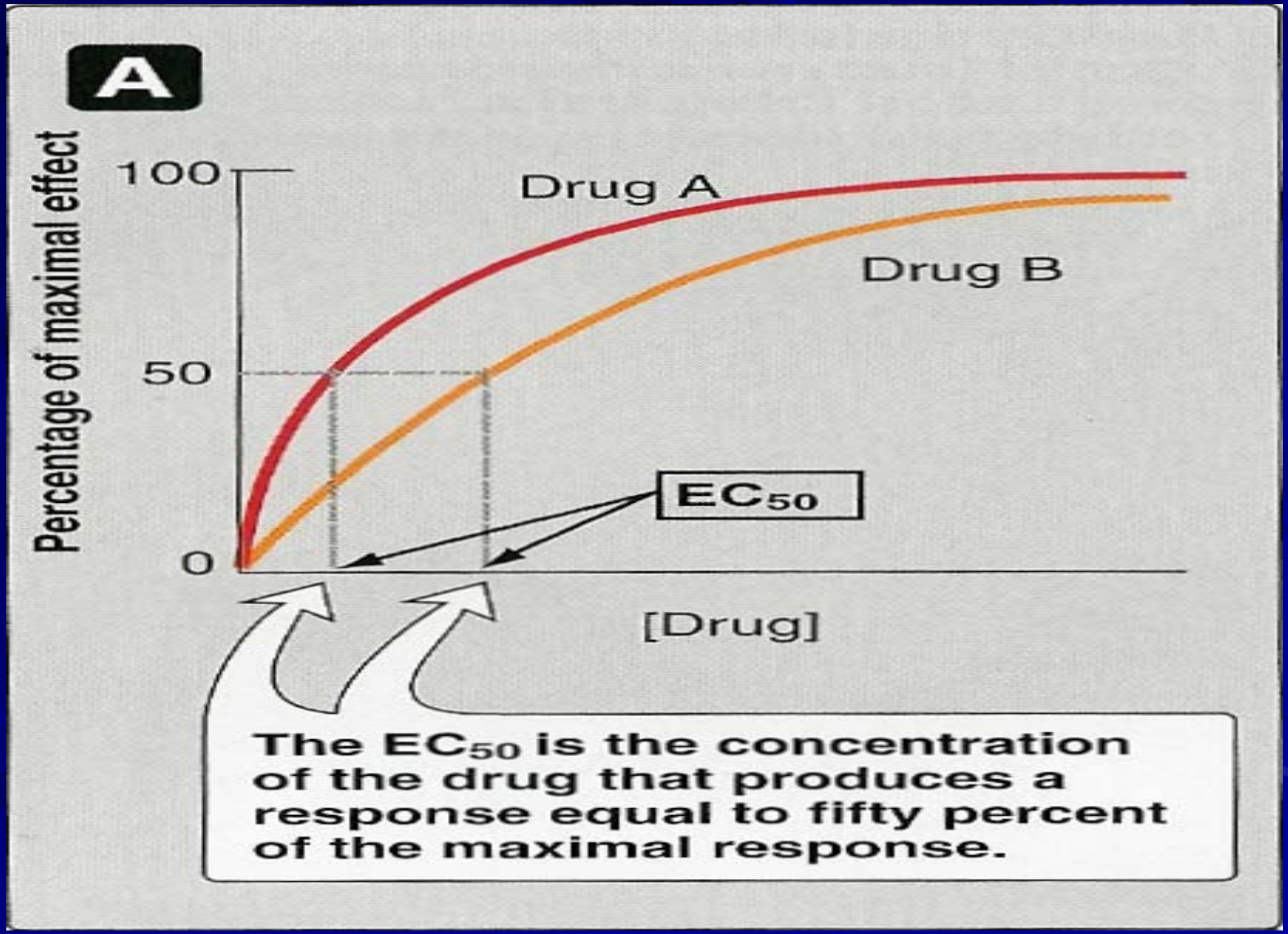
MEDIAN EFFECTIVE DOSE (ED50).

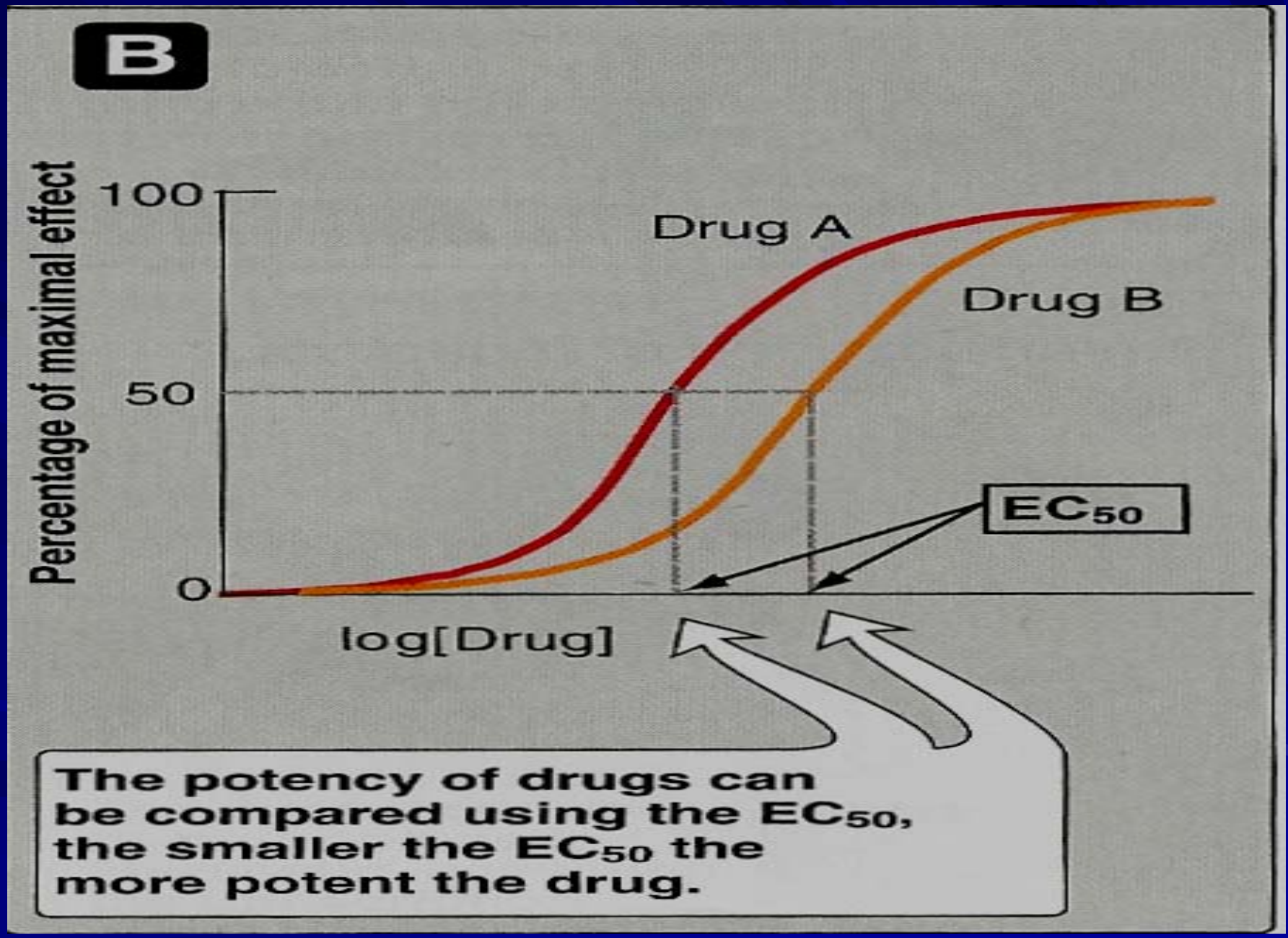
- is a dose of the drug that gives a response equals to 50% of the maximal response.

- is a measure of the **potency**.

POTENCY

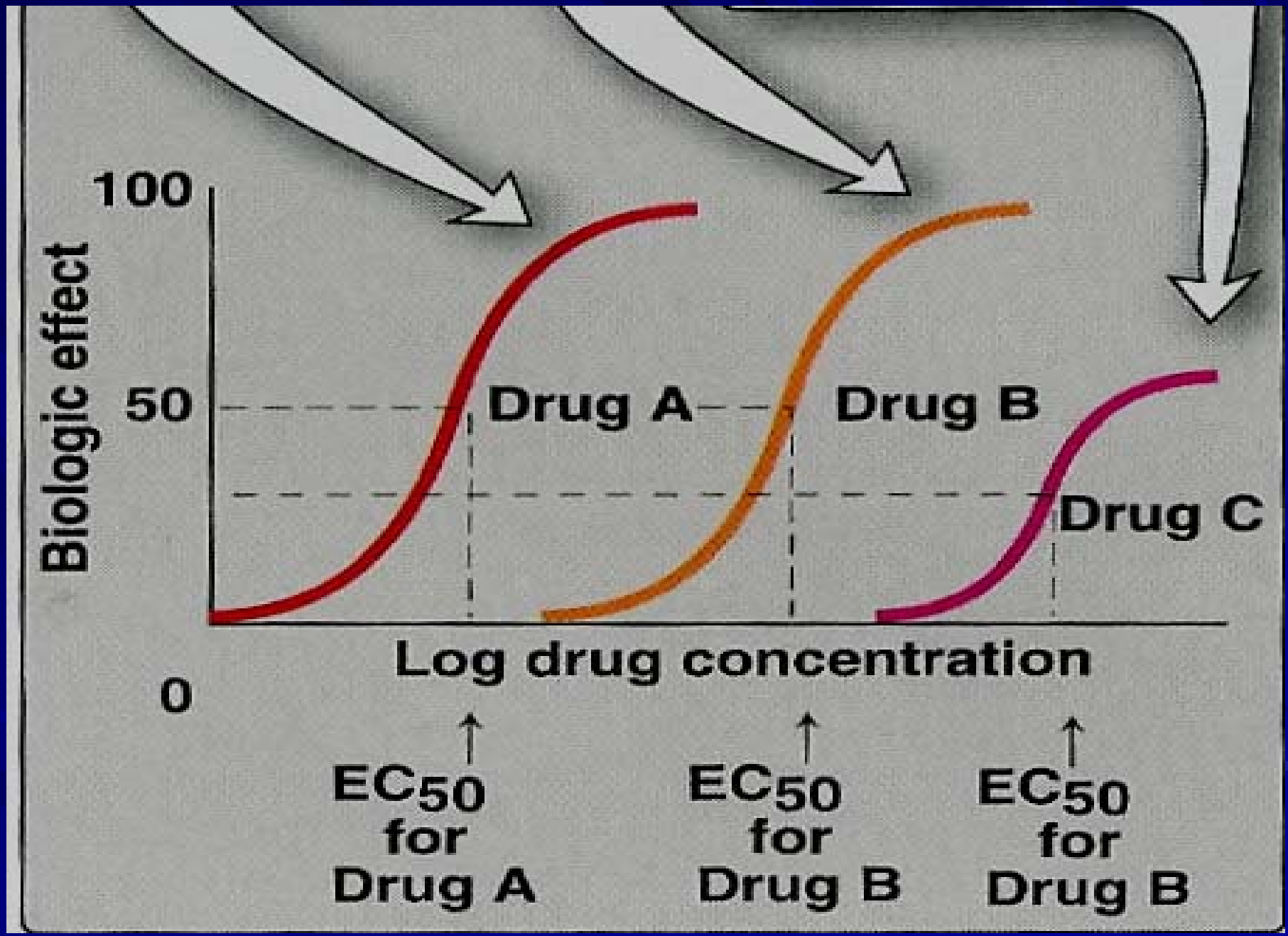
- Is inversely proportional to ED 50.
- Is a measure (in weight) of the amount of the drug required to produce an action of a given magnitude (50% of the maximal response = ED50).
- The smaller is the EC50, the more potent is the drug.
- Efficacy is more important than potency.

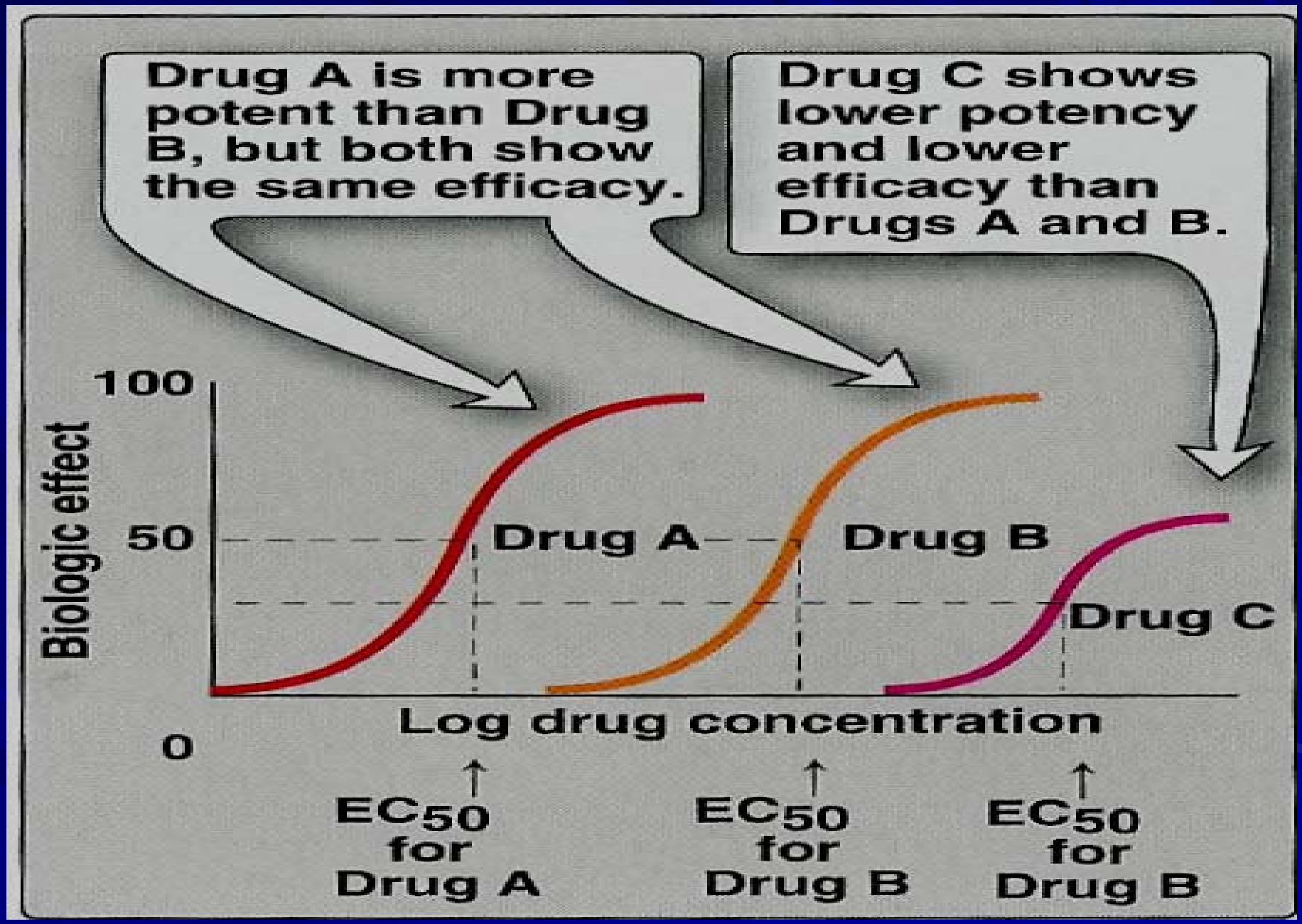

A
Percentage of maximal effect
100
50
0
Drug A
Drug B
EC50
[Drug]
The EC50 is the concentration of the drug that produces a response equal to fifty percent of the maximal response.


B
Percentage of maximal effect
100
50
0
Drug A
Drug B
EC50
log[Drug]
The potency of drugs can be compared using the EC50, the smaller the EC50 the more potent the drug.

EFFICACY

- Depends on the number of drug-receptors formed.
- Efficacy is more important than potency.


100
50
0
Biologic effect
Drug A
Drug B
Drug C
Log drug concentration
EC50 for Drug A
EC50 for Drug B
EC50 for Drug B


Drug A is more potent than Drug B, but both show the same efficacy.
Drug C shows lower potency and lower efficacy than Drugs A and B.
100
50
0
Biologic effect
Drug A
Drug B
Drug C
Log drug concentration
EC50 for Drug A
EC50 for Drug B
EC50 for Drug B

Quantal (all or none) curve

- Shows the effect of the magnitude of the dose on the proportion of patients responding (**Quantal responses**).

- Used to determine doses to which most population respond.

Quantal (all or none) curve

MEDIAN EFFECTIVE DOSE (ED50).

is a dose of the drug that gives response in 50% of patients.

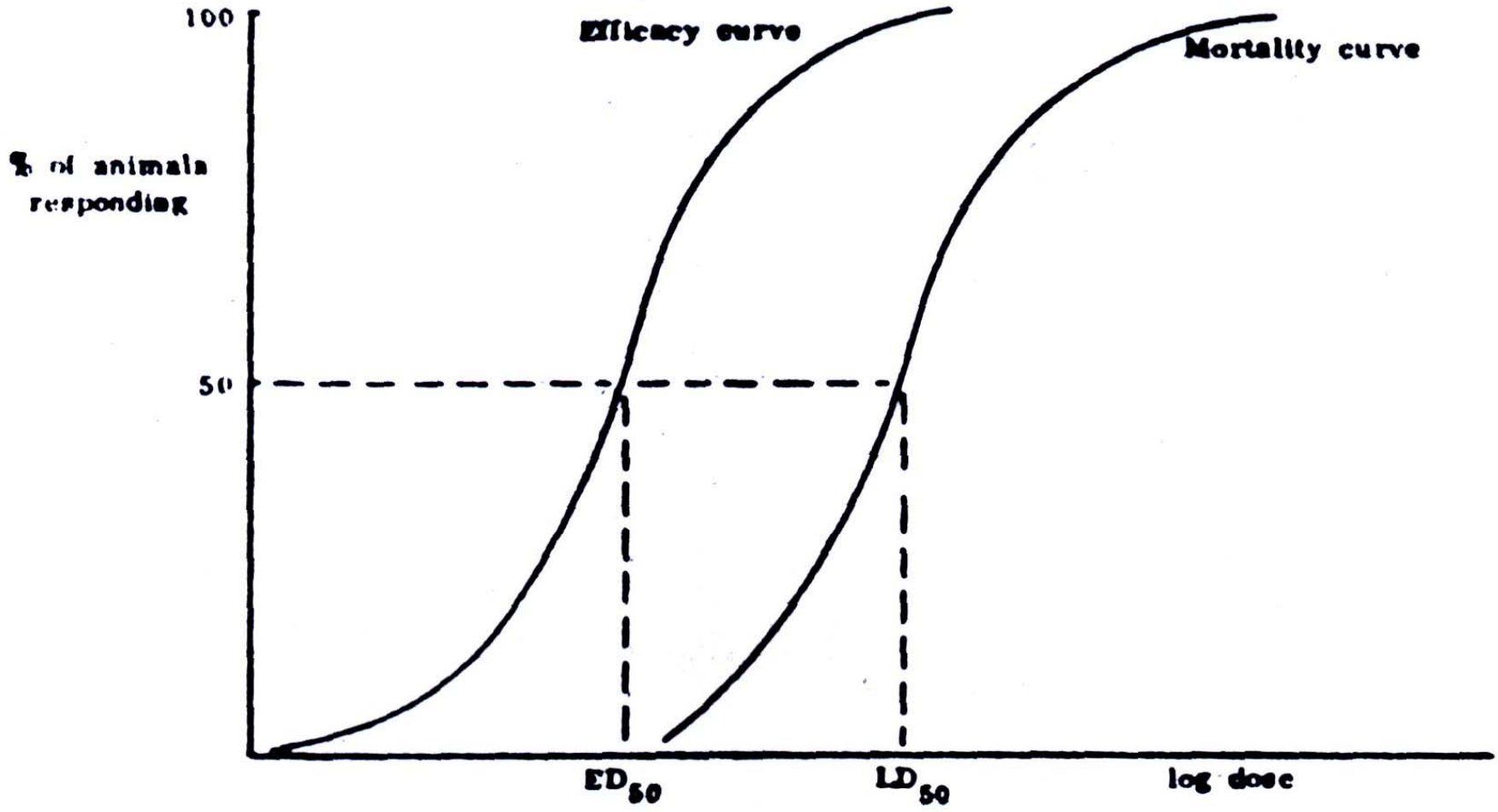
MEDIAN LETHAL DOSE (LD 50 or TD 50)

is the dose of a drug required to produce toxicity in 50 % of patients.

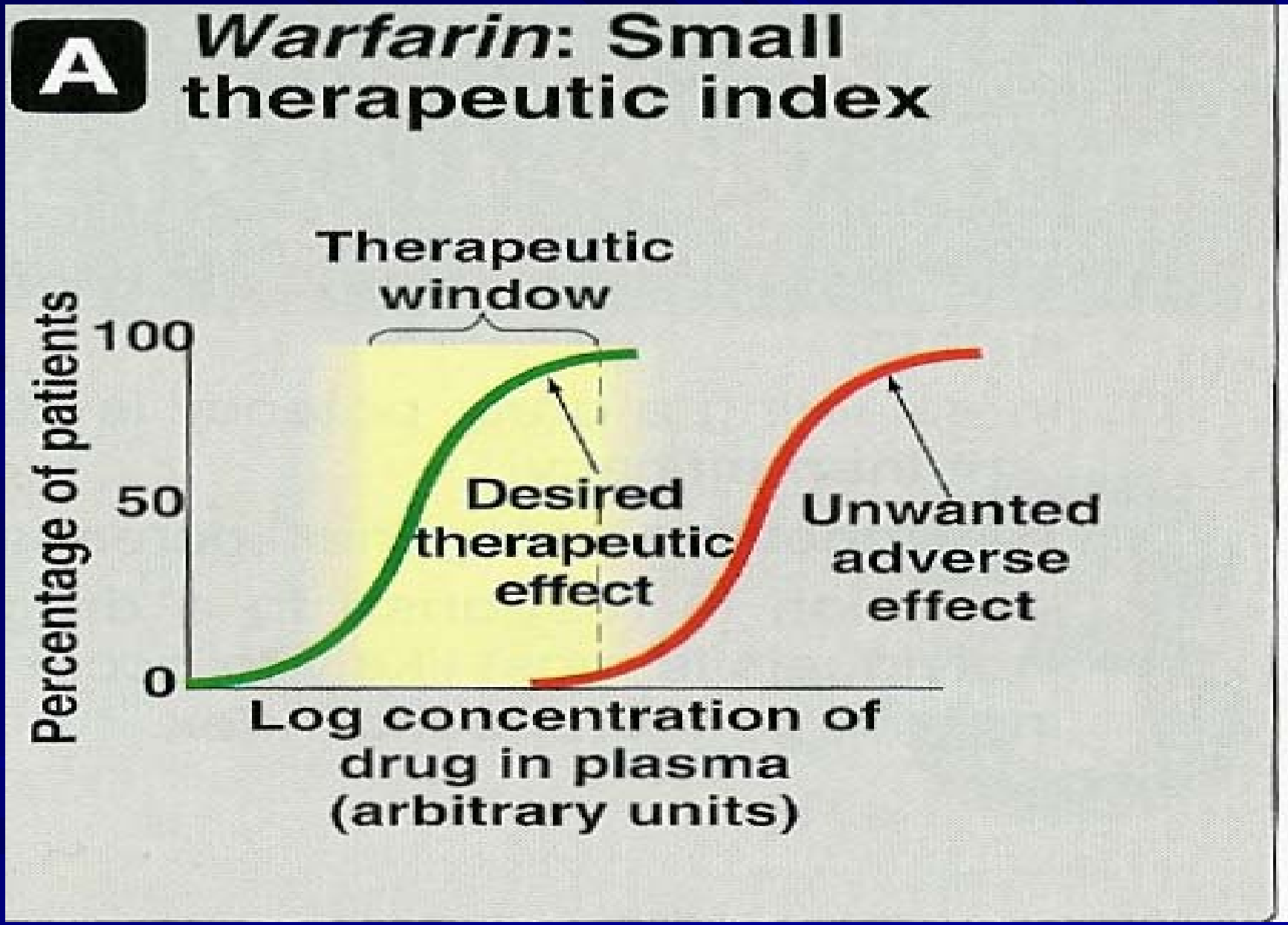
THERAPEUTIC INDEX (TI)

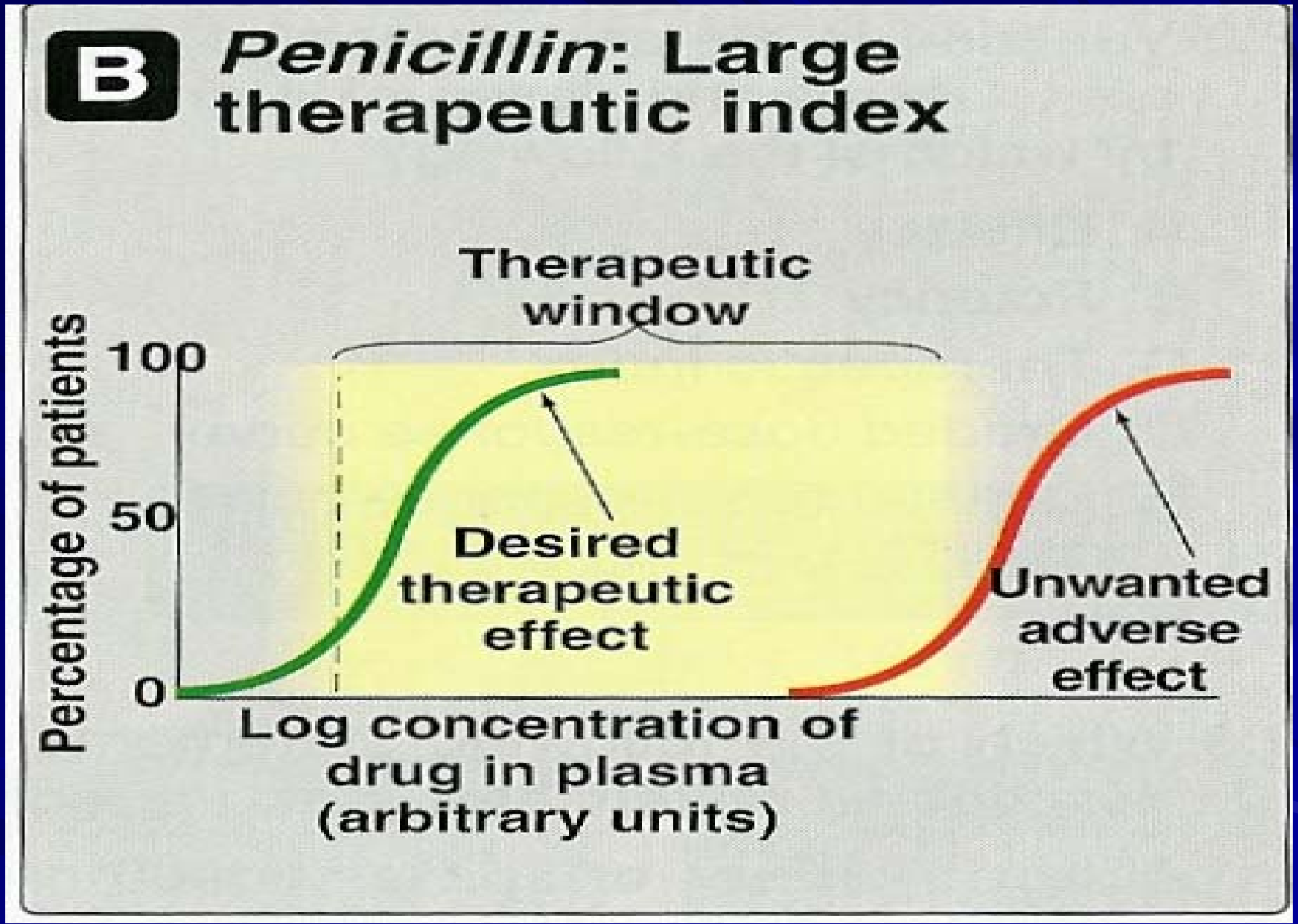
- Therapeutic index = $\frac{\text{LD50}}{\text{ED50}}$
- Is a measure of safety
- Large value ⇨ a wide margin of safety. **Penicillin**
- Small value ⇨ a narrow margin of safety **warfarin**
- If (TI) is equal to or less than one, drug is ???

$$\text{Therapeutic index} = \frac{\text{median lethal dose}}{\text{median effective dose}} = \frac{LD_{50}}{ED_{50}}$$



Graph for calculation of therapeutic indices


A
Warfarin: Small therapeutic index
Therapeutic window
Percentage of patients
100
50
0
Desired therapeutic effect
Unwanted adverse effect
Log concentration of drug in plasma (arbitrary units)


B
Penicillin: Large therapeutic index
Therapeutic window
Percentage of patients
100
50
0
Desired therapeutic effect
Unwanted adverse effect
Log concentration of drug in plasma (arbitrary units)

Antagonist

Types

- Physiological antagonist.
- Chemical antagonist.
- Pharmacological antagonist.

- **Antagonism**
  - **Physiological antagonism.**
  - **Chemical antagonism.**
  - **Pharmacological antagonism.**
    - **Competitive → Reversible.**
    - **Non-competitive → Irreversible.**

Drug Antagonism•

- **Chemical Antagonism**
  - Simple chemical reaction.
  - No receptor.

Examples

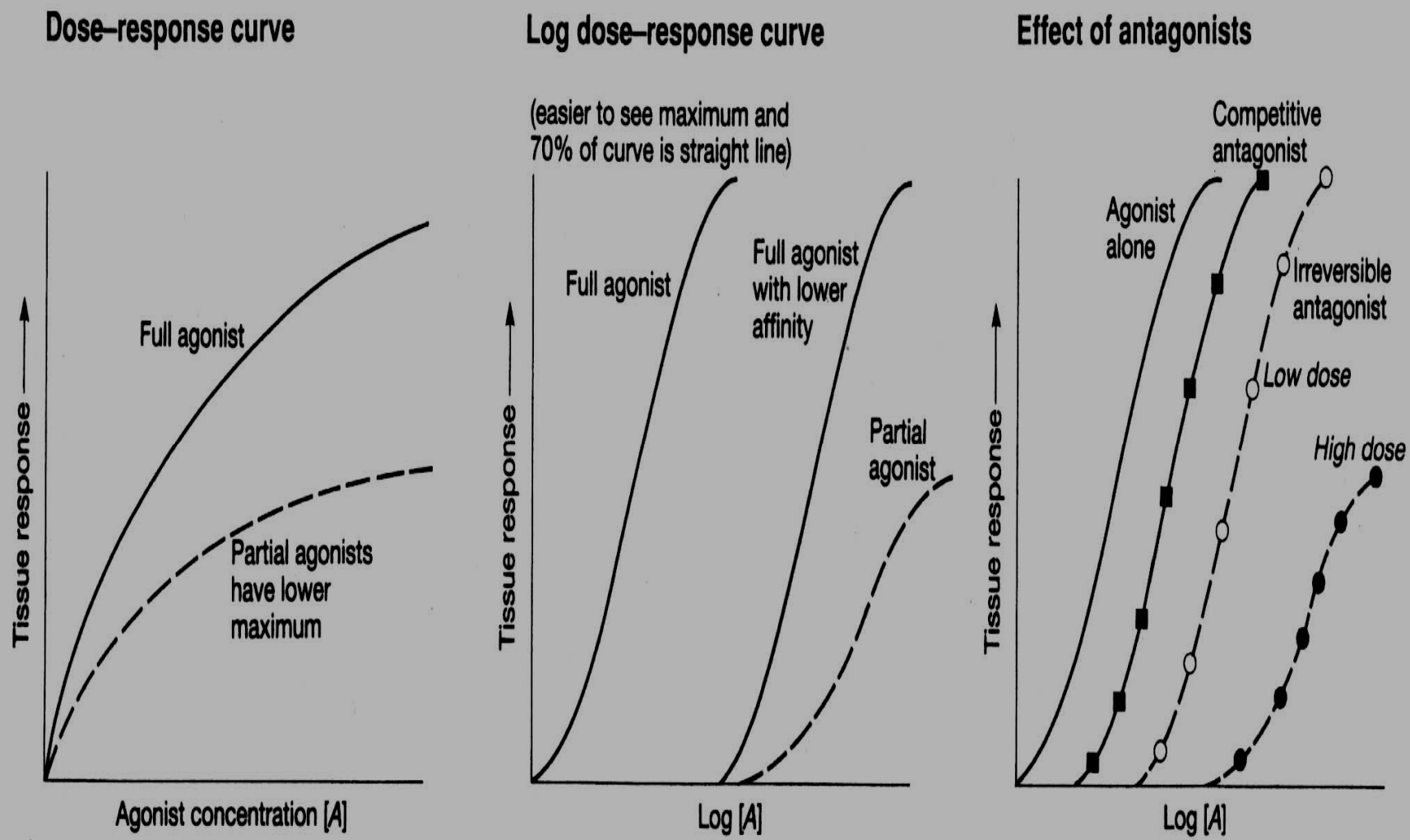
- Antacid & tetracyclines.
- Heparin & proteamine sulfate
- Iron & Deferoxamine.

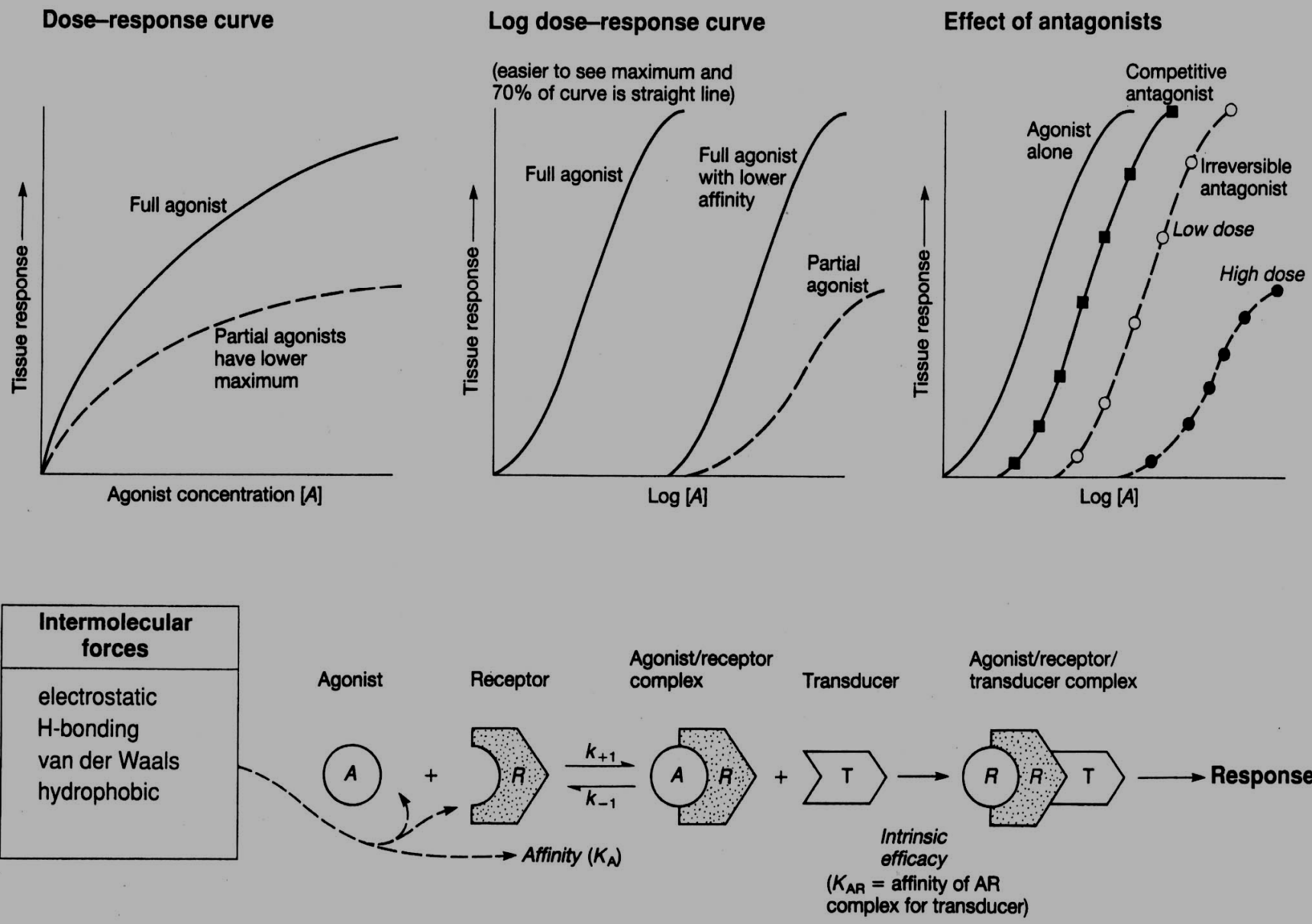
Physiological Antagonism

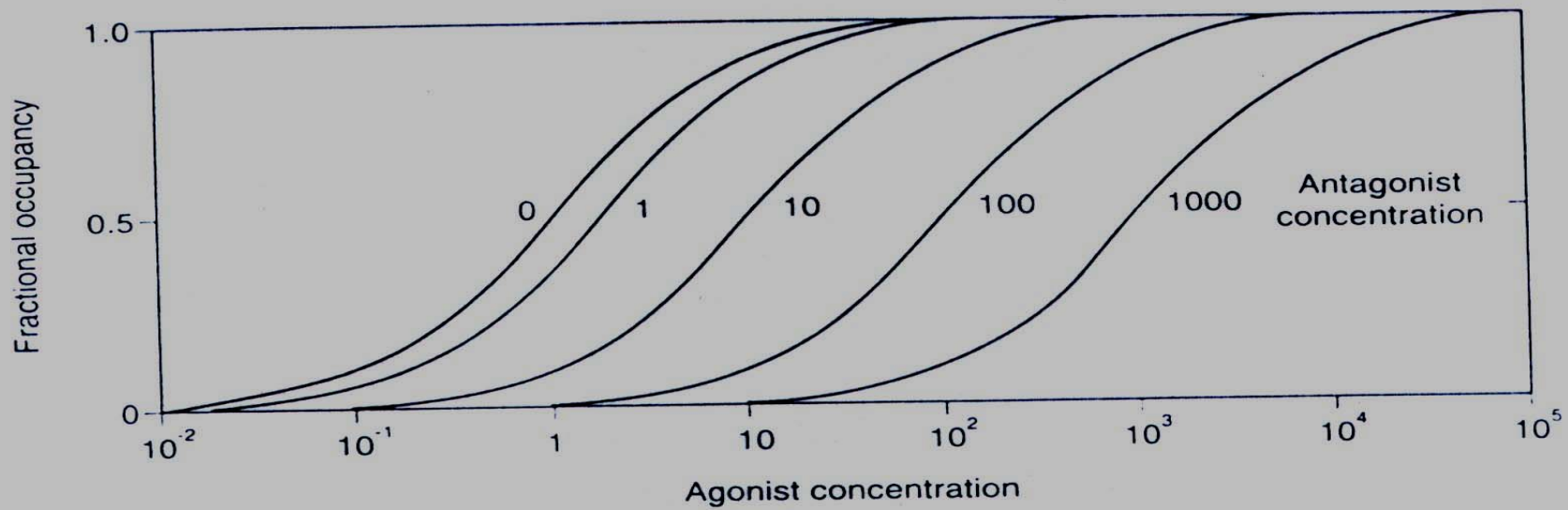
- Physiological effect is antagonized.
- Drugs acting on different receptors:
- Noradrenaline → Vasoconstriction → ↑ BP.
- Histamine → Relax vascular smooth muscle→ ↓BP
- Noradrenaline is used in anaphylactic shock to raise BP.

Pharmacological Antagonism

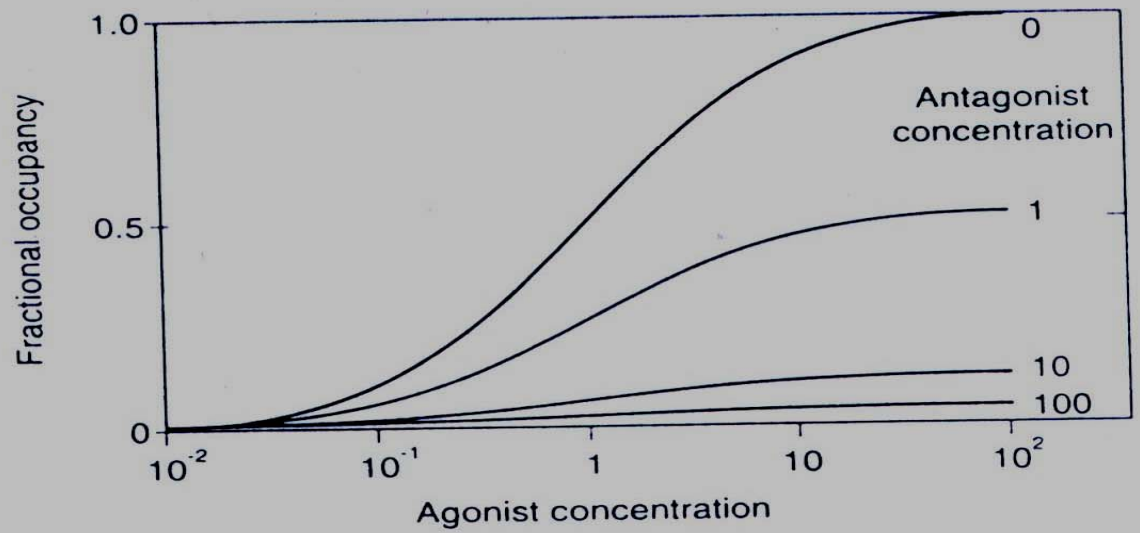
- Two drugs compete for the same receptor.
- The antagonist partially or completely prevents the pharmacological agonist effect.
- **Pharmacological antagonist**
  - Competitive
    - Reversible
  - Non-competitive
    - Irreversible


Dose–response curve
Tissue response
Full agonist
Partial agonists have lower maximum
Agonist concentration [A]
Log dose–response curve
(easier to see maximum and 70% of curve is straight line)
Tissue response
Full agonist
Full agonist with lower affinity
Partial agonist
Log [A]
Effect of antagonists
Tissue response
Agonist alone
Competitive antagonist
Irreversible antagonist
Low dose
High dose
Log [A]


Dose–response curve
Tissue response
Full agonist
Partial agonists have lower maximum
Agonist concentration [A]
Log dose–response curve
(easier to see maximum and 70% of curve is straight line)
Tissue response
Full agonist
Full agonist with lower affinity
Partial agonist
Log [A]
Effect of antagonists
Tissue response
Competitive antagonist
Agonist alone
Irreversible antagonist
Low dose
High dose
Log [A]
Intermolecular forces
electrostatic
H-bonding
van der Waals
hydrophobic
Agonist
Receptor
Agonist/receptor complex
Transducer
Agonist/receptor/ transducer complex
A
+
R
k+1
k−1
A R
+
T
R R T
Response
Affinity (KA)
Intrinsic efficacy
(KAR = affinity of AR complex for transducer)

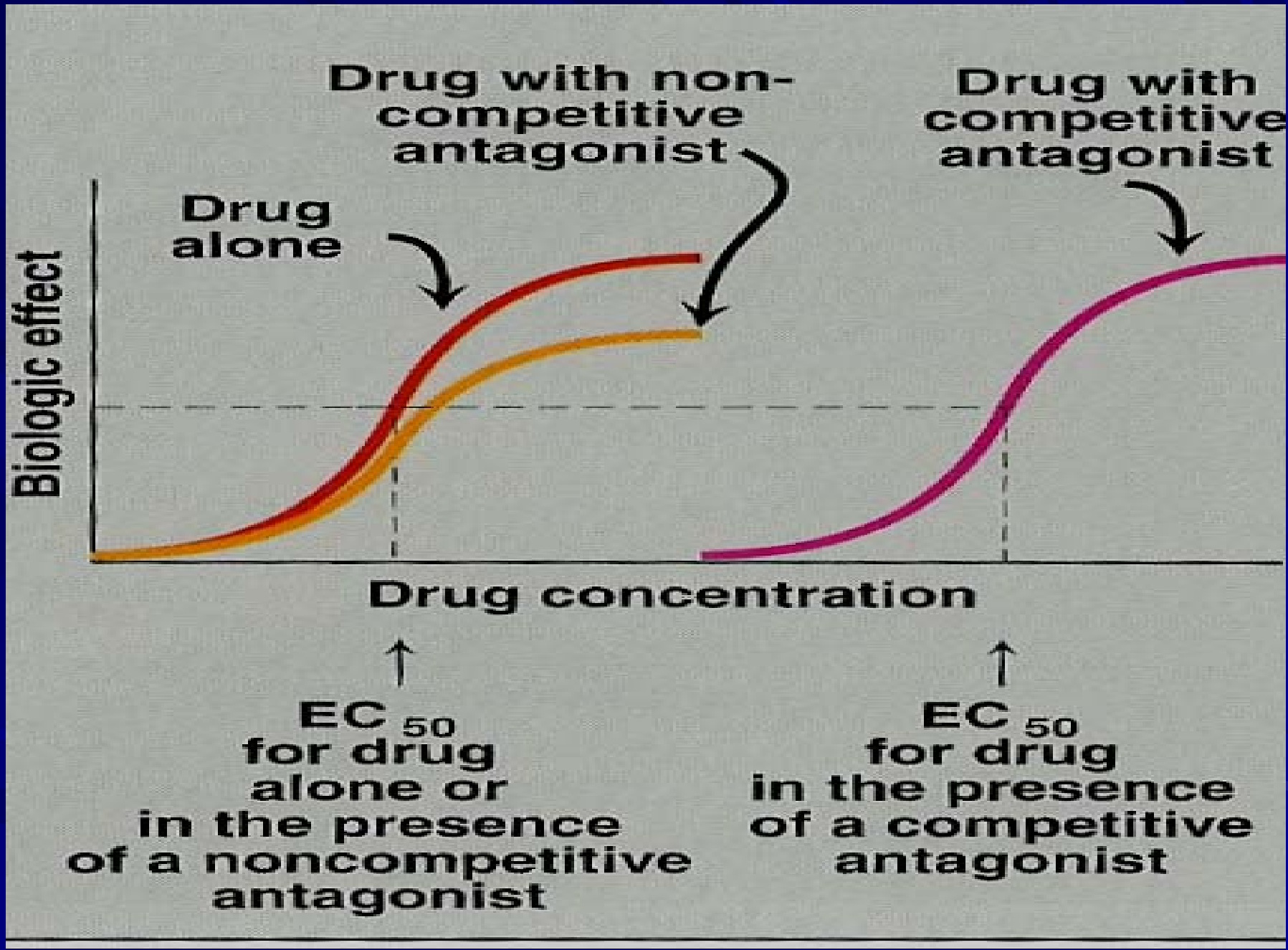


B Irreversible competitive antagonism



Competitive Antagonist

- The antagonist dissociates rapidly from the receptor.
- The antagonist effect can be overcome by increasing the agonist concentration.
- The dose-response curve is shifted to right.
- Dose-Response curve is parallel.
- Emax is maintained.
- e.g. acetylcholine and atropine.


Drug with non-competitive antagonist
Drug with competitive antagonist
Drug alone
Biologic effect
Drug concentration
EC 50 for drug alone or in the presence of a noncompetitive antagonist
EC 50 for drug in the presence of a competitive antagonist

Irreversible noncompetitive Antagonist

- The antagonist dissociates very slowly or not at all from the receptor .
- The action of antagonist cannot be overcome by increasing the agonist concentration .
- The dose-response curve is shifted to right.
- The two curves are not parallel.
- Emax is not maintained.
- Phenoxybenzamine .

Prodrug

A drug that is pharmacologically inactive but is chemically changed into active form in the body by the action of enzymes.

Dose

The amount of a drug to produce an effect.

Therapeutic Dose

The dose required to produce therapeutic effect.

Toxic Dose

The dose which produce toxic effect.

Variation in drug response

- Drug resistance
- intolerance
- Tolerance
- Tachyphylaxis
- Idiosyncrasy

DRUG RESISTANCE

The loss of the effectiveness of antimicrobial or antitumour drugs.

INTOLERANCE (HYPE-RACTIVITY)

- Increase in response within the therapeutic dose.
- Orthostatic hypotension after Chlorpromazine (tranquilizer).

TOLERANCE

- A gradual decrease in response to repeated administration of a drug.
- Slow in onset (takes days or weeks to develop).
- Original effect can be produced by increasing the dose.
  e.g. alcohols, morphine, barbiturates.

TACHYPHYLAXIS

- A decrease in response to the rapidly repeated administration of a drug.
- Rapid in onset.
- Original effect cannot be reproduced even with a larger dose of the drug.
- e.g. B-agonists, ephedrine, amphetamine,

RECEPTOR DESENSITIZATION

Definition

Changes in the responsiveness of the receptor upon repeated or continuous administration of the drug.

Causes of desensitization

- Excessive stimulation of the receptors
- Genetic causes.
- Down regulation of receptors.
- Enzyme induction

Causes of desensitization

- Genetic causes.
- Down regulation of receptors.

(Decrease in the total number of receptors available).

- Enzyme induction

Types

- Tolerance
- Tachyphylaxis