CLINICAL PHARMACOKINETICS

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USES OF PHARMACOKINETICS

- Basis for *rational dose selection* in therapeutics
- Development and *evaluation of new drugs*
- Basic studies of *drug distribution* (PET Scan)

TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE

TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE

⇩

BEGIN THERAPY

⇩

ASSESS THERAPY
PATIENT RESPONSE
DRUG LEVEL

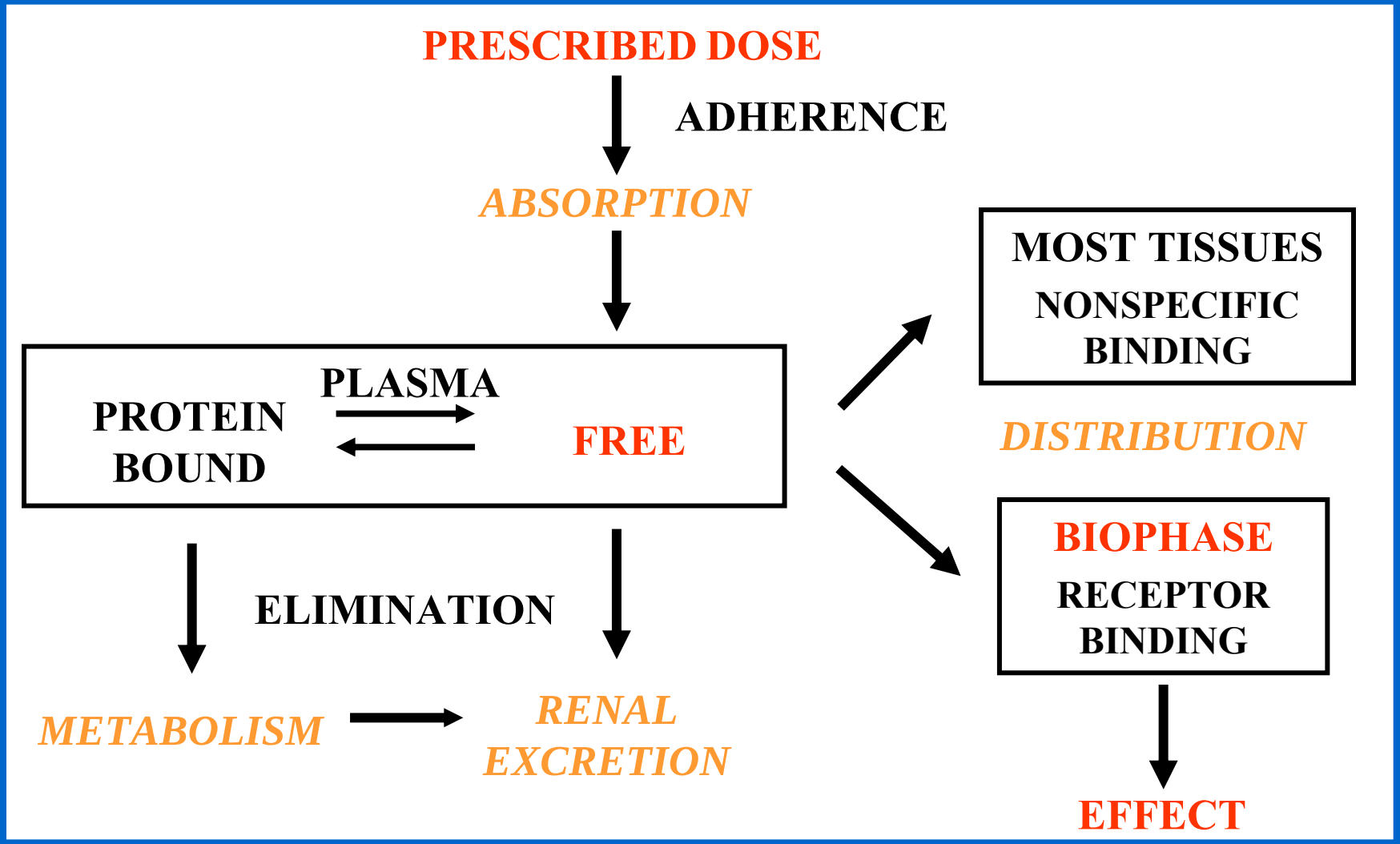
⇩

REFINE DOSE ESTIMATE

⇩

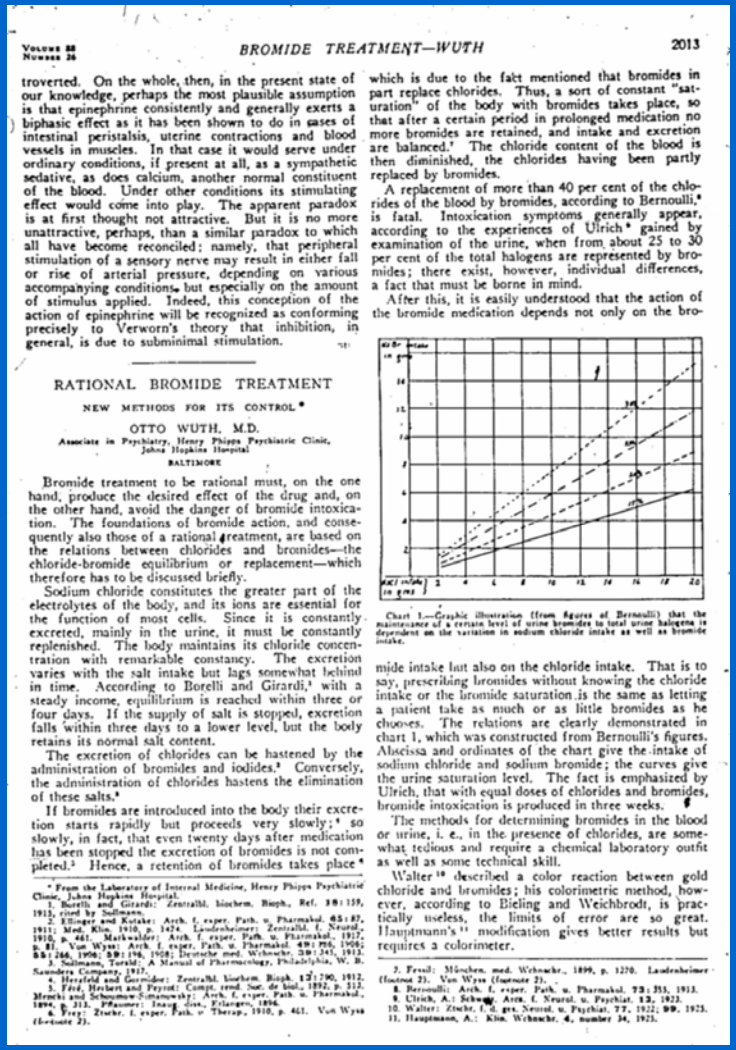
ADJUST DOSE

RATIONALE FOR PLASMA LEVEL MONITORING



FIRST DESCRIPTION OF THERAPEUTIC DRUG MONITORING

Wuth O. JAMA 1927;88:2013-17.



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BROMIDE TREATMENT—WUTH

2013

troverted. On the whole, then, in the present state of our knowledge, perhaps the most plausible assumption is that epinephrine consistently and generally exerts a biphasic effect as it has been shown to do in cases of intestinal peristalsis, uterine contractions and blood vessels in muscles. In that case it would serve under ordinary conditions, if present at all, as a sympathetic sedative, as does calcium, another normal constituent of the blood. Under other conditions its stimulating effect would come into play. The apparent paradox is at first thought not attractive. But it is no more unattractive, perhaps, than a similar paradox to which all have become reconciled; namely, that peripheral stimulation of a sensory nerve may result in either fall or rise of arterial pressure, depending on various accompanying conditions, but especially on the amount of stimulus applied. Indeed, this conception of the action of epinephrine will be recognized as conforming precisely to Verworn's theory that inhibition, in general, is due to subminimal stimulation.

RATIONAL BROMIDE TREATMENT

NEW METHODS FOR ITS CONTROL *

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Bromide treatment to be rational must, on the one hand, produce the desired effect of the drug and, on the other hand, avoid the danger of bromide intoxication. The foundations of bromide action, and consequently also those of a rational treatment, are based on the relations between chlorides and bromides—the chloride-bromide equilibrium or replacement—which therefore has to be discussed briefly.

Sodium chloride constitutes the greater part of the electrolytes of the body, and its ions are essential for the function of most cells. Since it is constantly excreted, mainly in the urine, it must be constantly replenished. The body maintains its chloride concentration with remarkable constancy. The excretion varies with the salt intake but lags somewhat behind in time. According to Borelli and Girardi,[1] with a steady income, equilibrium is reached within three or four days. If the supply of salt is stopped, excretion falls within three days to a lower level, but the body retains its normal salt content.

The excretion of chlorides can be hastened by the administration of bromides and iodides.[2] Conversely, the administration of chlorides hastens the elimination of these salts.[3]

If bromides are introduced into the body their excretion starts rapidly but proceeds very slowly;[4] so slowly, in fact, that even twenty days after medication has been stopped the excretion of bromides is not completed.[5] Hence, a retention of bromides takes place which is due to the fact mentioned that bromides in part replace chlorides. Thus, a sort of constant "saturation" of the body with bromides takes place, so that after a certain period in prolonged medication no more bromides are retained, and intake and excretion are balanced.[6] The chloride content of the blood is then diminished, the chlorides having been partly replaced by bromides.

A replacement of more than 40 per cent of the chlorides of the blood by bromides, according to Bernoulli,[8] is fatal. Intoxication symptoms generally appear, according to the experiences of Ulrich [9] gained by examination of the urine, when from about 25 to 30 per cent of the total halogens are represented by bromides; there exist, however, individual differences, a fact that must be borne in mind.

After this, it is easily understood that the action of the bromide medication depends not only on the bromide intake but also on the chloride intake. That is to say, prescribing bromides without knowing the chloride intake or the bromide saturation is the same as letting a patient take as much or as little bromides as he chooses. The relations are clearly demonstrated in chart 1, which was constructed from Bernoulli's figures. Abscissa and ordinates of the chart give the intake of sodium chloride and sodium bromide; the curves give the urine saturation level. The fact is emphasized by Ulrich, that with equal doses of chlorides and bromides, bromide intoxication is produced in three weeks.

Chart 1.—Graphic illustration (from figures of Bernoulli) that the maintenance of a certain level of urine bromides to total urine halogens is dependent on the variation in sodium chloride intake as well as bromide intake.

The methods for determining bromides in the blood or urine, i. e., in the presence of chlorides, are somewhat tedious and require a chemical laboratory outfit as well as some technical skill.

Walter [10] described a color reaction between gold chloride and bromides; his colorimetric method, however, according to Bieling and Weichbrodt, is practically useless, the limits of error are so great. Hauptmann's [11] modification gives better results but requires a colorimeter.

* From the Laboratory of Internal Medicine, Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital.

1. Borelli and Girardi: Zentralbl. biochem. Biophy., Ref. 18: 159, 1915, cited by Sollmann.
2. Ellinger and Kotake: Arch. f. exper. Path. u. Pharmakol. 65: 87, 1911; Med. Klin. 1910, p. 1424; Landesheimer: Zentralbl. f. Neurol., 1910, p. 461; Mailwalder: Arch. f. exper. Path. u. Pharmakol., 1917; 81: 1; Von Wyss: Arch. f. exper. Path. u. Pharmakol. 49: 196, 1906; 55: 266, 1906; 59: 194, 1908; Deutsche med. Wchnschr. 30: 345, 1913.
3. Sollmann, Torald: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1917.
4. Herzfeld and Gerrider: Zentralbl. biochem. Biophy. 12: 290, 1912.
5. Féré, Herbert and Feyrot: Compt. rend. Soc. de biol., 1892, p. 512; Mercki and Schoumow-Simanowsky: Arch. f. exper. Path. u. Pharmakol., 1894, p. 313; Pfaumer: Inaug. diss., Erlangen, 1896.
6. Frey: Ztschr. f. exper. Path. u. Therap., 1910, p. 461; Von Wyss (footnote 2).
7. Freud: München. med. Wchnschr., 1899, p. 1270; Landesheimer (footnote 2); Von Wyss (footnote 2).
8. Bernoulli: Arch. f. exper. Path. u. Pharmakol. 73: 351, 1913.
9. Ulrich, A.: Schweiz. Arch. f. Neurol. u. Psychiat. 13, 1923.
10. Walter: Ztschr. f. d. ges. Neurol. u. Psychiat. 77, 1922; 99, 1925.
11. Hauptmann, A.: Klin. Wchnschr. 4, number 34, 1925.

RADIOIMMUNOASSAY

Rosalyn Sussman Yalow -1977 Nobel Laureate

GAS LIQUID CHROMATOGRAPHY

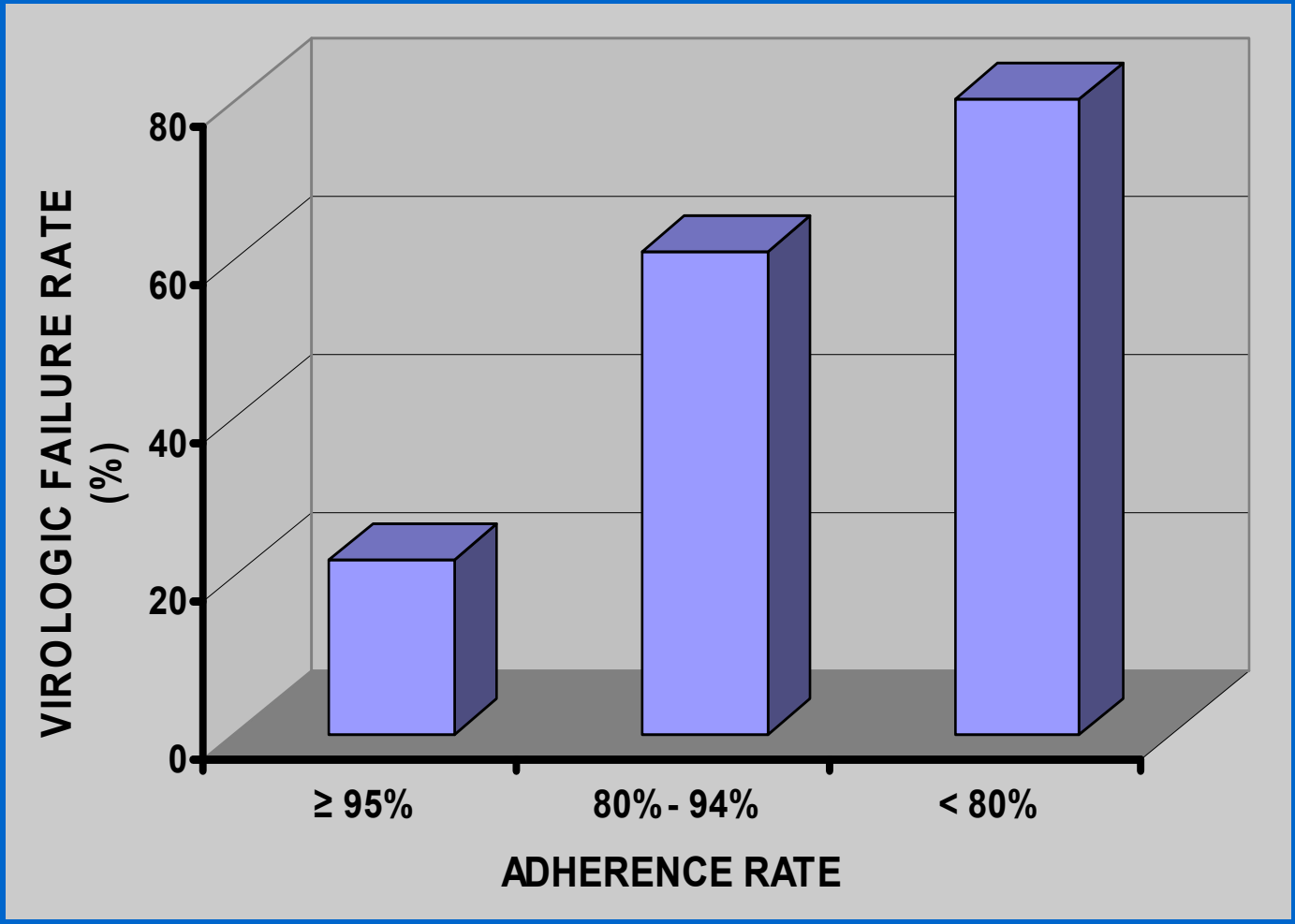
HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

FLUORESCENCE POLARIZATION IMMUNOASSAY

DRUG CANDIDATES FOR TDM

- Low therapeutic index
- No physiologic or therapeutic endpoints to guide dosage
- Pharmacokinetics vary widely between individuals
- Need to monitor adherence?

EFFECT OF *ADHERENCE* RATE ON OUTCOME IN HIV INFECTED PATIENTS



From: Paterson DL, et al. Ann Intern Med 2000;133:21-30.

INDICATIONS for Measuring Blood Levels

- To evaluate *suspected toxicity*
- To evaluate actual or potential *lack of therapeutic efficacy*
- To monitor *prophylactic therapy*
- To guide *dose adjustment*

TARGET CONCENTRATION STRATEGY

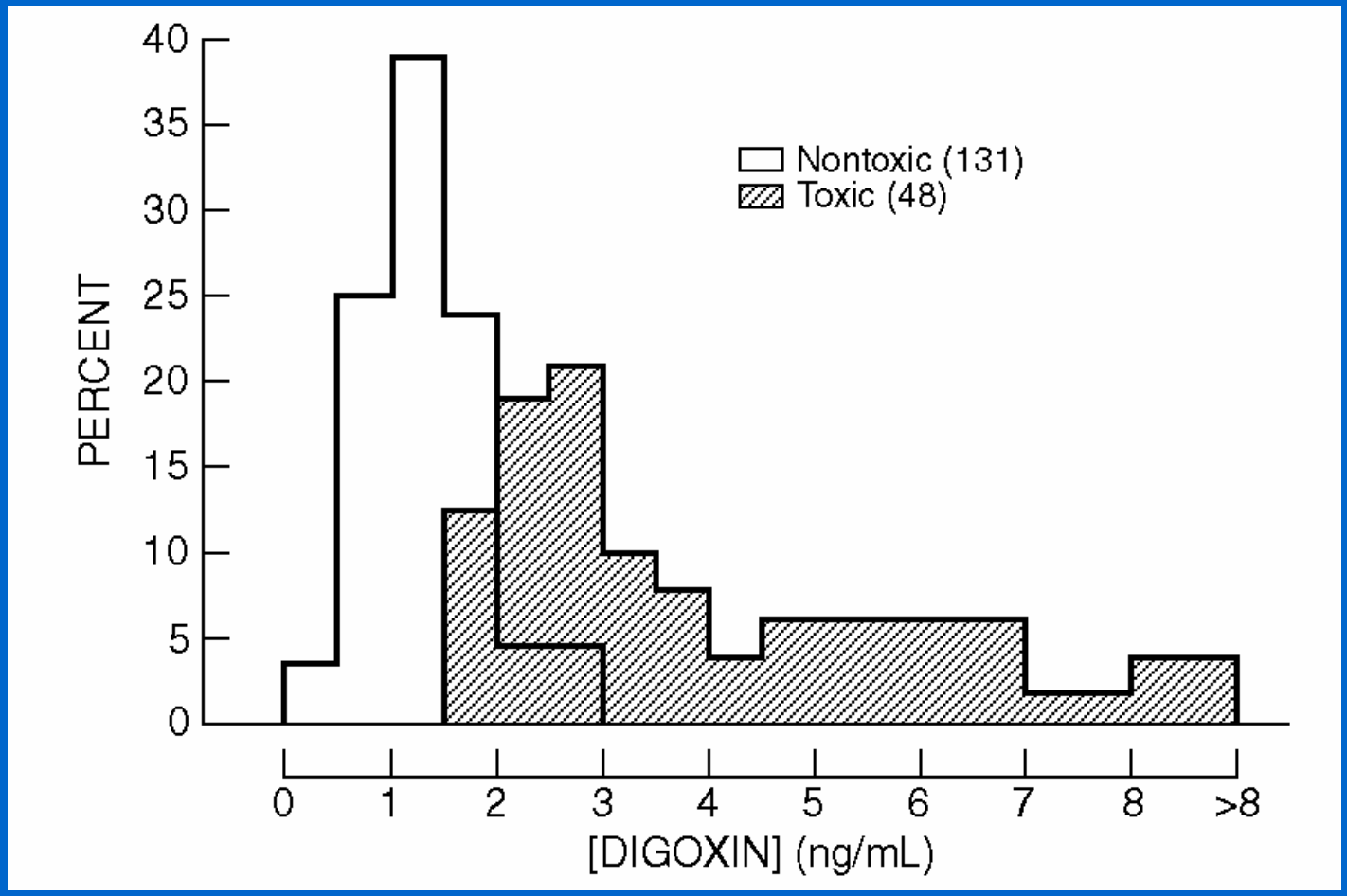
ESTIMATE INITIAL DOSE

TARGET LEVEL

LOADING DOSE

MAINTENANCE DOSE

DIGOXIN Levels in *TOXIC* and *NONTOXIC* Patients*



* From Smith TW and Haber E. J Clin Invest 1970;49:2377-86.

DIGOXIN: Factors Influencing *OUTCOME in "GREY ZONE"*

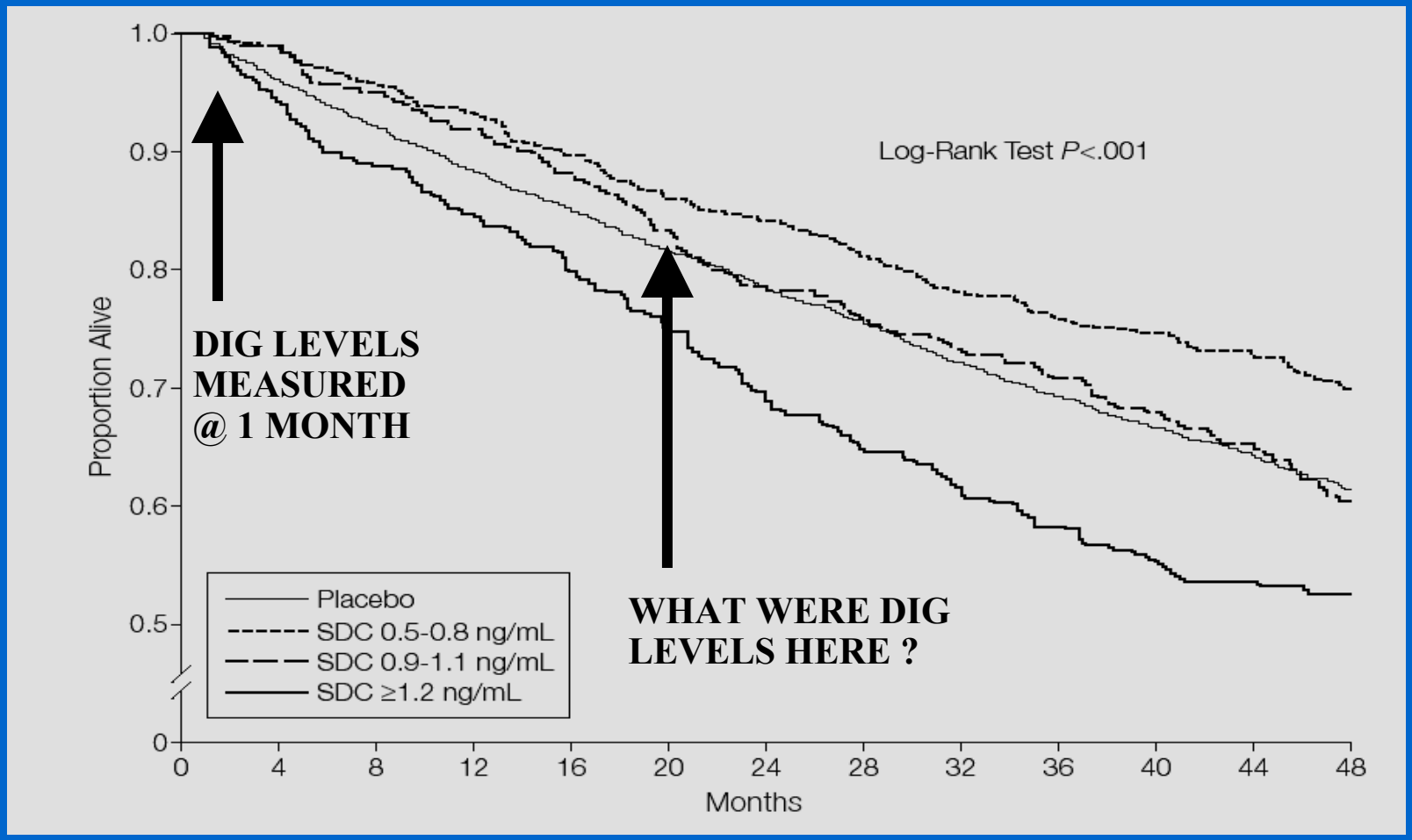
↑ **Risk of toxicity in patients with coronary heart disease, hypoxemia, and/or hypokalemia, hypomagnesemia**

↓ **ECG evidence of toxicity if concurrent therapy with antiarrhythmic drugs**

TRADITIONAL Guidelines for DIGOXIN Levels

THERAPEUTIC RANGE:	**0.8 - 1.6 ng/mL**
***POSSIBLY* TOXIC LEVELS:**	**1.6 - 3.0 ng/mL**
***PROBABLY* TOXIC LEVELS:**	**> 3.0 ng/mL**

SURVIVAL as a function of DIGOXIN LEVEL measured after 1 Month Rx*



* Rathore SS, et al. JAMA 2003;289:871-8.

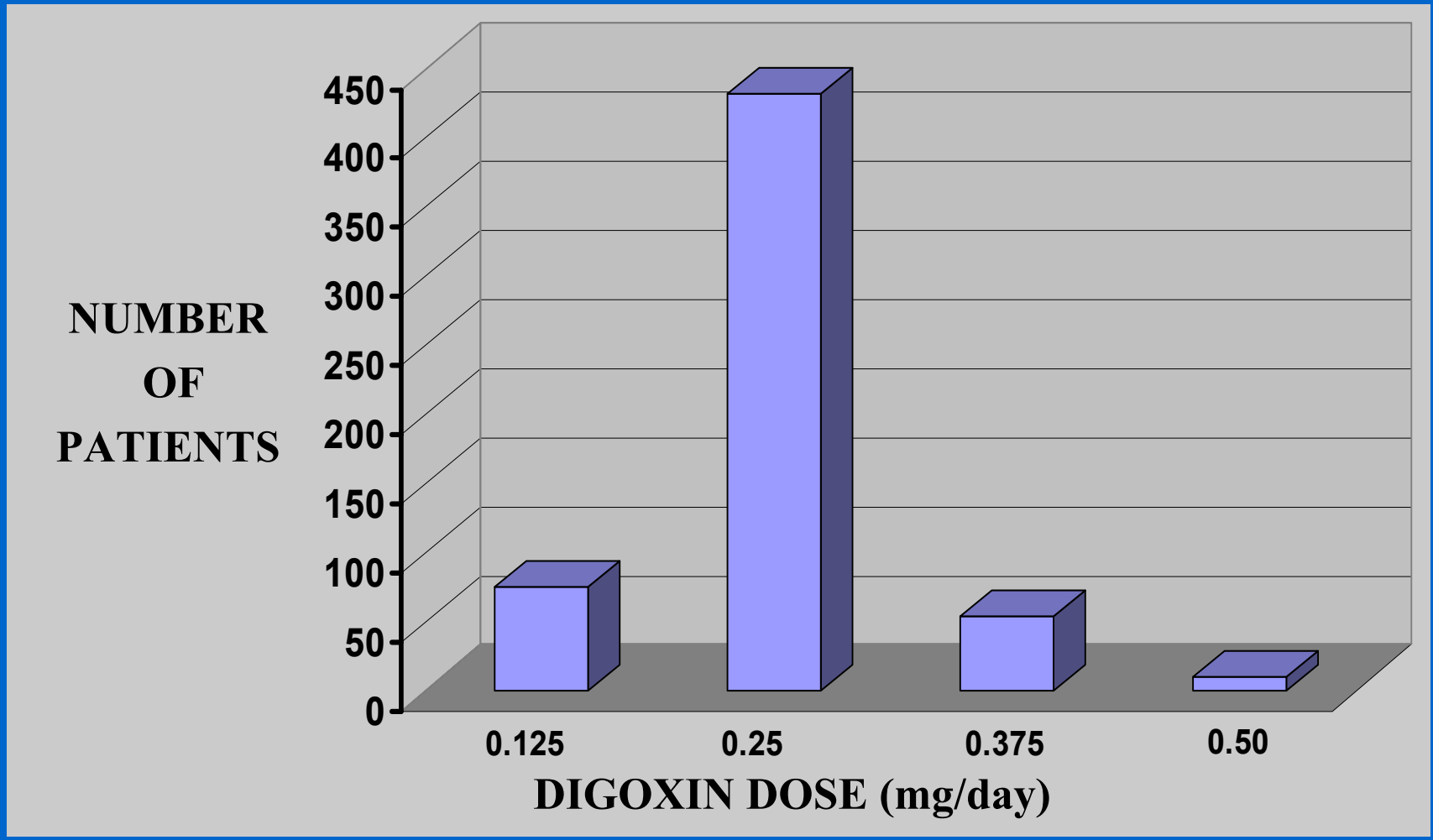
PROPOSED Range of DIGOXIN LEVELS for *OPTIMAL THERAPY* in CHF

New Therapeutic Range: 0.5 - 0.9 ng/mL

Benefit results from *INHIBITION OF SYMPATHETIC NERVOUS SYSTEM* rather than ↑ INOTROPY

BUT DIGOXIN *DOSES PRESCRIBED* FOR PATIENTS WITH THIS RANGE OF DIGOXIN LEVELS *SHOULD HAVE BEEN ASSOCIATED WITH HIGHER LEVELS*?

DIGOXIN DOSES for Patients with Levels of 0.5 - 0.8 ng/mL



Rathore SS, et al. JAMA 2003, 289:871-8.

TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE

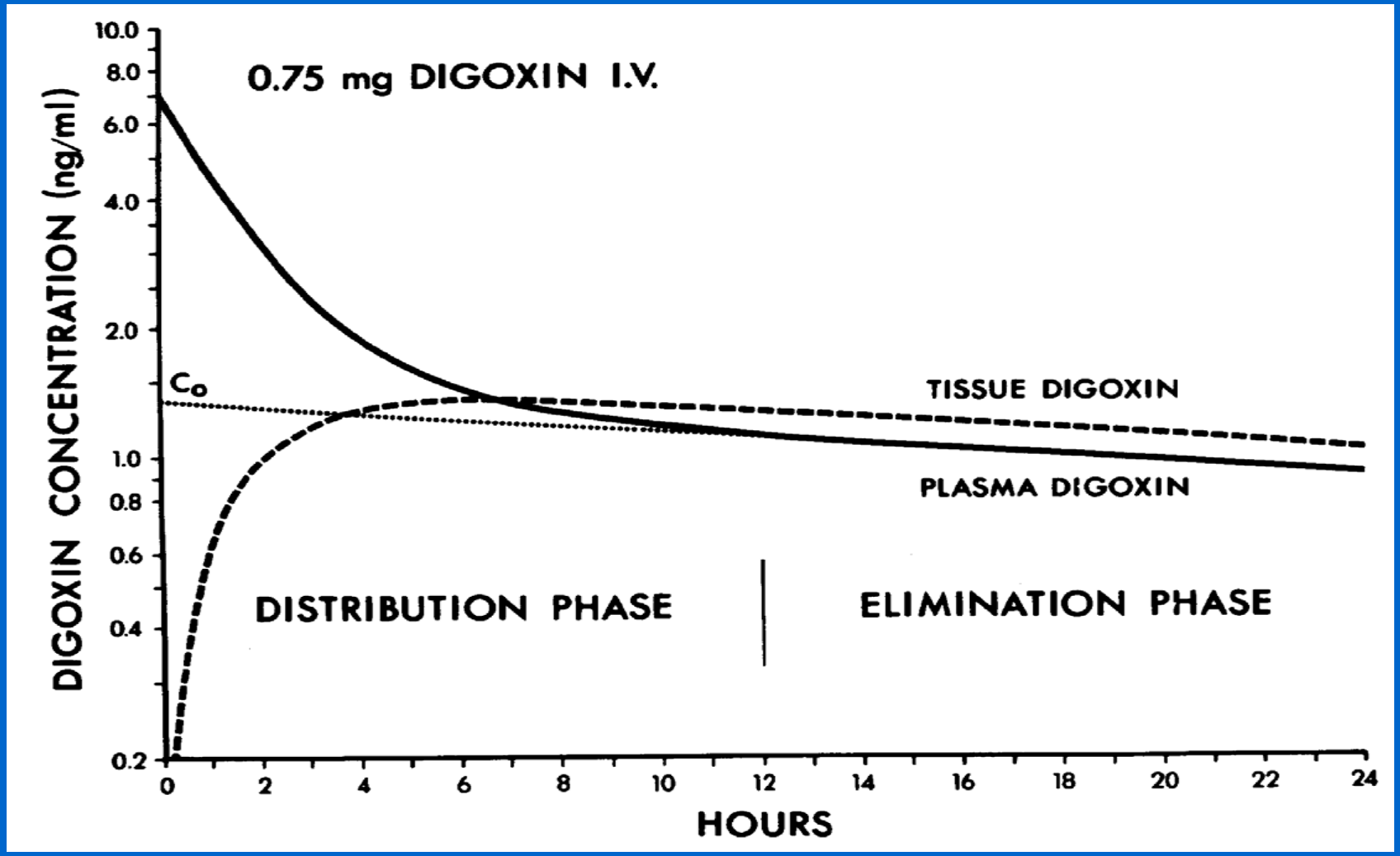
TARGET LEVEL

LOADING DOSE

MAINTENANCE DOSE

BASED ON CONCEPT OF DISTRIBUTION VOLUME

DIGOXIN LEVELS after IV Dose

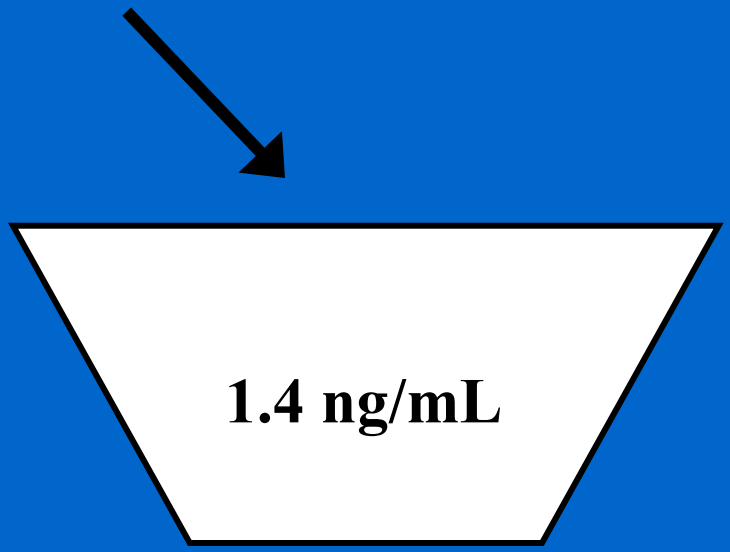


INITIAL *DIGITALIZATION*

DIGITALIZING DOSE

0.75 mg = 750 x 10^3 ng

$$V_d = \frac{750 \times 10^3 \text{ ng}}{1.4 \text{ ng/mL}} = 536 \text{ L}$$



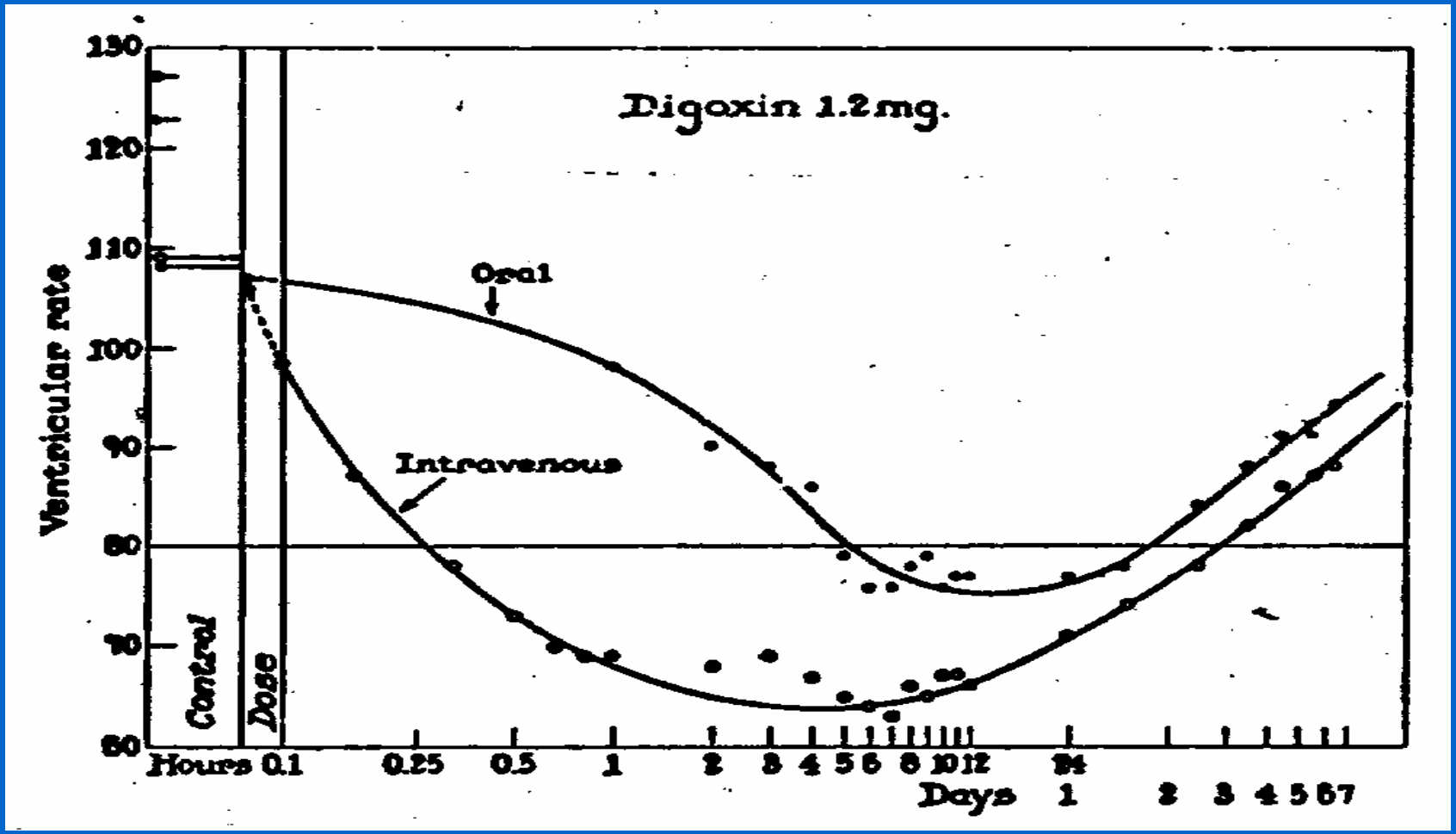
3 DISTRIBUTION VOLUMES

$$V_{d\,(extrap.)} = DOSE \,/\, C_0$$

$$V_{d\,(area)} = \frac{t_{1/2} \bullet CL_E}{0.693}$$

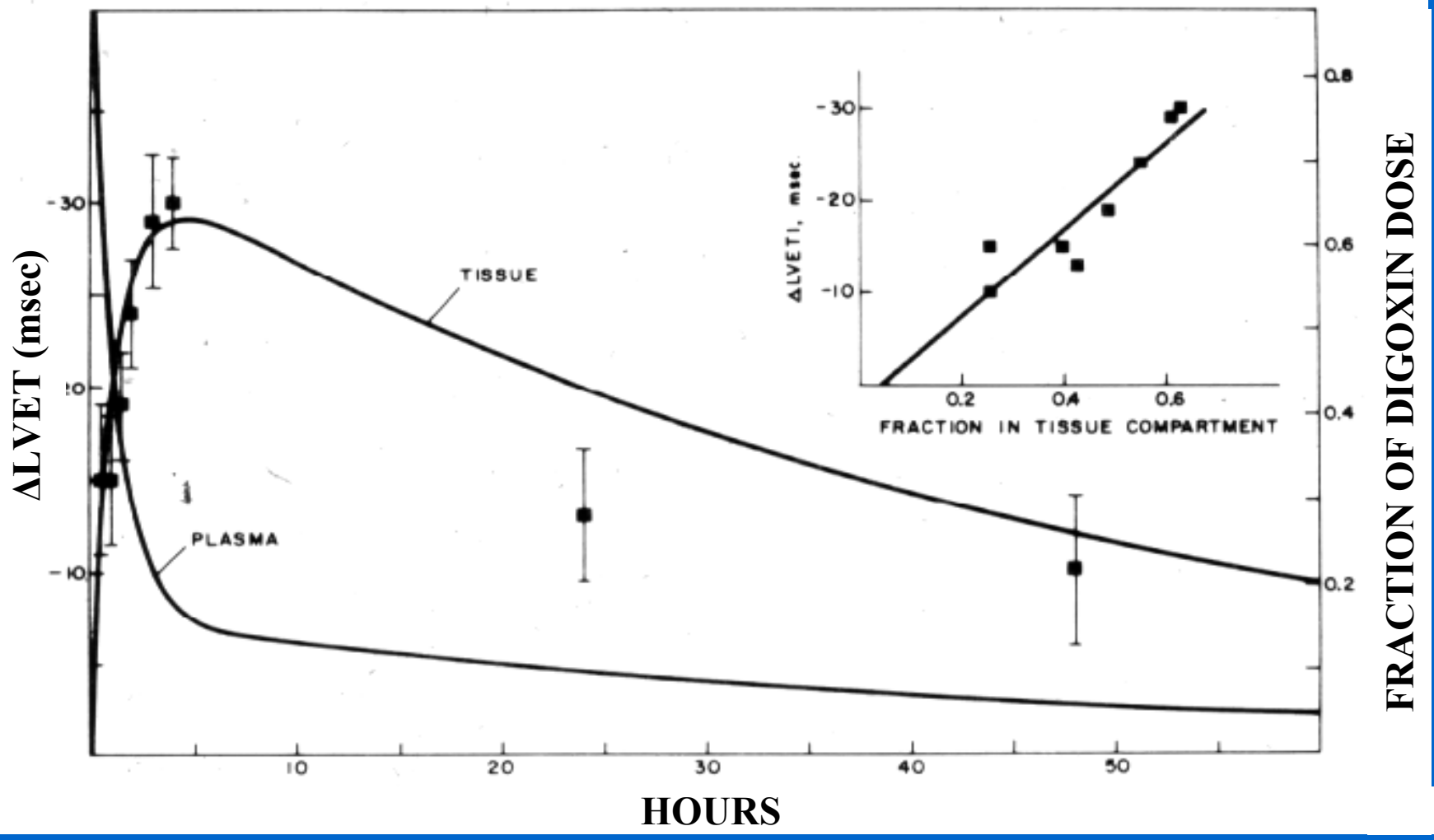
$$V_{d\,(ss)} = V_1 + V_2 + \ldots\ldots V_n$$

DISTRIBUTION DELAYS ONSET of DIGOXIN Chronotropic Action*



* From Gold H, et al. J Pharmacol Exp Ther 1953;109:45-57.

DISTRIBUTION DELAYS ONSET of DIGOXIN Inotropic Action*



TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE

TARGET LEVEL

LOADING DOSE

MAINTENANCE DOSE

BASED ON CONCEPTS OF ELIMINATION HALF LIFE AND CLEARANCE

ELIMINATION HALF-LIFE

ELIMINATION HALF-LIFE IS THE *TIME REQUIRED* FOR THE PLASMA CONCENTRATION (OR TOTAL BODY STORES) OF A DRUG *TO FALL TO HALF* OF THE CONCENTRATION (OR AMOUNT) PRESENT AT SOME PREVIOUS TIME.

ELIMINATION PARAMETERS

$$t_{1/2} = \frac{0.693 \ V_d}{CL_E}$$

$$k = \frac{0.693}{t_{1/2}}$$

$$CL_E = k \times V_d$$

$t_{1/2}$ = elimination half life

k = elimination rate constant

CL_E = elimination clearance

MAINTENANCE DIGOXIN THERAPY

MAINTENANCE DOSE
0.25 mg

NORMAL DAILY LOSS:
= 1/3 Total Body Stores
= 1/3 (0.75) mg
= 0.25 mg

DAILY LOSS
0.25 mg

DIGOXIN CUMULATION

.25 x 2/3 = .17 DOSE #1

+.25 DOSE #2

.42 x 2/3 = .28

+.25 DOSE #3

.53 x 2/3 = .36

+.25 DOSE #4

.61 x 2/3 = .41

+.25 DOSE #5

.66 x 2/3 = .44

+.25 DOSE #6

.69 x 2/3 = .46

+.25 DOSE #7

.71

CUMULATION FACTOR

$$CF = \frac{1}{\left(1 - e^{-k\tau}\right)}$$

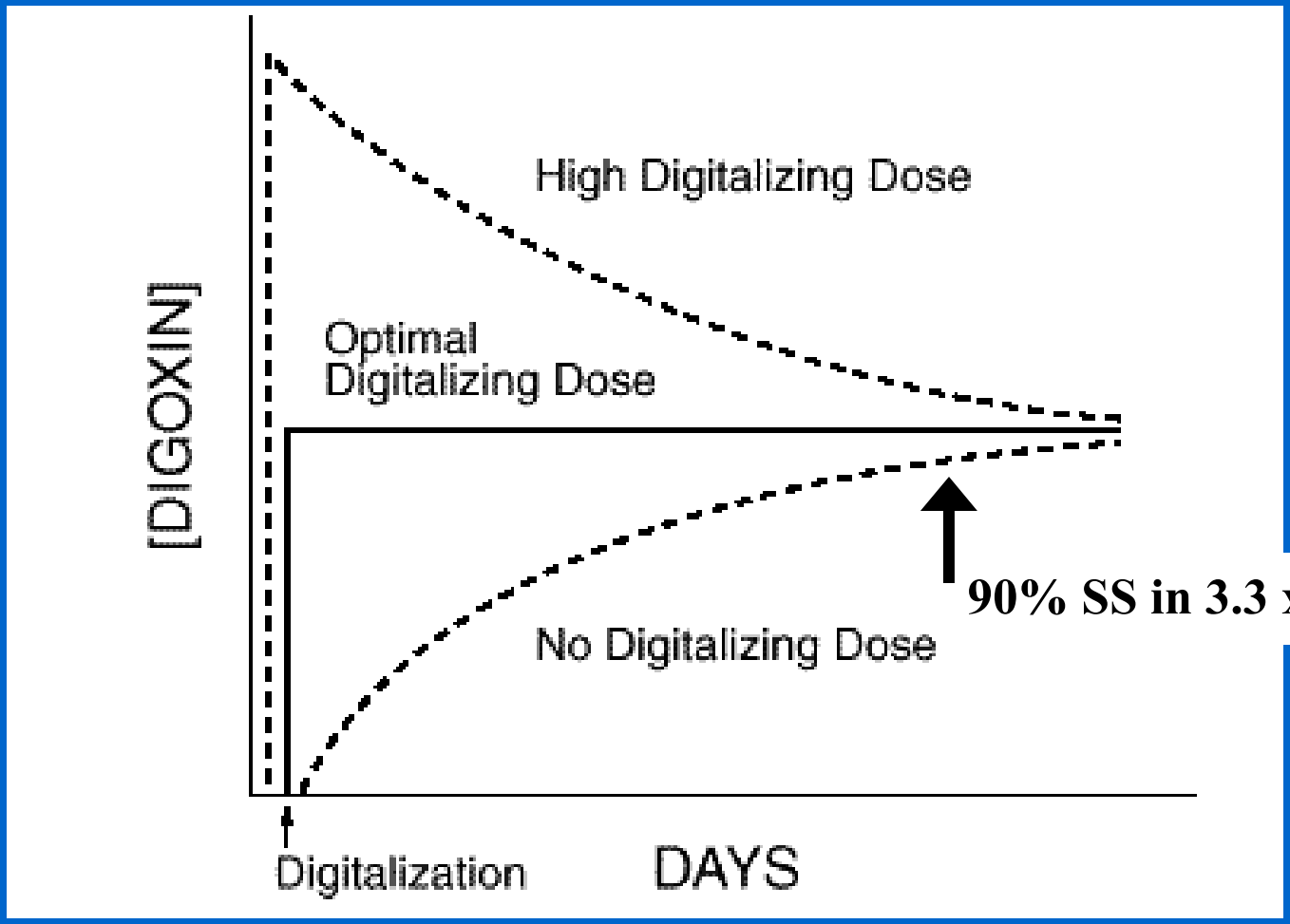
τ = dose interval

k = elimination rate constant

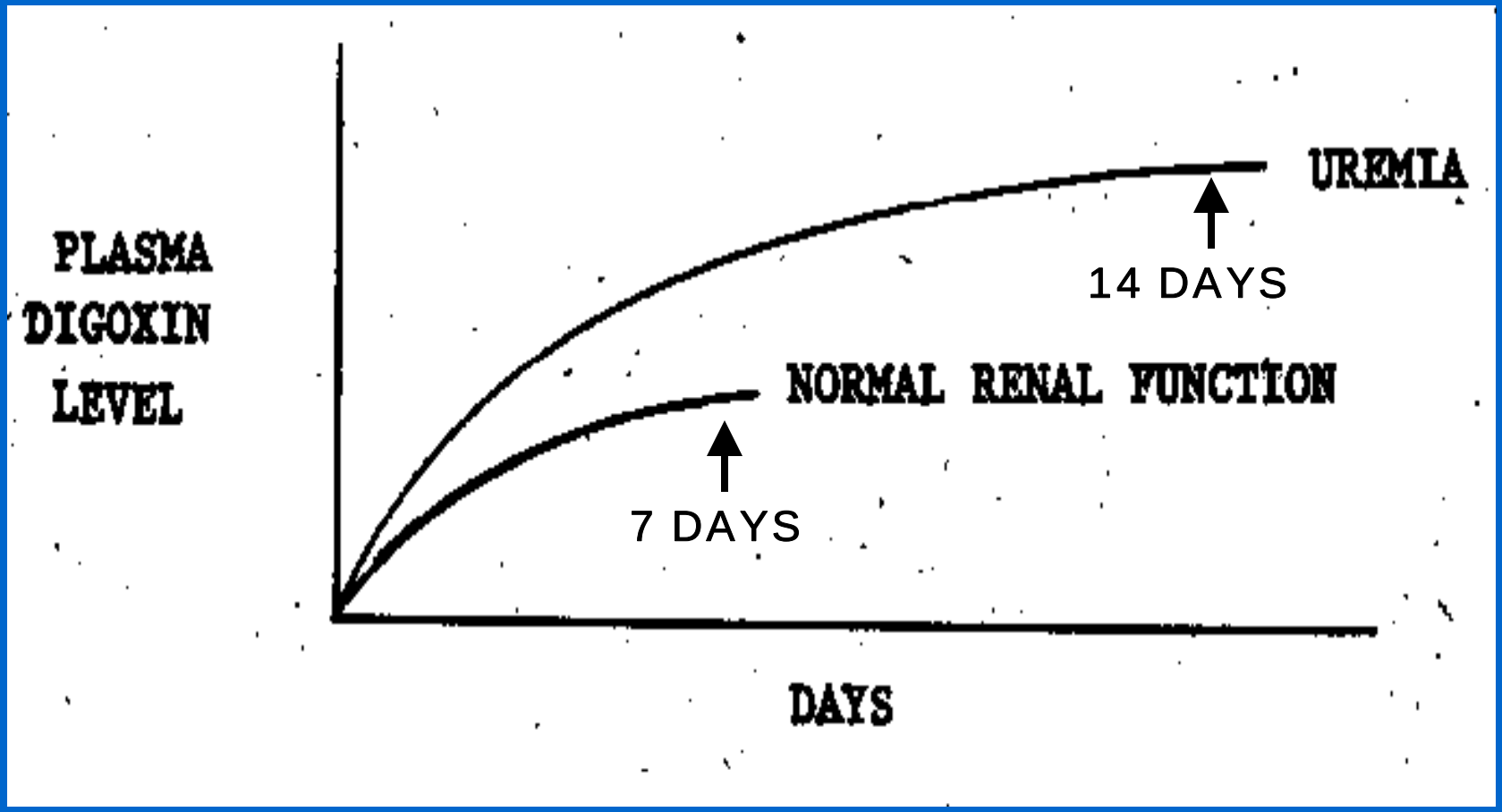
ELIMINATION RATE CONSTANT

$$k = \frac{0.693}{t_{1/2}}$$

LOADING & MAINTENANCE DOSES



TIME-COURSE OF DIGOXIN CUMULATION



DIGOXIN CASE HISTORY

A 39 year-old man with *mitral stenosis* was hospitalized for mitral valve replacement (October 1981). He had a history of *chronic renal failure* resulting from interstitial nephritis and was maintained on *hemodialysis*. His mitral valve was replaced with a prosthesis and *digoxin* therapy was initiated postoperatively in a dose 0.25 mg/day.

DIGOXIN CASE HISTORY (cont.)

Two weeks later, he was noted to be unusually *restless* in the evening. The following day, *he died shortly after he received his morning digoxin dose*. Blood was obtained during an unsuccessful resuscitation attempt, and the measured *plasma digoxin* concentration was 6.9 ng/mL.

TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE

TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE

⇩

BEGIN THERAPY

⇩

ASSESS THERAPY

PATIENT RESPONSE

DRUG LEVEL

⇩

REFINE DOSE ESTIMATE

⇩

ADJUST DOSE

TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE

TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE

⇩

BEGIN THERAPY

⇩

ASSESS THERAPY

PATIENT RESPONSE
DRUG LEVEL

⇩

REFINE DOSE ESTIMATE

⇩

ADJUST DOSE

PHARMACOKINETIC ANALYSIS OF DIGOXIN CASE HISTORY

ESTIMATED $T_{1/2}$:

4.3 days (k = 0.16 day^{-1})

TIME TO 90% STEADY STATE:

3.3 x 4.3 = 14.2 days

STEADY STATE PEAK LEVEL:

6.2 ng/mL (post distribution phase)

MEASURED LEVEL:

6.9 ng/mL (pre distribution)

STEADY STATE CONCENTRATION

CONTINUOUS INFUSION:

$$C_{SS} = \frac{I}{CL_E}$$

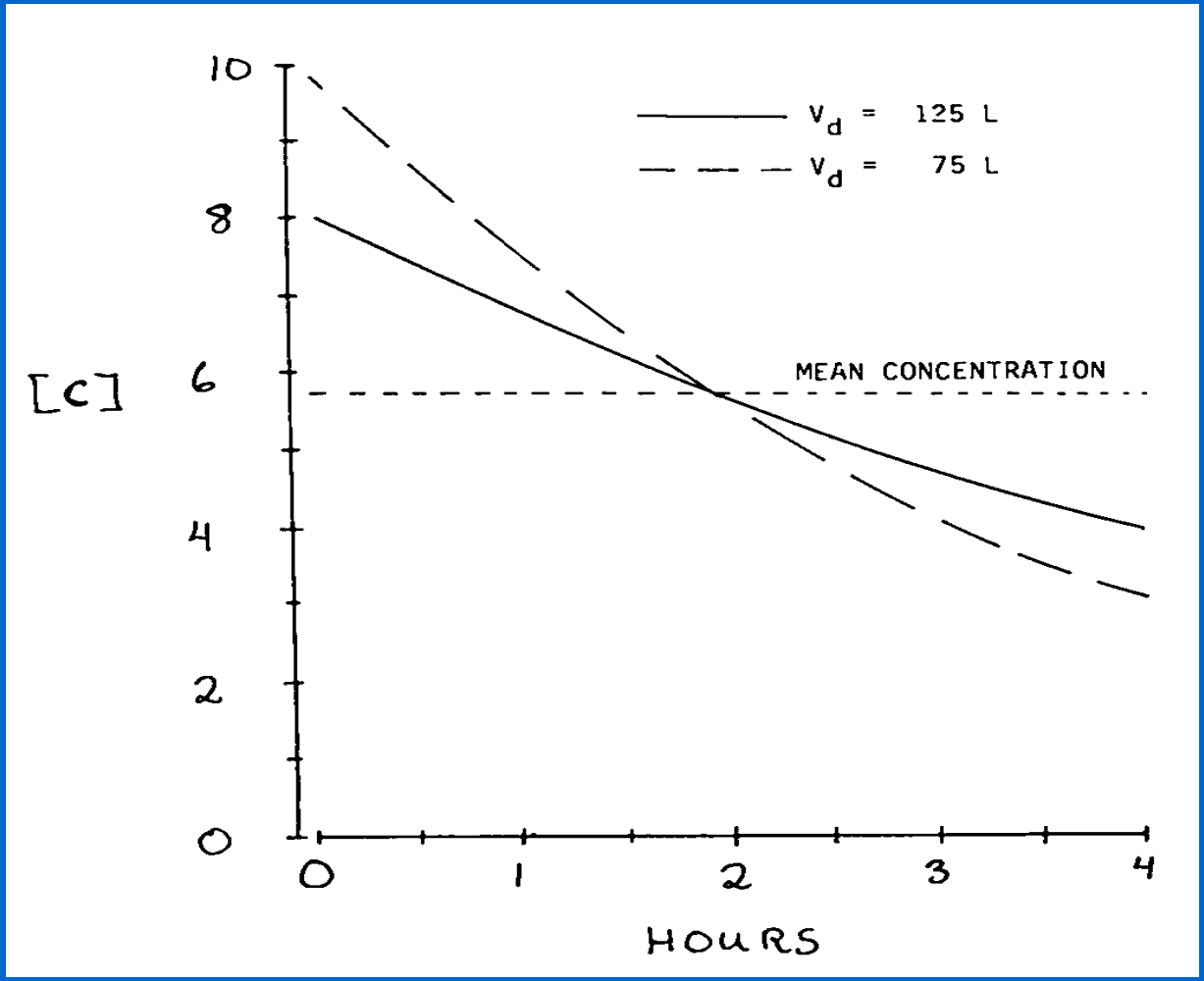
INTERMITTENT DOSING:

$$\overline{C}_{SS} = \frac{DOSE/\tau}{CL_E}$$

STEADY STATE CONCENTRATION

- ***NOT*** **DETERMINED BY LOADING DOSE**
- **MEAN STEADY STATE CONCENTRATION *NOT* DETERMINED BY V_d**
- **PEAK AND TROUGH *ARE* AFFECTED BY V_d**

V_d *AFFECTS* PEAK AND TROUGH BUT *NOT* MEAN LEVELS



FOR MOST DRUGS, C_{ss} IS PROPORTIONAL TO DOSE (Dosing Rate)

CONTINUOUS INFUSION:

$$C_{SS} = \frac{I}{CL_E}$$

INTERMITTENT DOSING:

$$\overline{C}_{SS} = \frac{DOSE/\tau}{CL_E}$$

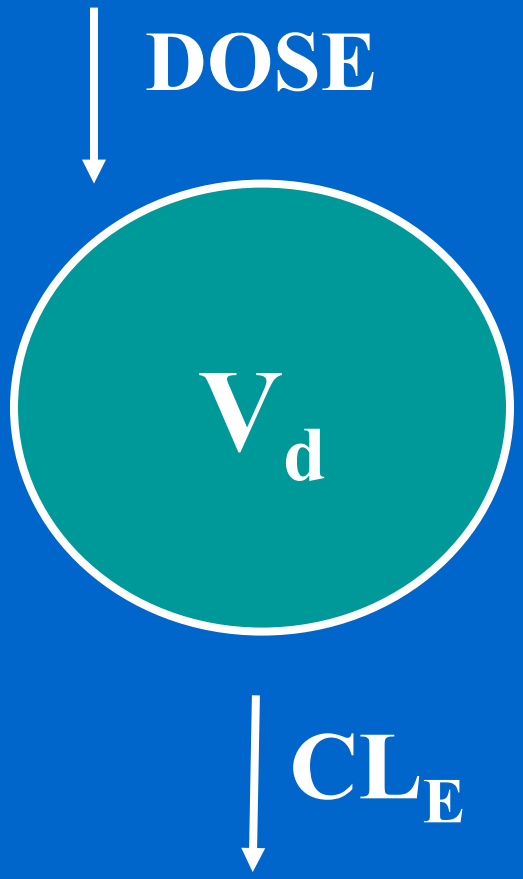
STEADY STATE CONCENTRATION

- ***NOT*** **DETERMINED BY LOADING DOSE**
- **MEAN STEADY STATE CONCENTRATION *NOT* DETERMINED BY V_d**
- **CHANGES IN MAINTENANCE DOSE RESULT IN DIRECTLY PROPORTIONAL CHANGES IN C_{SS} FOR MOST DRUGS**

PHARMACOKINETIC MODELS

WHAT PHARMACOKINETIC PARAMETERS ARE PRIMARY?

SINGLE COMPARTMENT MODEL



ELIMINATION HALF-LIFE

$$t_{1/2} = \frac{0.693 \bullet V_{d(area)}}{CL_E}$$

THEREFORE, $t_{1/2}$ IS *NOT* A PRIMARY PHARMACOKINETIC PARAMETER

3 *DISTRIBUTION VOLUMES*

$$V_{d\,(extrap.)} = DOSE \,/\, C_0$$

$$V_{d\,(area)} = \frac{t_{1/2} \bullet CL_E}{0.693}$$

$$V_{d\,(ss)} = V_1 + V_2 + \ldots\ldots V_n$$

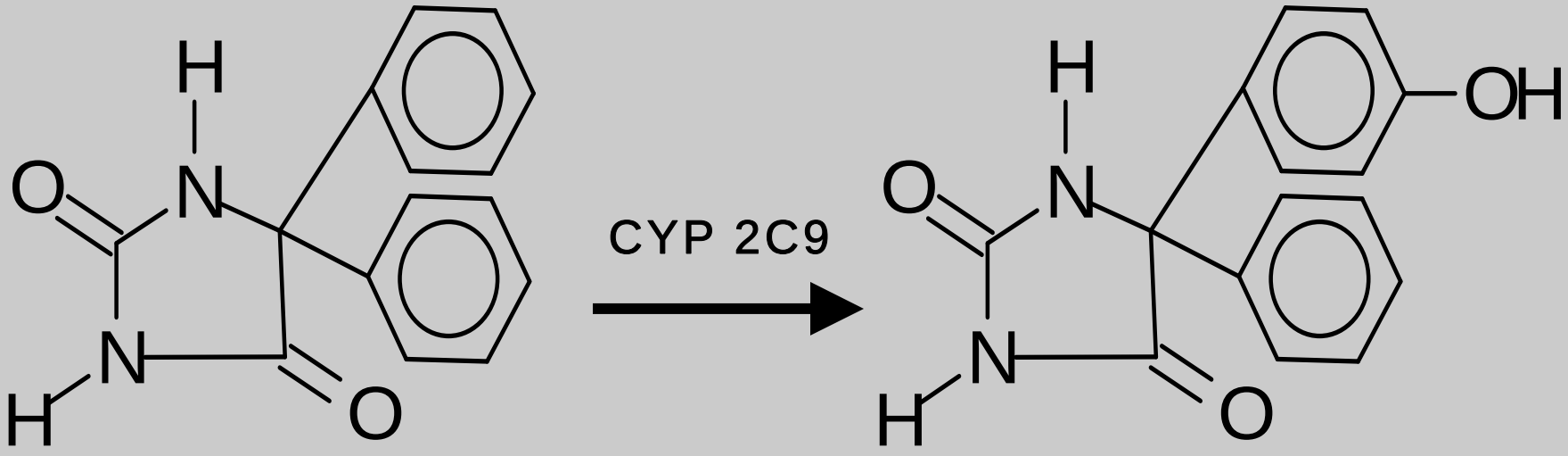
SOME DRUGS *NOT* ELIMINATED BY FIRST ORDER KINETICS

PHENYTOIN **(DILANTIN)**

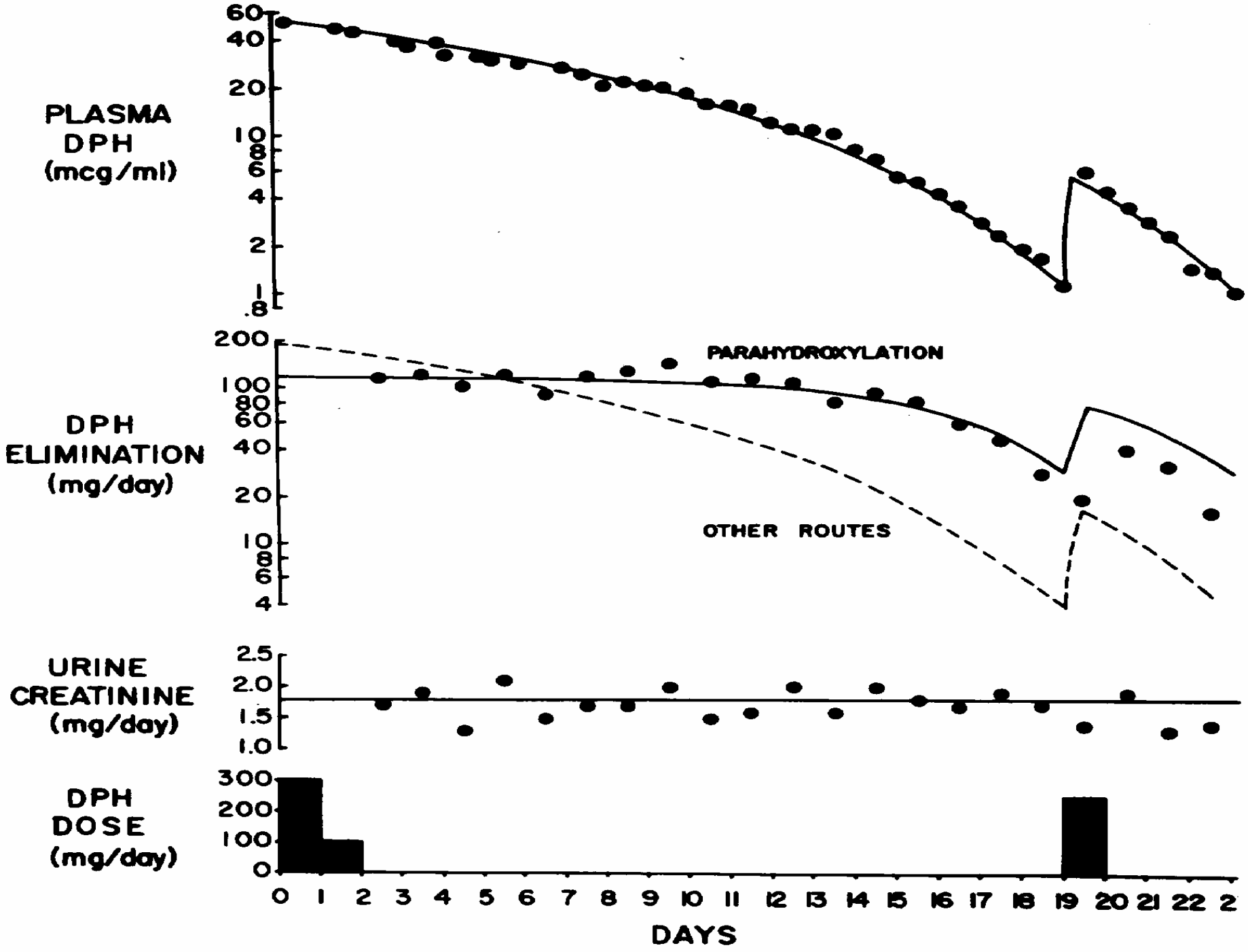
ETHYL ALCOHOL

ACETYLSALICYLIC ACID **(ASPIRIN)**

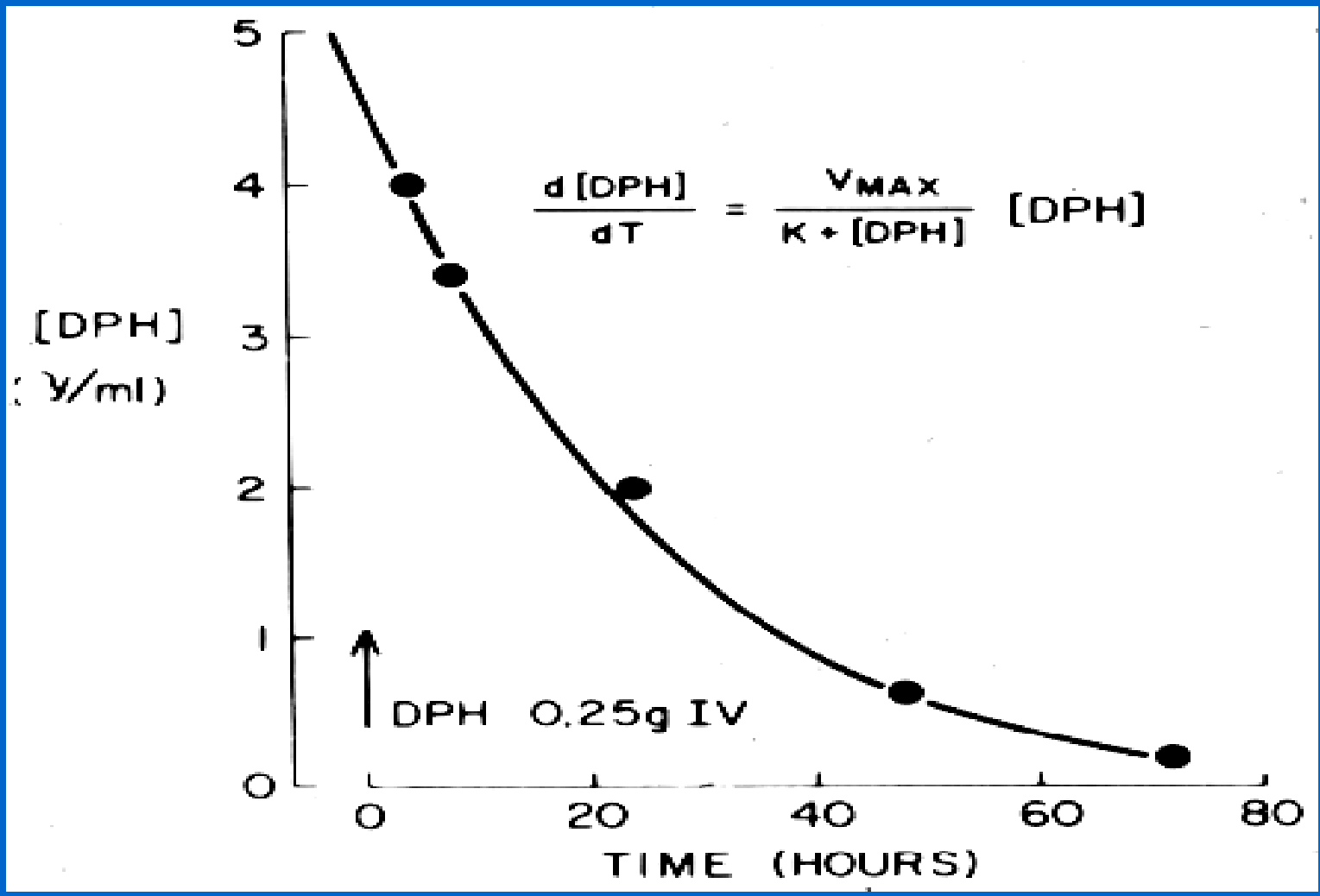
PHENYTOIN HYDROXYLATION



PHENYTOIN ***p*-HPPH**


PLASMA DPH (mcg/ml)
60
40
20
10
8
6
4
2
1
.8
DPH ELIMINATION (mg/day)
200
100
80
60
40
20
10
8
6
4
PARAHYDROXYLATION
OTHER ROUTES
URINE CREATININE (mg/day)
2.5
2.0
1.5
1.0
DPH DOSE (mg/day)
300
200
100
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 2
DAYS

PHENYTOIN KINETICS
in Normal Subjects



STEADY STATE EQUATIONS

FIRST ORDER KINETICS

$$\text{DOSE}/\tau = CL_E \bullet \overline{C}_{SS}$$

MICHAELIS - MENTEN KINETICS

$$\text{DOSE}/\tau = \left[\frac{V_{max}}{K_m + \overline{C}_{SS}} \right] \overline{C}_{SS}$$

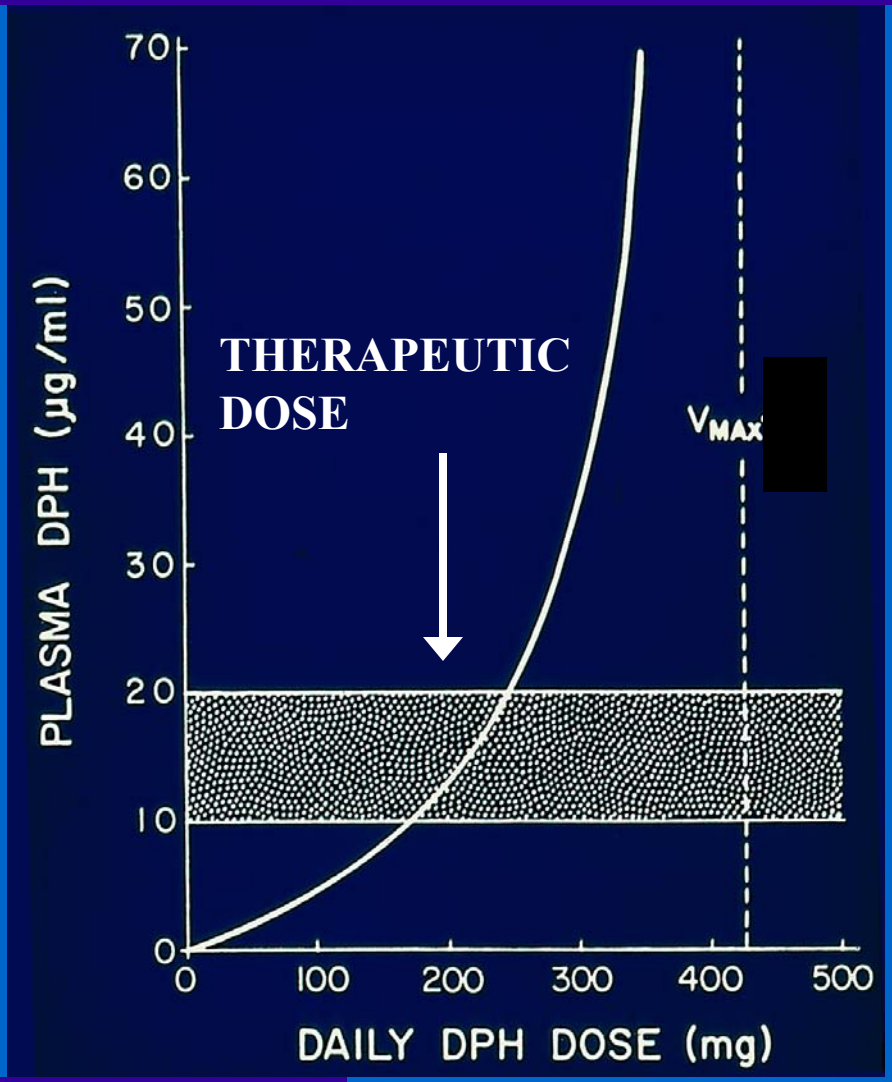
RELATIONSHIP OF PLASMA LEVEL TO PHENYTOIN DOSE*

PHENYTOIN DOSE (mg/day)	PLASMA LEVEL µg/mL
300	10
400	20
500	30

(THERAPEUTIC RANGE: 10 – 20 µg/mL)

* From: Kutt H, McDowell F: J Am Med Assoc 1968;203:969-72.

PATIENT WHO BECAME *TOXIC* ON A PHENYTOIN DOSE OF 300 mg/day



PHENYTOIN CASE HISTORY

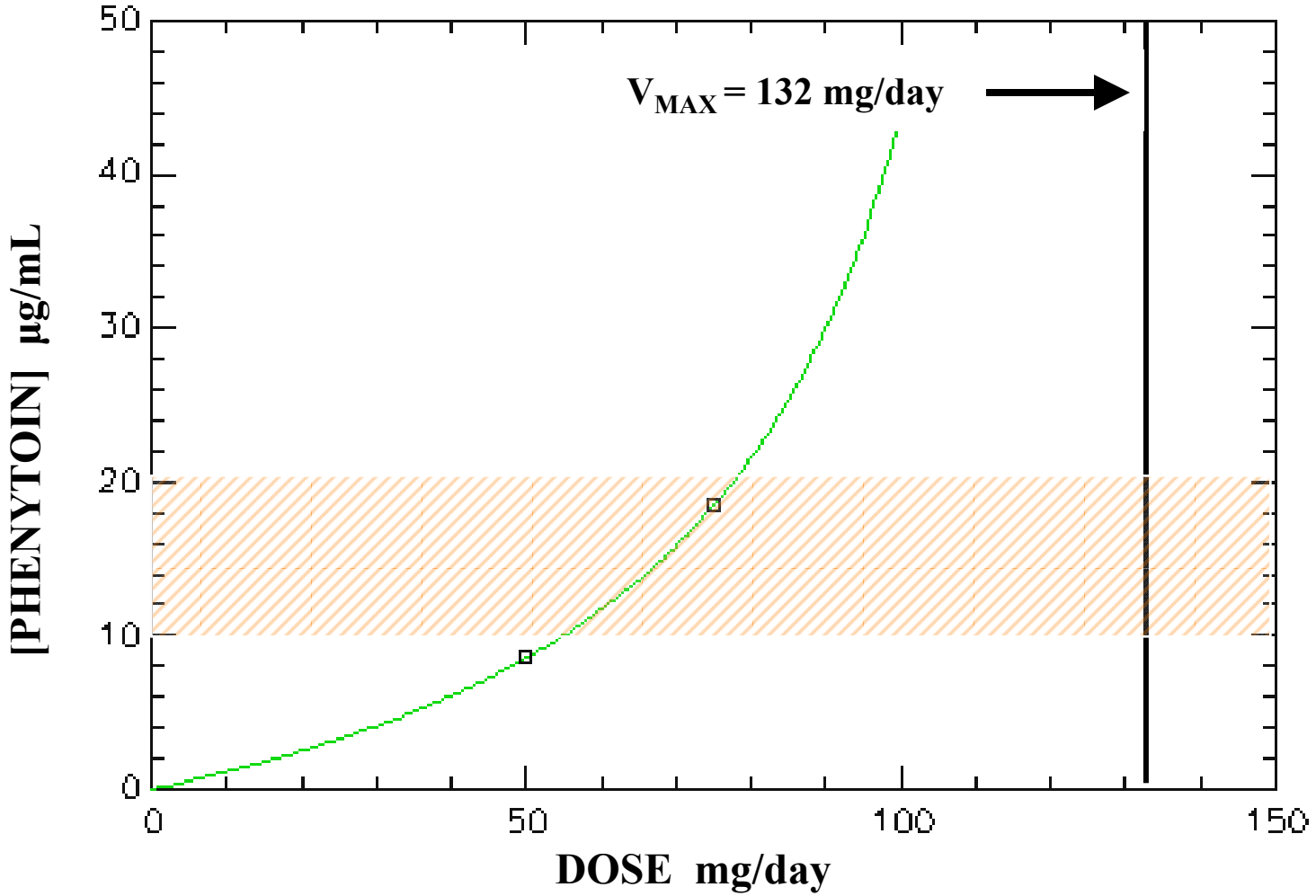
After inpatient evaluation for a generalized seizure, a 28-year-old woman was discharged on *phenytoin* therapy at a dose of 300 mg/day.

After 5 days of therapy, she presented to the hospital's emergency department with marked *ataxia*. Her phenytoin plasma concentration was found to be 27 µg/mL. She was sent home on a *reduced* phenytoin dose of 200 mg/day.

PHENYTOIN CASE HISTORY (cont.)

Two days later, she returned to the emergency department with more *severe ataxia*. Her phenytoin plasma concentration was *now* 32 µg/mL. Non-compliance was suspected but a clinical pharmacology evaluation was requested.

PATIENT with *VERY LOW* V_{MAX}



BASIS OF *APPARENT* FIRST-ORDER KINETICS

$$\frac{dC}{dt} = \left[\frac{V_{max}}{K_m + C} \right] C$$

If $K_m > C$:

$$\frac{dC}{dt} = \left[\frac{V_{max}}{K_m} \right] C = \text{"k"}\, C$$

CONCLUDING THOUGHTS

- *PRACTICE PROBLEMS* AT END OF CHAPTER 2 WITH *ANSWERS* IN APPENDIX II
- *EQUATIONS* DERIVED IN "PRINCIPLES OF CLINICAL PHARMACOLOGY" TEXTBOOK
- *LAPLACE TRANSFORMS* INTRODUCED WITH TABLES IN APPENDIX I