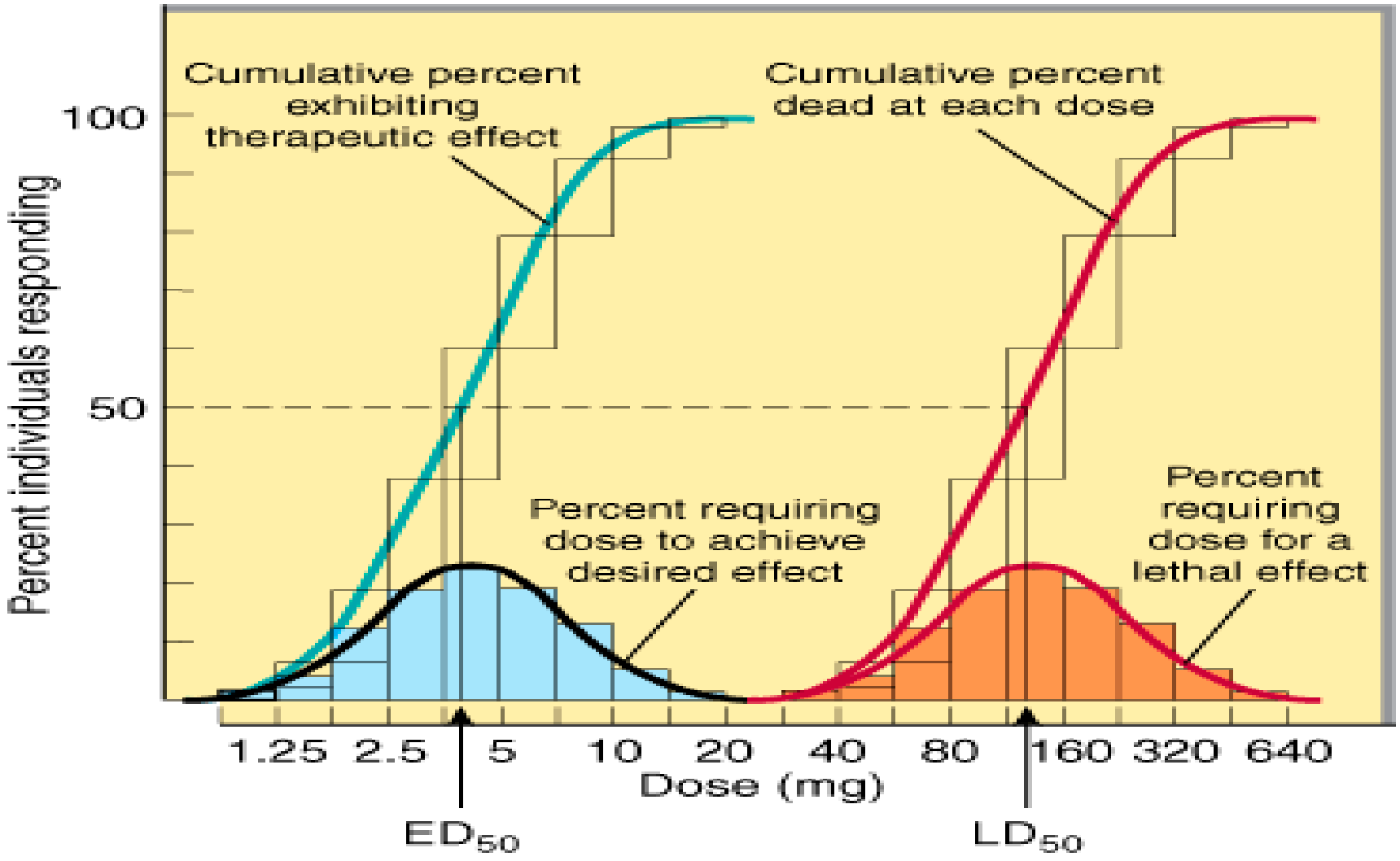
Pharmacodynamics

Quantal Dose-Response Curves



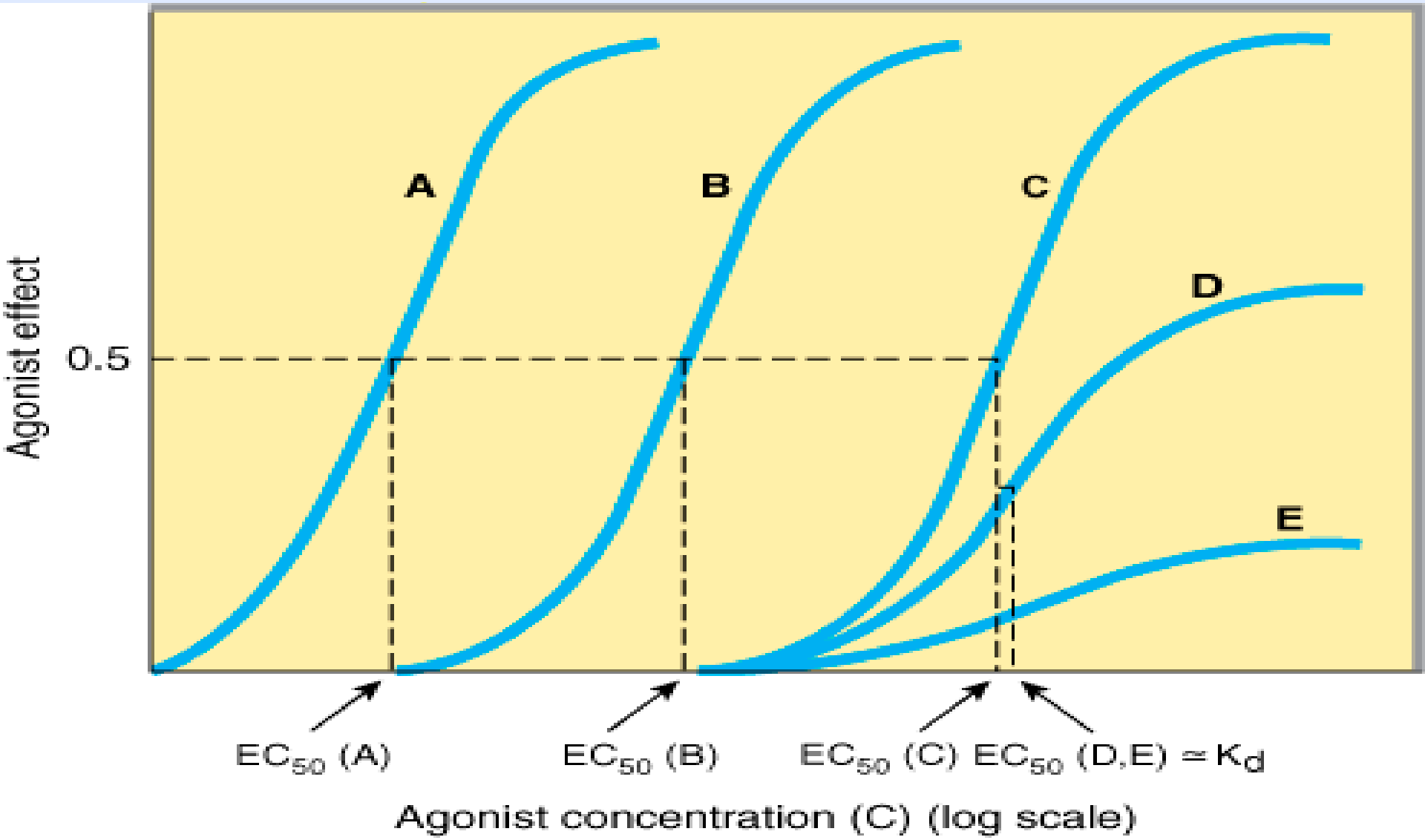
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Features of Quantal Dose-Effect Curves

- Involves all or non responses.
- Obeys Normal Frequency Distribution.
- When transformed into cumulative, will result in a sigmoid curve.
  - Straight line for most of the line .
- Can calculate Therapeutic Index= LD50/ED50

Quantal Dose-Effect Curves

- **Effective Dose (ED50): is the dose at which 50% of individuals exhibit the specified quantal effect.**
- **Toxic Dose (TD50): is the dose required to produce a particular toxic effect in 50% of animals.**
- **Lethal Dose (LD50): is the dose required to produce death in 50% of the of the animals.**



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Features of Quantal Dose-Effect Curves

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- **Can calculate Therapeutic Index= LD50/ED50**

Therapeutic index and margin of safety

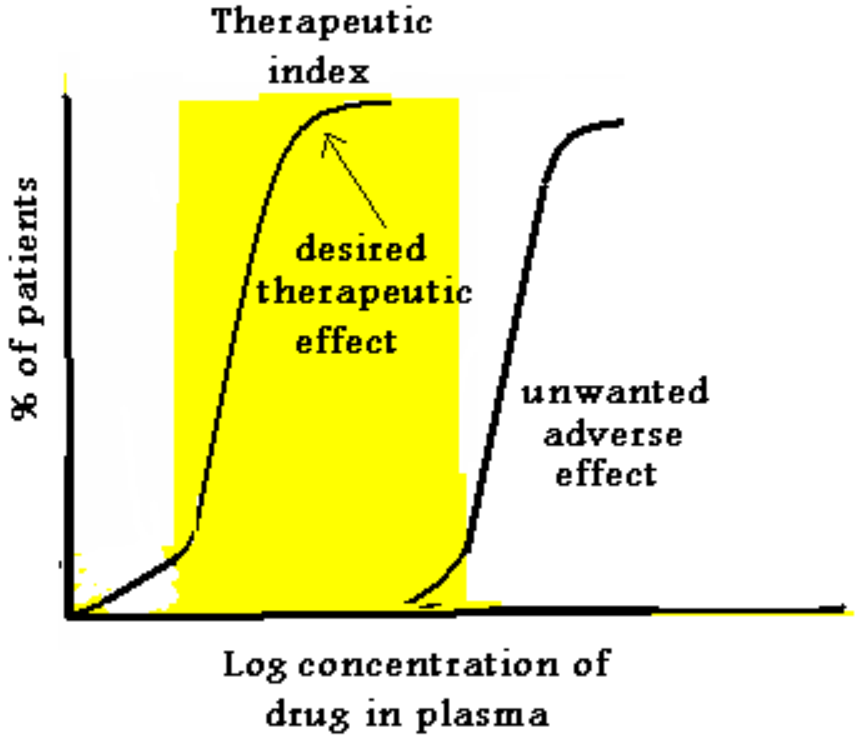
Therapeutic index of a drug is a ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population individuals:

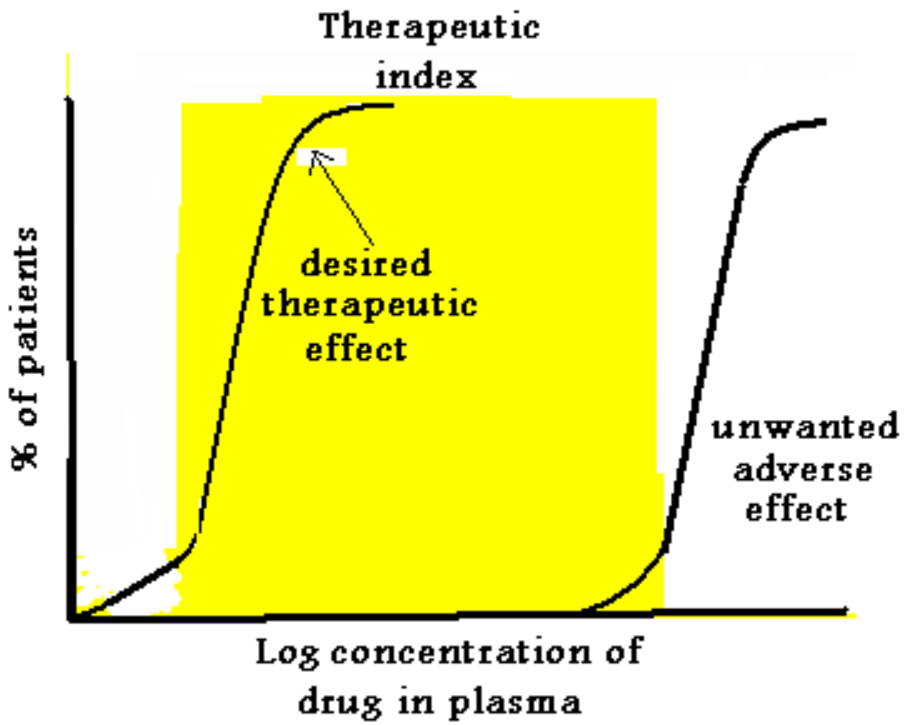
$$TI = \frac{TD_{50}}{ED_{50}}$$

Where TD_{50} is the minimum dose that is lethal or toxic for 50% of the population, and ED_{50} is the minimum dose that is effective for 50% of the population.

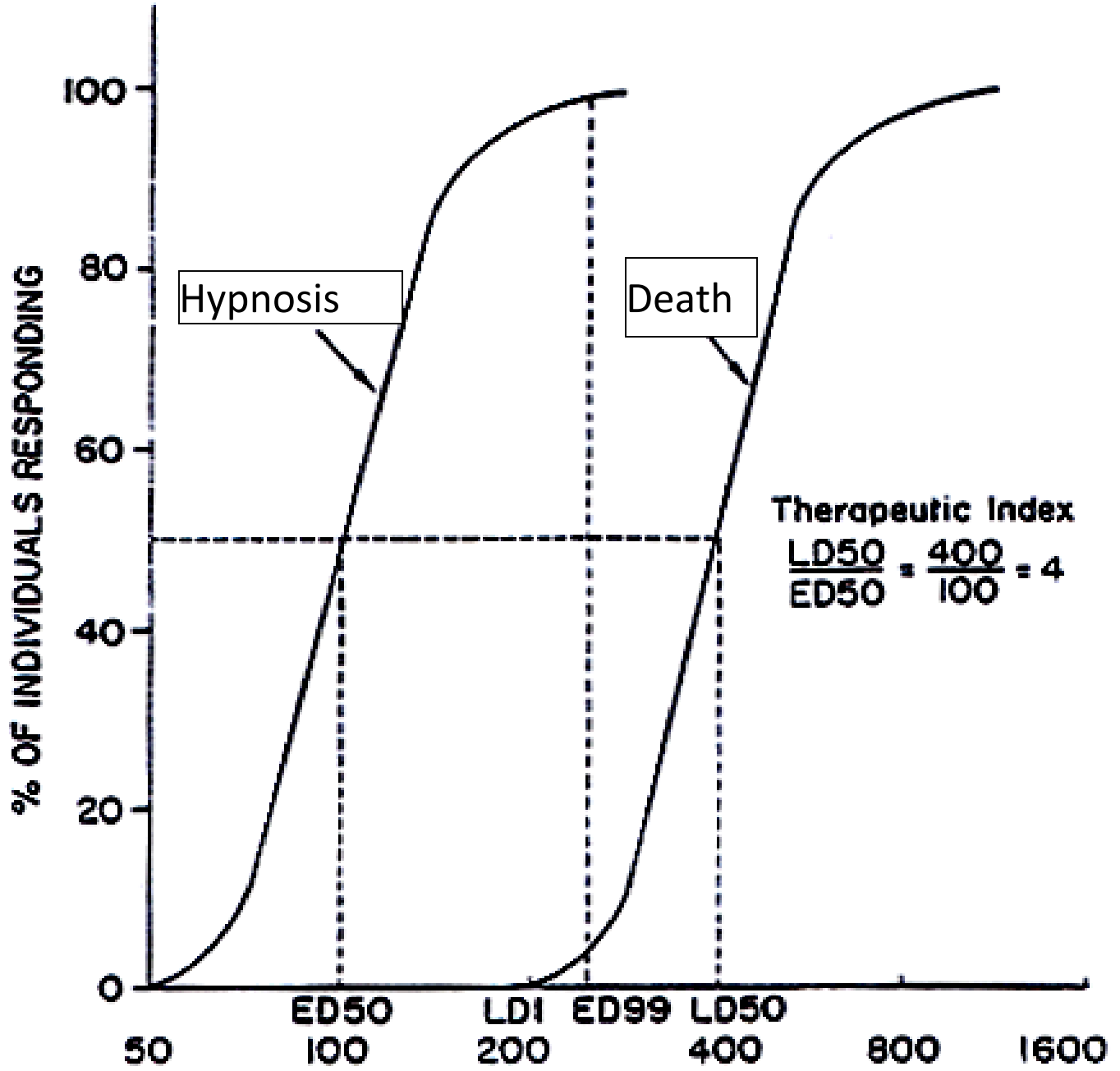
Ideally the TD_{50} Should be a much higher dose than the ED_{50} so that the therapeutic index would be large.

Therapeutic index and margin of safety





THERAPEUTIC INDEX – AN INDEX OF SAFETY



Receptor Regulation

- **Sensitization or Up-regulation**

  1. Prolonged/continuous use of receptor blocker
  2. Inhibition of synthesis or release of hormone/neurotransmitter - Denervation

- **Desensitization or Down-regulation**

  1. Prolonged/continuous use of agonist
  2. Inhibition of degradation or uptake of agonist

Possibilities of Drug Combinations

- **Antagonistic Effects**
- **Additive Effects.**
- **Synergistic Effects.**
- **No effect.**

Possibilities of Drug Combinations

- **Antagonistic Effects**
- **Additive Effects**

Additive drug effect occurs if two drugs with the same effect , when given together produce an effect that is equal in magnitude to the sum of the effect.

$E_{AB} = E_A + E_B$ 1 + 1 = 2

- **Synergistic Effects:**

Interaction between two or more **drugs** or agents resulting in a pharmacologic response greater than the sum of individual responses to each **drug** or agent

$E_{AB} > E_A + E_B$ 1 + 1 > 2

Sulfamethoxazole + trimethoprim

- **Potentiation Effects:**

Potentiation drug effect occurs if a drug lacking an effect of its own increase the effect of a second active drug.

$E_{AB} > E_A + E_B$ 0 + 1 > 1

Causes of Variability in Drug Response

Those related to the biological system

1. Body weight and size
2. Age and Sex
3. Genetics - pharmacogenetics
4. Condition of health
5. Placebo effect

Causes of Variability in Drug Response

- **Those related to the conditions of administration**

1. Dose, formulation, route of administration.

2. Resulting from repeated administration of drug:

drug resistance; drug tolerance-tachyphylaxis; drug allergy

3. Drug interactions:

chemical or physical;
GI absorption;
protein binding/distribution;
metabolism (stimulation/inhibition);
excretion (pH/transport processes);
receptor (potentiation/antagonism);
changes in pH or electrolytes.

Sources of Variability in Therapeutic Responses

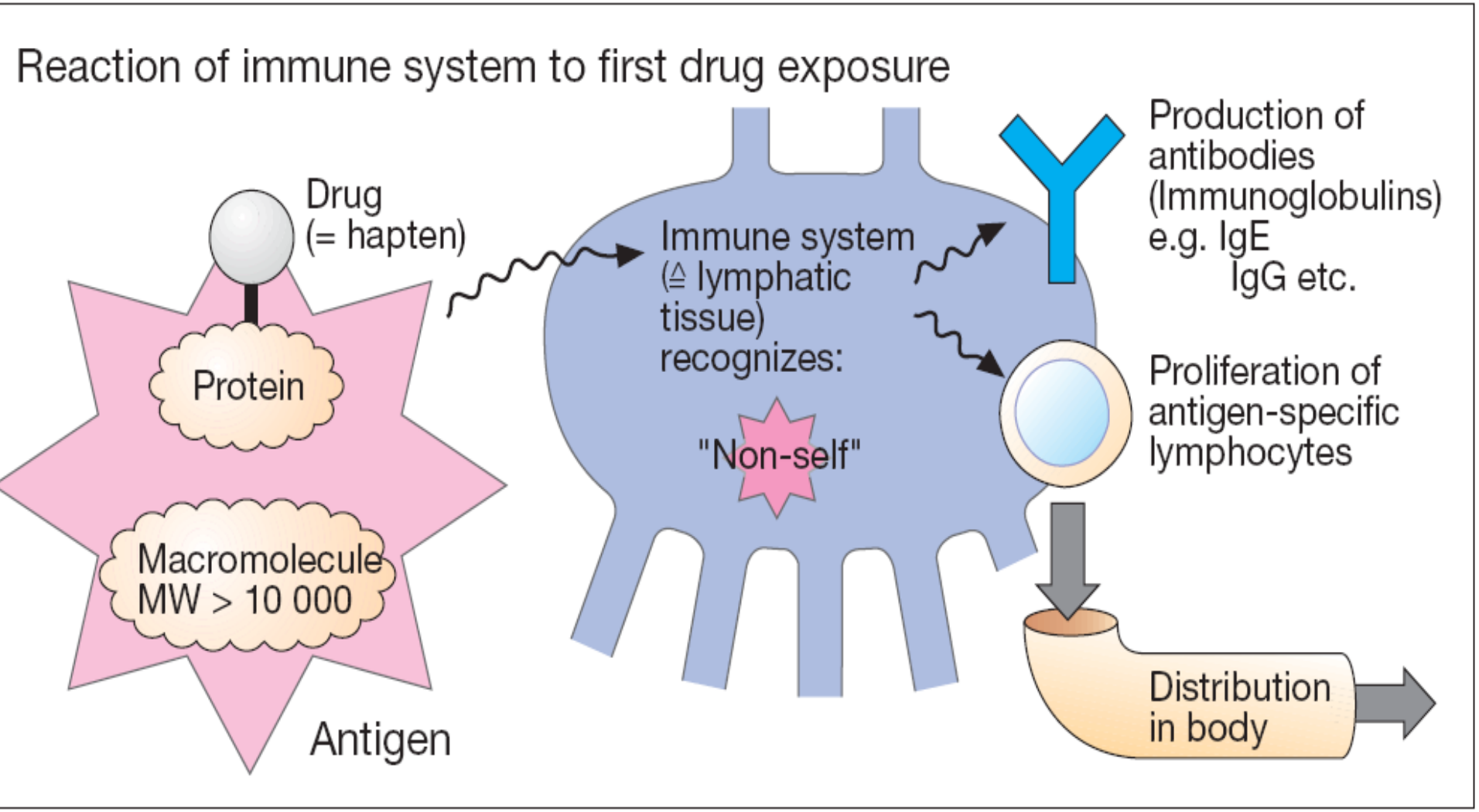
Similar drugs usually produce similar qualities of responses in patients, but might produce different intensities and duration of effects.

- **Dose, Dosage schedule, and Route of administration.**
- **Diurnal variation ”Chronopharmacology”.**
- **Age and sex of the patient.**
- **Drug reactions.**
- **Drug interactions: other drugs, diet, and environment.**
- **Placebo effect.**
- **Intercurrent illnesses.**
- **Tolerance.**
- **Genetic or racial factors, “Pharmacogenetics”.**

Drug Allergy

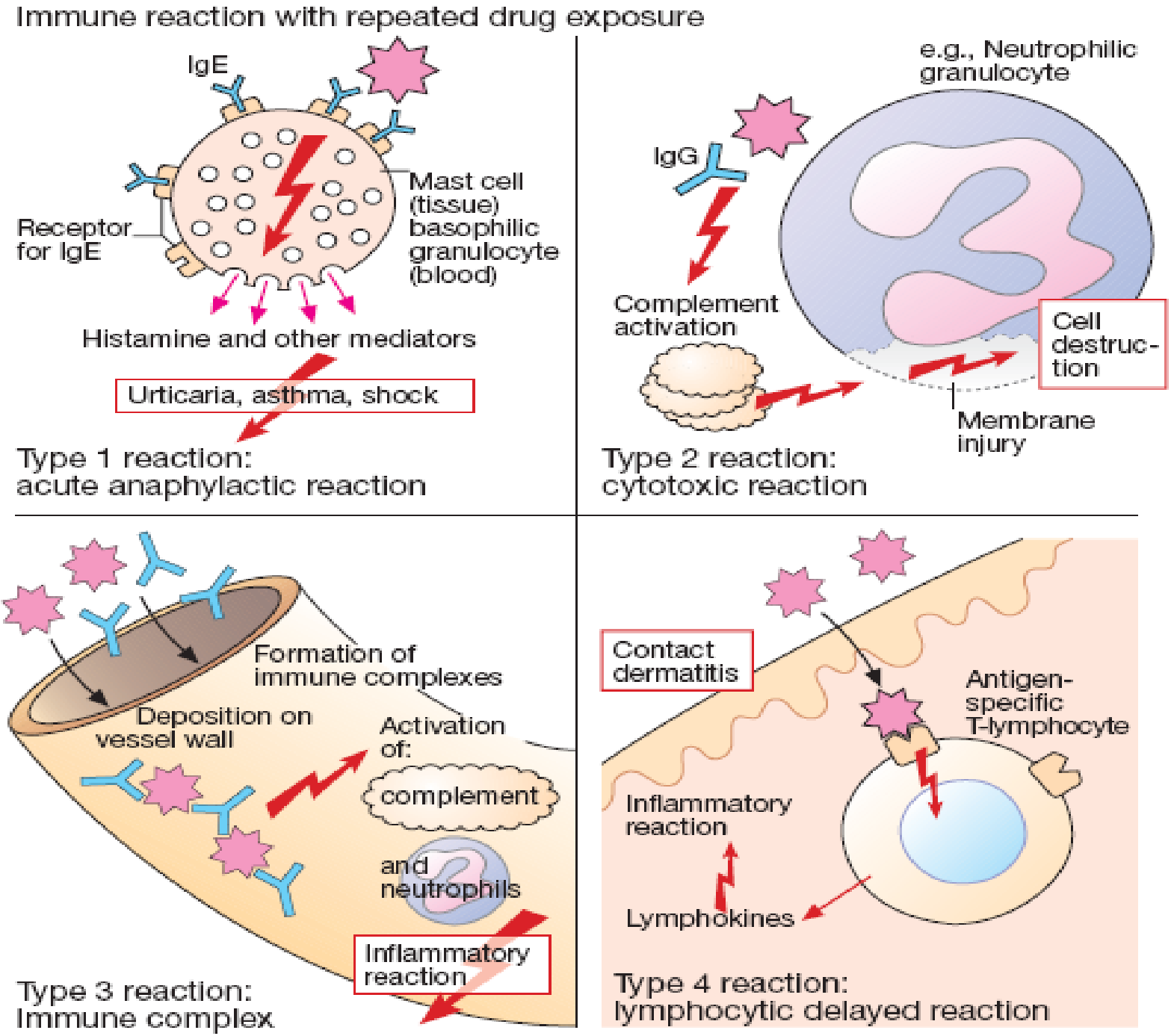
- It is defined as an adverse reaction to a drug by a specific immune response either directly to the drug or one or more of its metabolites alone, or to a drug bound to a body protein such as albumin, (*Hapten*).

- Such binding alters the structure of the drug/protein complex, rendering it antigenic.


Reaction of immune system to first drug exposure
Drug
(= hapten)
Protein
Macromolecule
MW > 10 000
Antigen
Immune system
(≙ lymphatic
tissue)
recognizes:
"Non-self"
Production of
antibodies
(Immunoglobulins)
e.g. IgE
IgG etc.
Proliferation of
antigen-specific
lymphocytes
Distribution
in body

Classification of Allergic Reactions

Type	Mechanism	Time	Example
I	Anaphylactic	sec/min	Angioedema
II	Cytotoxic	--	Transfusion rx
III	Immune	6-8hrs	Serum sickness complex
IV	Cell mediated	48 hrs	Contact dermatitis


Immune reaction with repeated drug exposure
IgE
Mast cell (tissue) basophilic granulocyte (blood)
Receptor for IgE
Histamine and other mediators
Urticaria, asthma, shock
Type 1 reaction: acute anaphylactic reaction
e.g., Neutrophilic granulocyte
IgG
Complement activation
Cell destruc-tion
Membrane injury
Type 2 reaction: cytotoxic reaction
Formation of immune complexes
Deposition on vessel wall
Activation of:
complement
and neutrophils
Inflammatory reaction
Type 3 reaction: Immune complex
Contact dermatitis
Antigen-specific T-lymphocyte
Inflammatory reaction
Lymphokines
Type 4 reaction: lymphocytic delayed reaction

Definitions

- **Two general principles that every student should always remember:**

1. **All substances can under certain conditions be toxic.**
2. **All dietary supplements and all substances promoted as health-enhancing should meet the same standards of efficacy and safety as drugs.**

Terms

- **Prescription:** the written direction for the preparation and the administration of the drug.

- **The therapeutic effect**: is the primary effect intended that is the reason the drug is prescribed such as morphine sulfate is analgesia.

- **Side effect:** secondary effect of the drug is one that unintended, side effects are usually predictable and may be either harmless

Conti…….

- **Drug toxicity:** deleterious effect of the drug on an organism or tissue, result from overdose or external use.

- **Drug interaction:** occur when administration of one drug before or after alter effect of one or both drug.

Conti…….

- **Drug misuse:** Is the improper use of common medications in way that lead to acute and chronic toxicity for example laxative, antacid and vitamins.

- **Drug abuse:** is an inappropriate intake of substance either continually or periodically.

Definitions

Pharmacotherapeutics:

Is the use of drugs in the prevention and treatment of disease (or the medical uses of drugs).

Chemotherapeutics:

Is the use of drugs to stop the growth or kill microorganisms or cancer cells.

Definitions

Pharmacogenomics:

The relation between the individual's genetic makeup to his/her response to specific drugs (entire genome).

Pharmacogenetics:

Interindividual variation in drug response that is due to genetic influences (specific gene).

Definitions

Idiosyncratic drug response:

Unusual response, infrequently observed in most patients. Usually caused by genetic differences in metabolism of drug, or by immunologic mechanisms including allergic reactions.

Definitions

Tolerance:

Is a decrease in the responsiveness to the drug with continued drug administration.

Tachyphylaxis:

Similar to tolerance but more rapid.

Areas of Pharmacology

Pharmacodynamics:

Is what the drug does to the body, which includes the biochemical and physiological effects of the drug, including the mechanism of action, interaction with receptors as well as the adverse effects.

Areas of Pharmacology

Pharmacokinetics:

- **Is what the body does to the drug.**
- **Deals with absorption, distribution, biotransformation and excretion of drugs:**

1. **Absorption: Is the movement of drug molecules from the site of administration into the circulation.**

Areas of Pharmacology

2. **Distribution: Is the movement of drug molecules from the circulation to tissues and between different parts of the body.**
3. **Biotransformation: Is conversion of the drug from one chemical structure into another by the action of metabolic enzymes (metabolism).**
4. **Excretion: Is the movement of drug molecules out of the body.**

Pharmacoepidemiology

- **The study of the utilization and effects of drugs in large numbers of patients.**
- **It applies epidemiological techniques to study drug use in a large population. Epidemiology is the study of the factors that determine the occurrence and distribution of diseases in populations.**

Properties of an Ideal Drug

- Effective
- Safety
- Selective
- Reversible Action
- Predictable
- Freedom from drug interactions
- Low cost
- Chemically stable