A critical review of PK / TD in preventing toxicity

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optimizing efficacy and prevention of resistance

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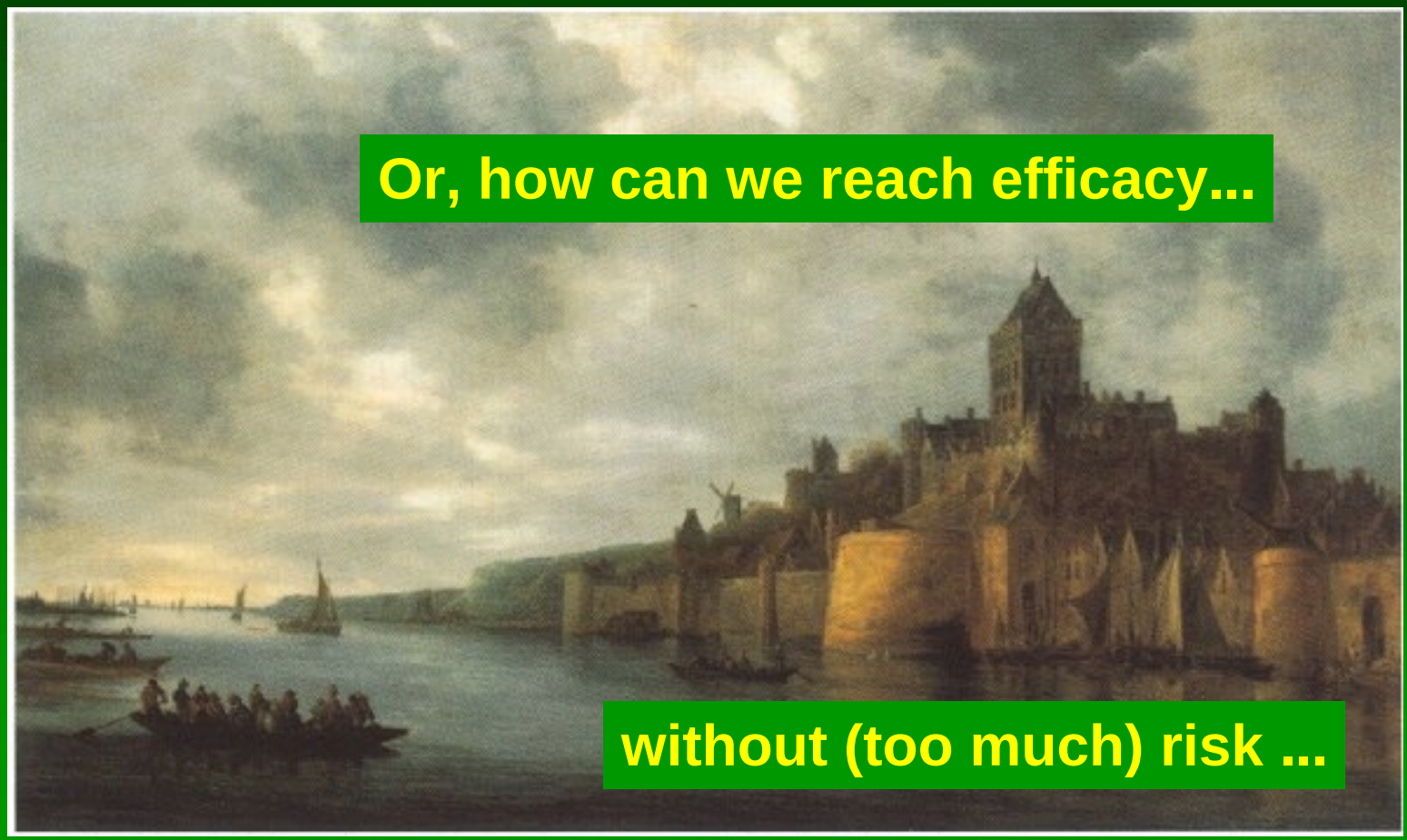
A critical review of PK / TD in preventing toxicity

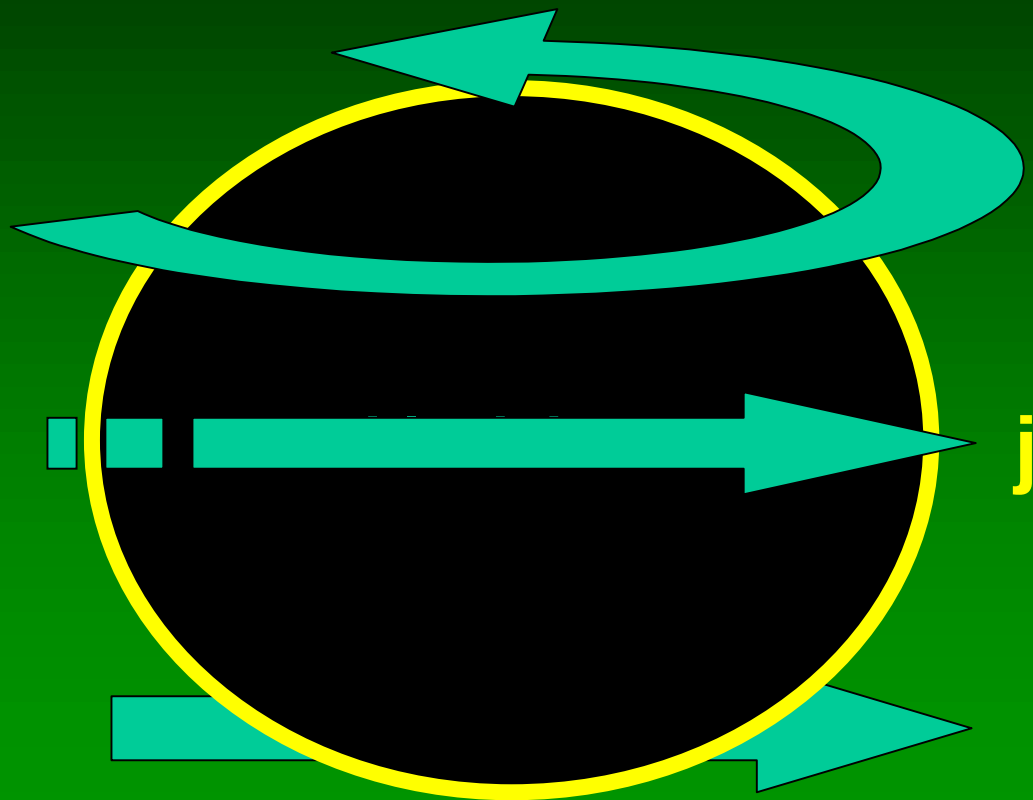


A critical review of PK / TD in preventing toxicity

Or, from the lab ...

to the patient...

What is research all about ?



basic

travelling

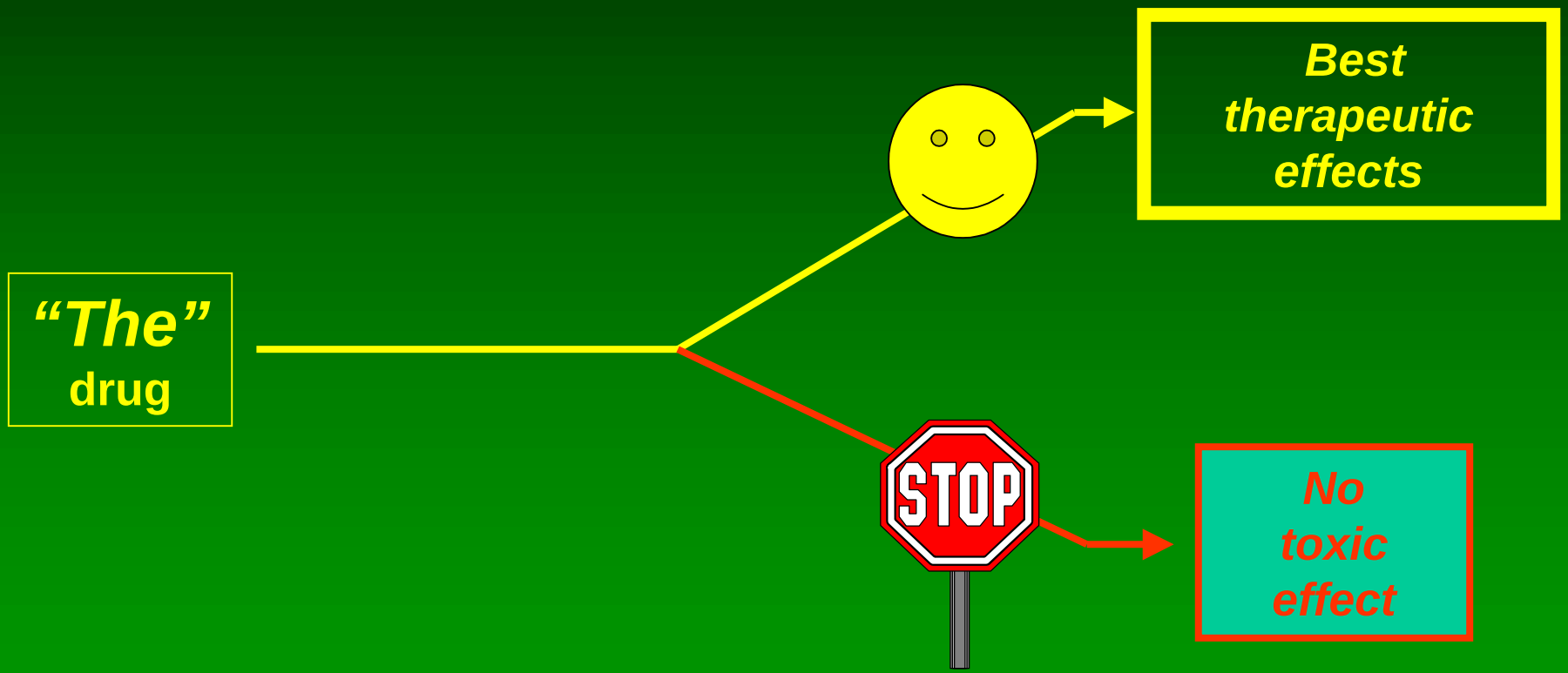
applied

journeying

clinical

Trying
to arrive
safely

Antibiotic treatments:
What does the clinician want ?



What did the textbooks say about antibiotic dosages and schedules in the 70's ?

1. Stay above the MIC... **but how much ?**
2. Remain around for a while… **but how long ?**
3. Hope it works... **against everything ?**
4. Hope it is not toxic…

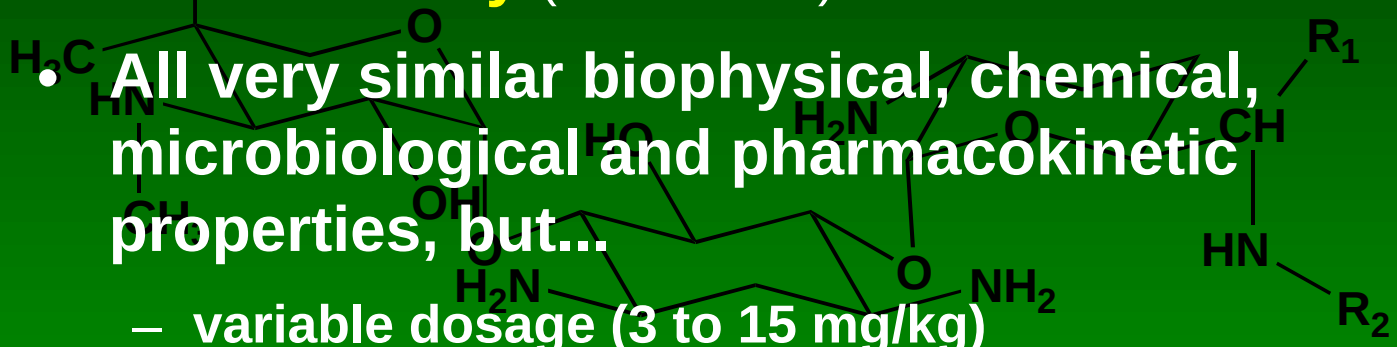
Sorry, but
I can't do much ...

What are we going to discuss ?

1. aminoglycosides … (29 slides)
2. macrolides … (5 slides)
3. Fluoroquinolones (3 slides)
4. β-lactams … (8 slides)
5. thanking people… (a lot of slides)

Aminoglycosides in the 70's ...

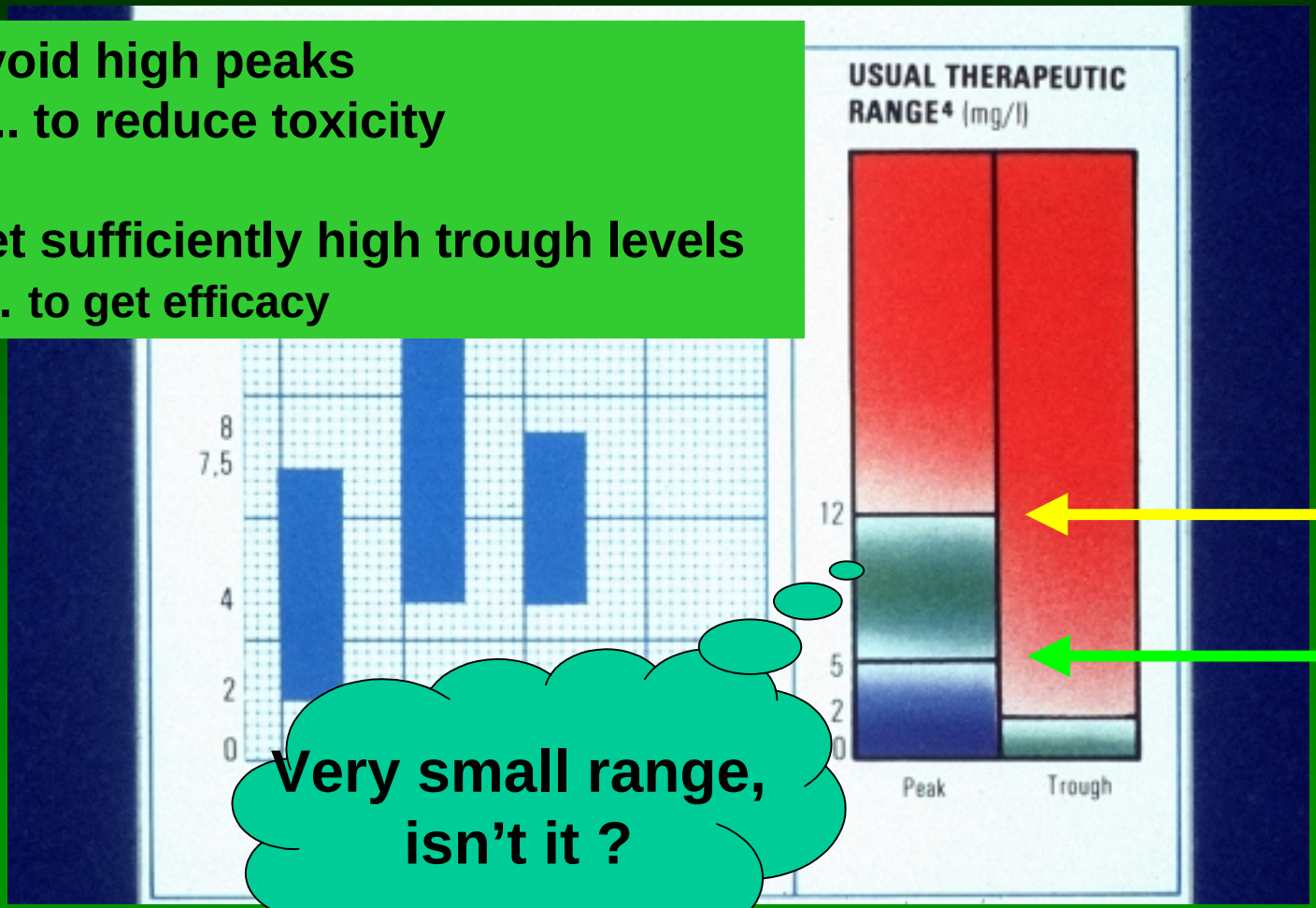
- **Potent antimicrobials but toxic**
  - ➔ **nephrotoxicity** (reversible)
  - ➔ **ototoxicity** (irreversible)
- **All very similar biophysical, chemical, microbiological and pharmacokinetic properties, but...**
  - **variable dosage (3 to 15 mg/kg)**
  - **variable schedules (1 - 2 - 3 x/day … or even continuous infusion, …**
- **"necessity" to monitor, but how ??**



Aminoglycosides monitoring in the 70's ...

avoid high peaks
... to reduce toxicity

get sufficiently high trough levels
… to get efficacy

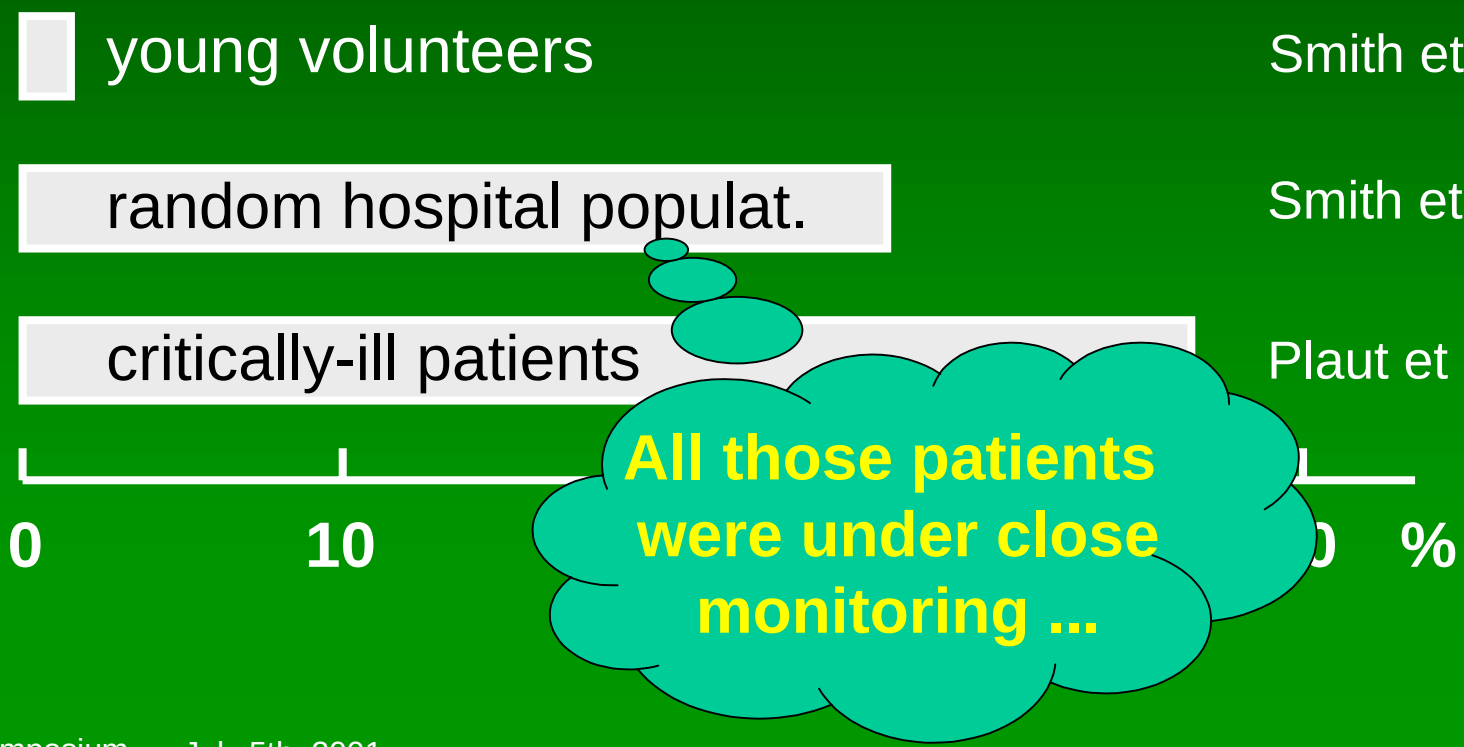


toxicity !!

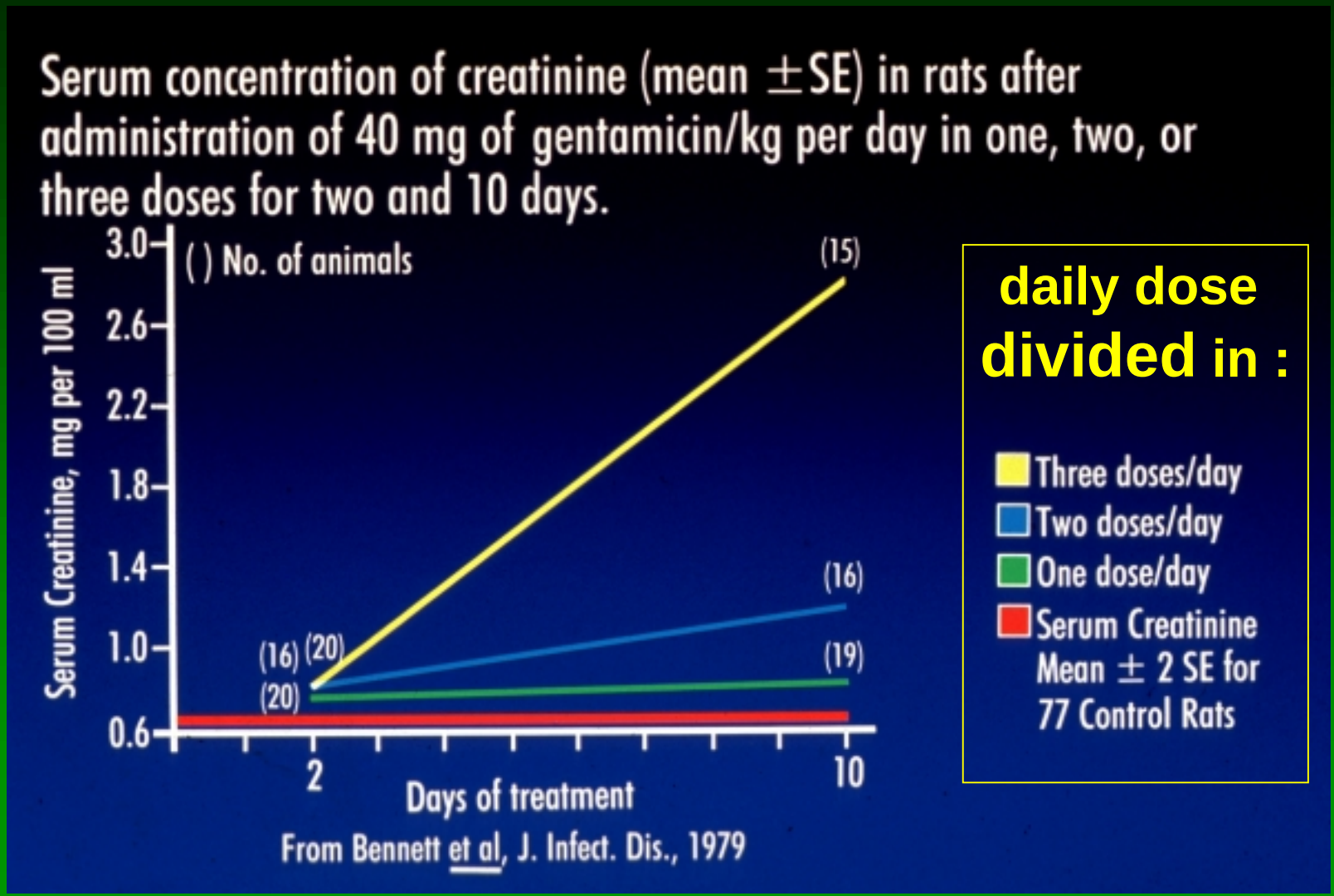
lack of efficacy

Aminoglycosides toxicity in the 70's - 80's ...

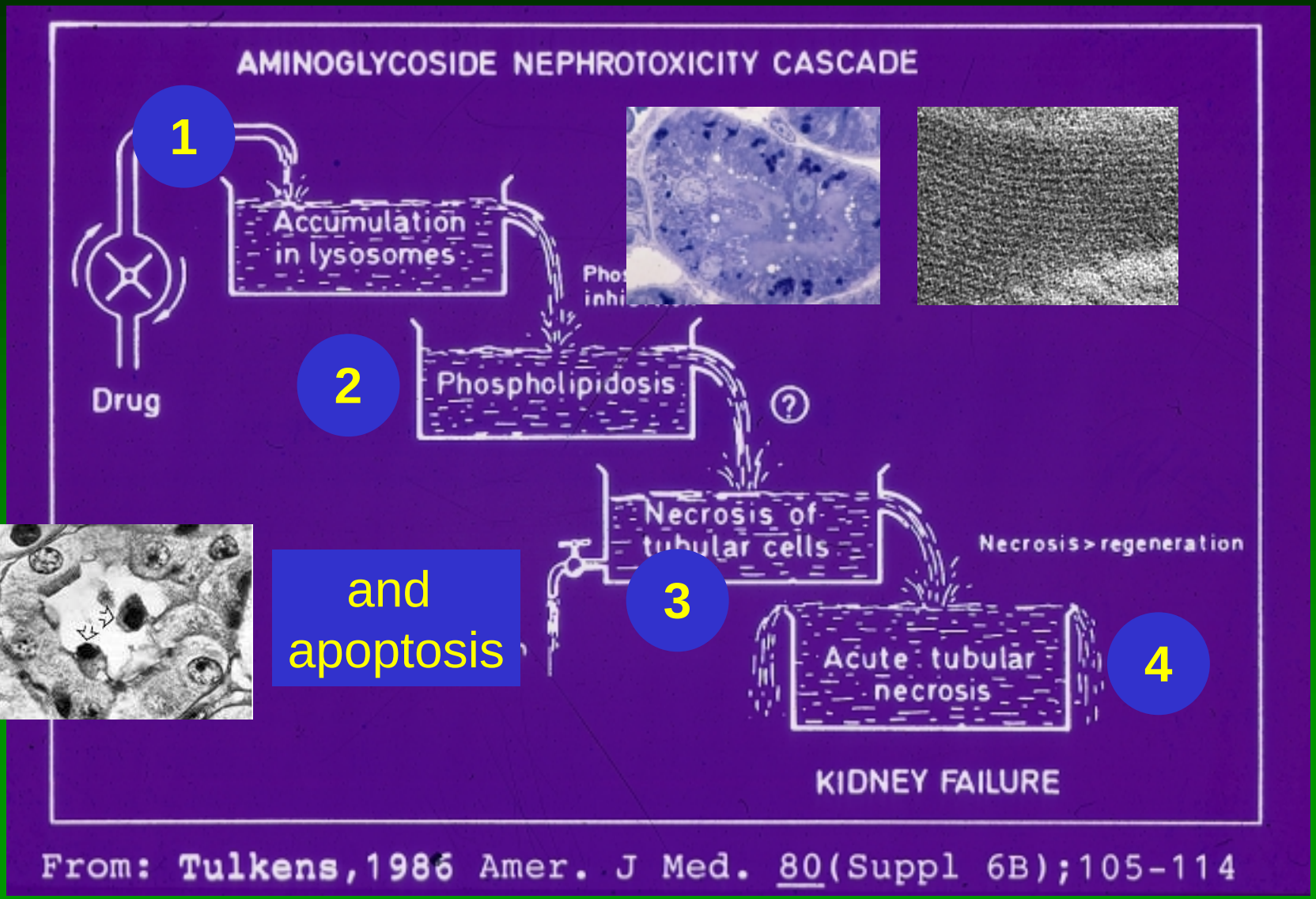
Patients with nephrotoxic reaction after treatment with gentamicin



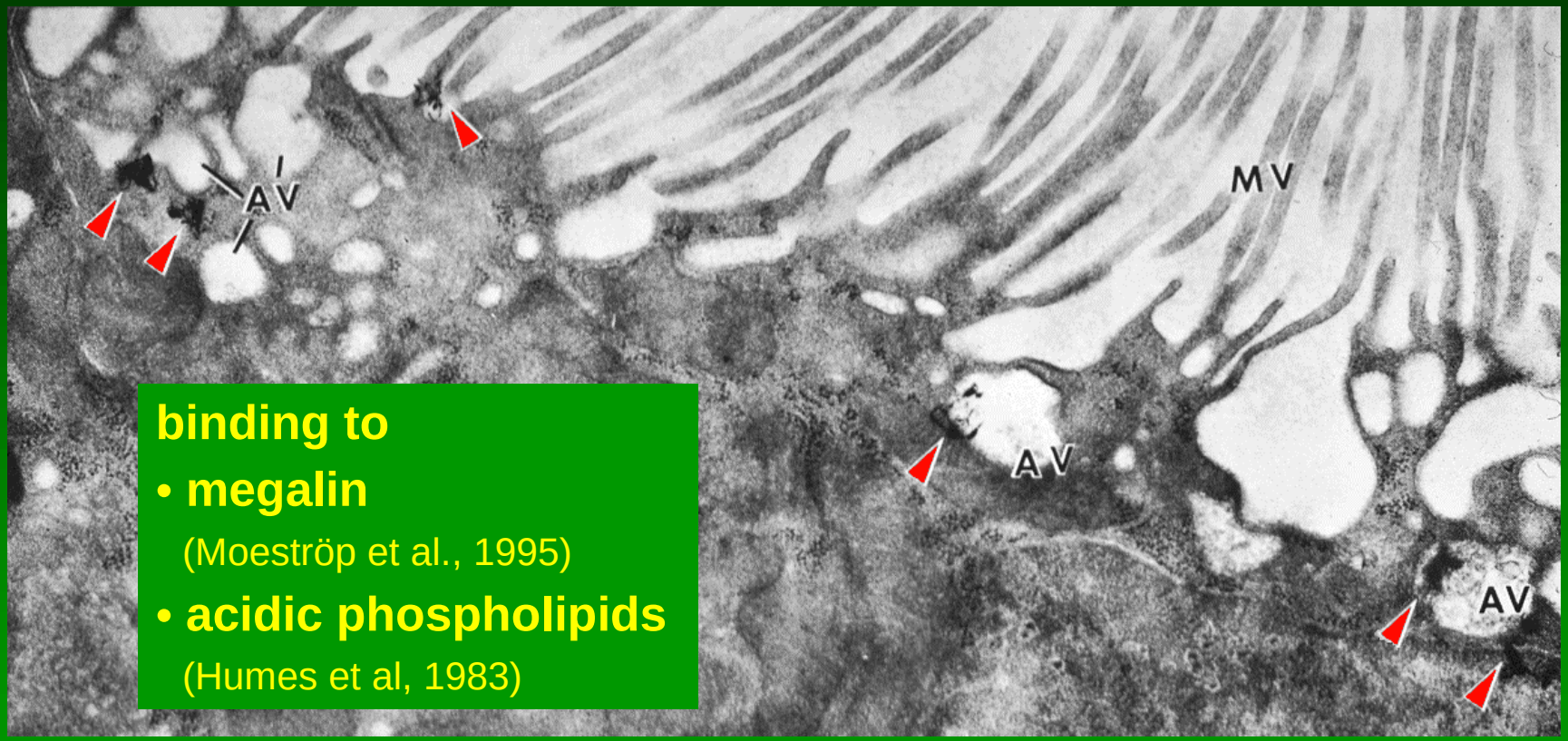
Aminoglycoside toxicity is **not** linked to peak ...



What is the (likely) mechanism of aminoglycoside nephrotoxicity ?...



Aminoglycoside entry in proximal tubular cells is via brush border binding *...

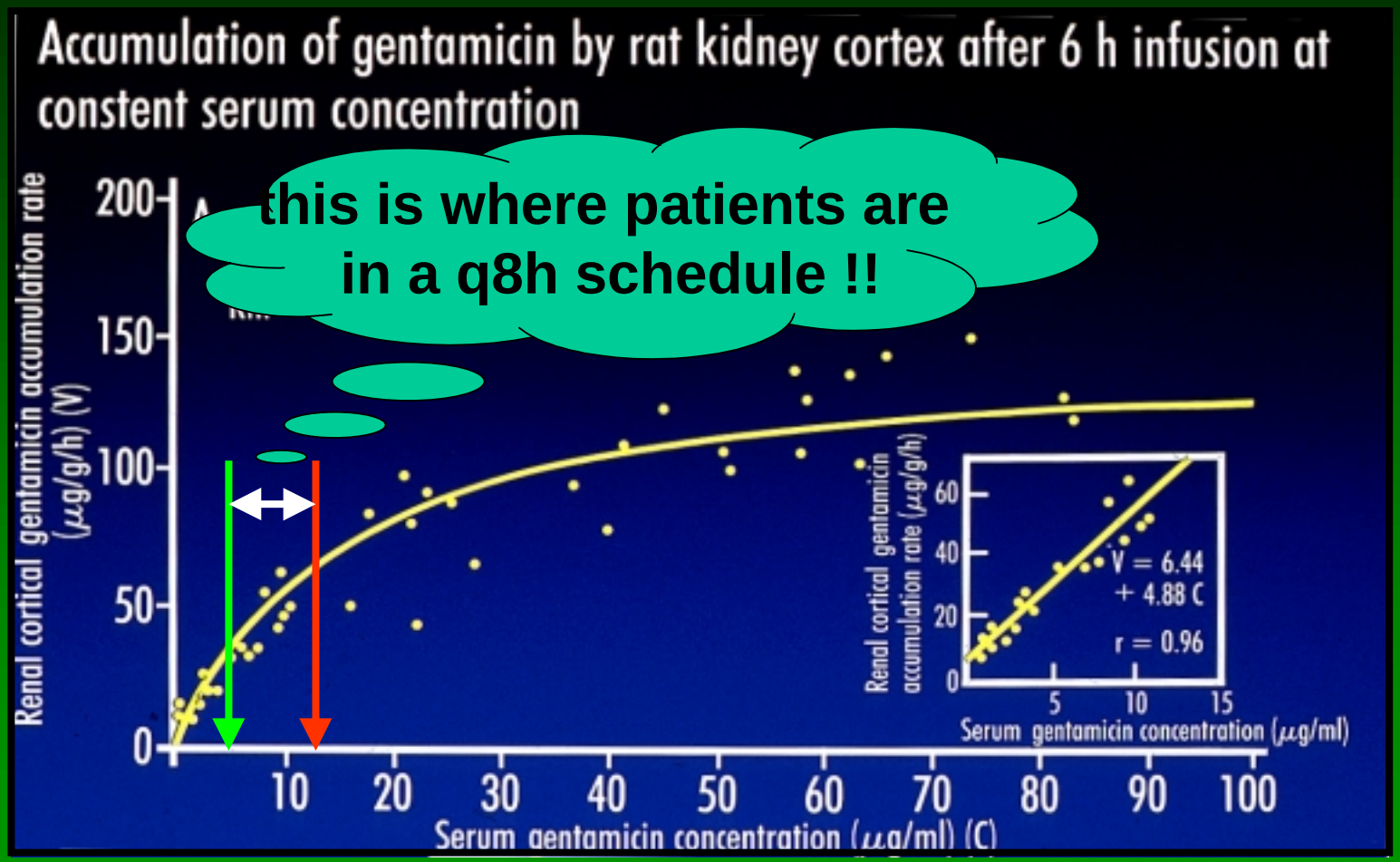


binding to

- **megalin**
  (Moeström et al., 1995)
- **acidic phospholipids**
  (Humes et al, 1983)

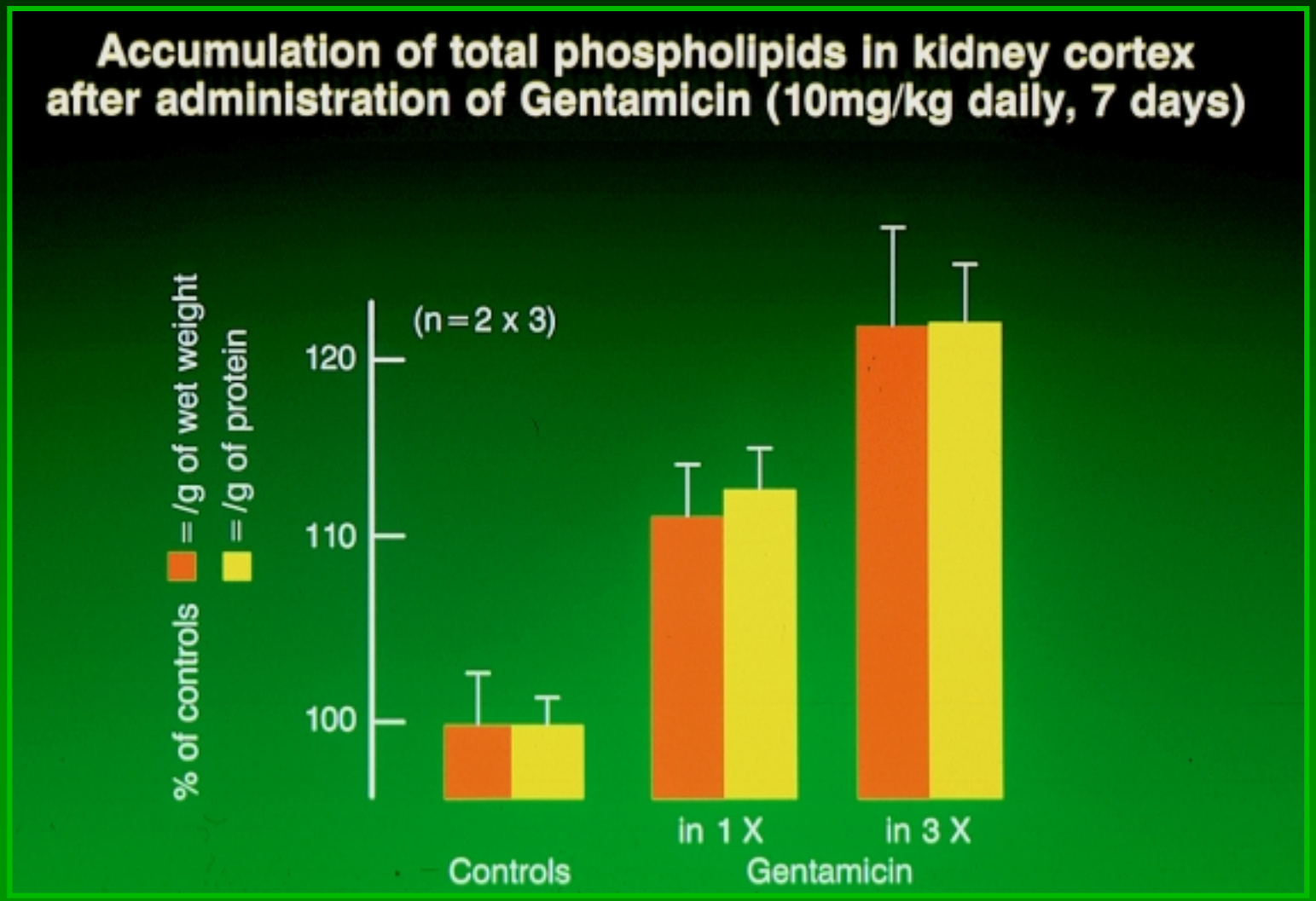
* Just *et al*, Naunym Schmied. Arch. Pharmacol, 1977
Silverblatt & Kuehen, Kidney Intern., 1979

Aminoglycoside accumulation is kidney is saturable at clinically meaningful concentrations * ...



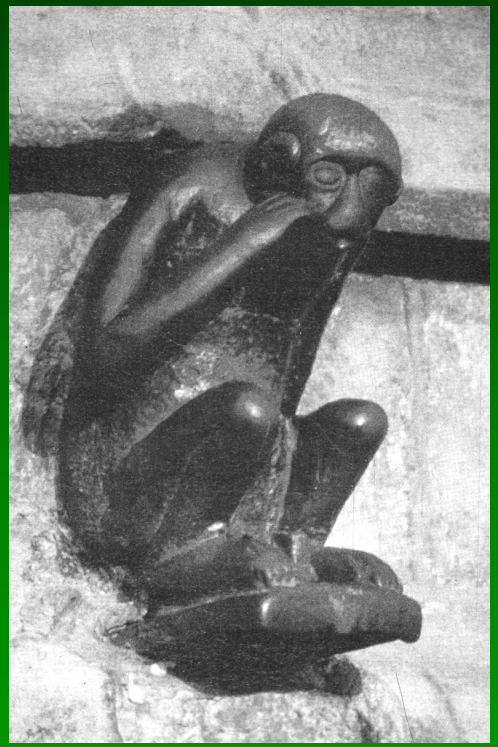
* Giuliano *et al.*, J. Pharm. Exp. Ther., 1986

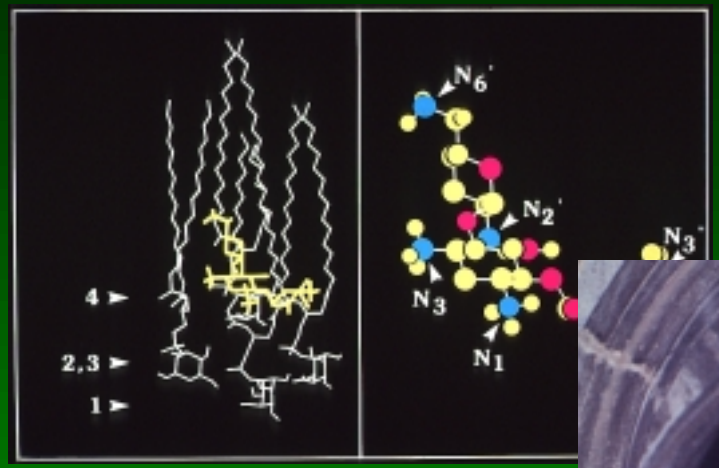
The once-a-day schedule gives less drug accumulation and less renal alterations in rats * ...



* Laurent et al., Amer. Soc. Microbiol., 1983 ; Laurent et al, Antimicrob. Agents Chemother., 1983

Shall you now go to humans ?

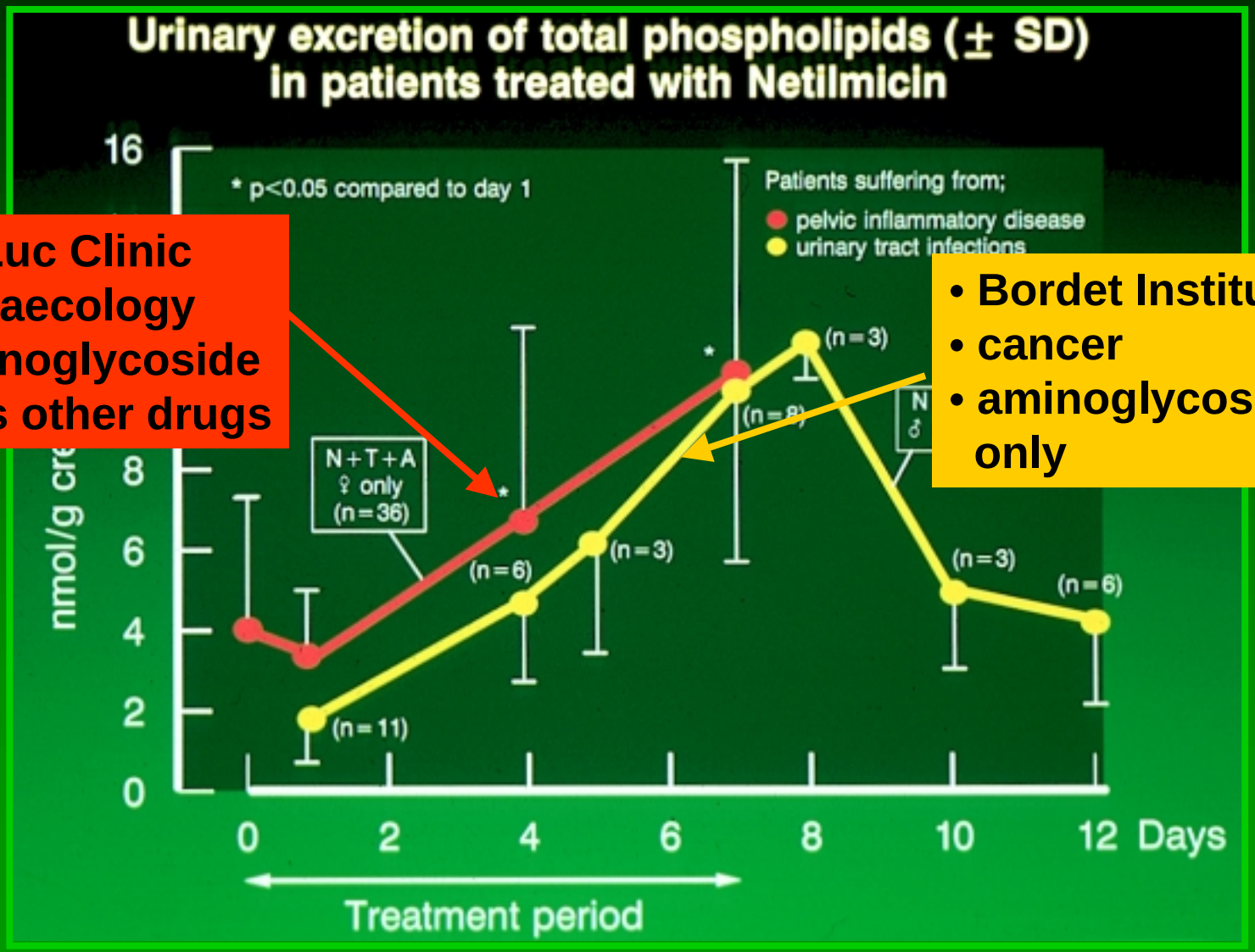




Aminoglycoside once-a-day: the philosophy of one of the first PK / TD clinical trials (1985 ...)

- choose an adapted drug (least toxic)
  - netimicin (study #1)
  - amikacin (study #2)
- patients with low risk
  - 2 x 40 young patients
- who need treatment
  - women suffering from PID
- do not depart from clinical standards if not part of the hypothesis to test
  - conventional daily doses (N: 6mg/kg; A: 15 mg/kg)
  - conventional treatment duration (7 days)
- "*primum non nocere*"
  - combine with ampicillin and tinidazole
- test your hypothesis as correctly as possible
  - randomized
  - blinded to evaluators
- use surrogate toxicity markers if avalaible and relevant
  - phospholipiduria
  - high tone audiometry

Phospholipiduria can be a surrogate marker of aminoglycoside-induced renal alterations



- St Luc Clinic
- gynaecology
- aminoglycoside plus other drugs

- Bordet Institute
- cancer
- aminoglycoside only

Pharmacokinetic results (day 7)...

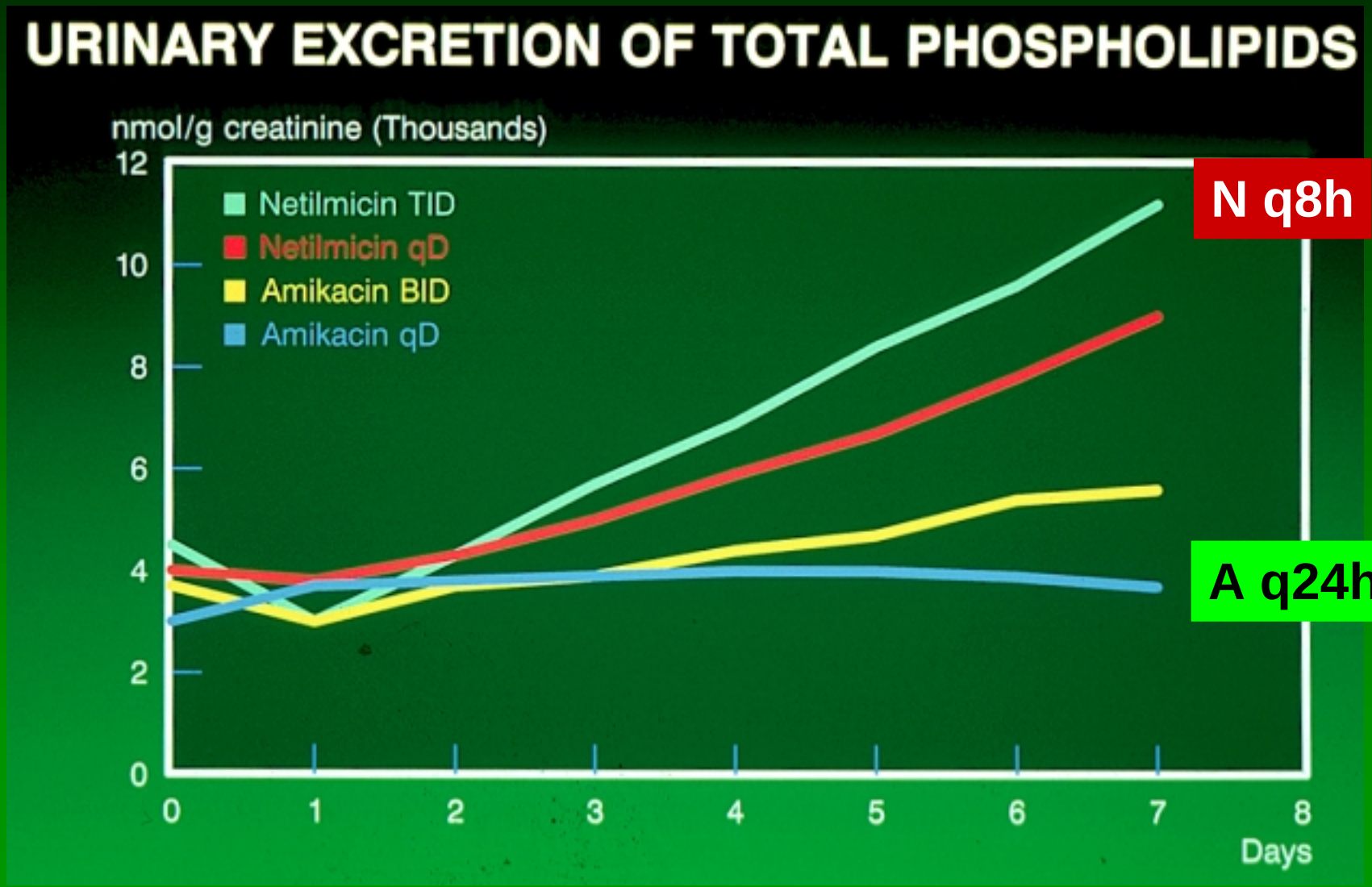
	amikacin [1]		netilmicin [2]	
	q24h	q12h	q24h	q8h
Vd (l/kg)	0.22 ± 0.04	0.24 ± 0.04	0.28 ± 0.04	0.34 ± 0.05 **
$t_{\frac{1}{2}}$ (h)	1.52 ± 0.15	1.54 ± 0.23	1.75 ± 0.25	1.97 ± 0.25 *
AUC(mg*h/L)	119 ± 17	109 ± 18	54 ± 14	51 ± 12
peak (ml/L)	55.3 ± 8.8	25.5 ± 1.9***	21.3 ± 3.7	6.5 ± 1.0***

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

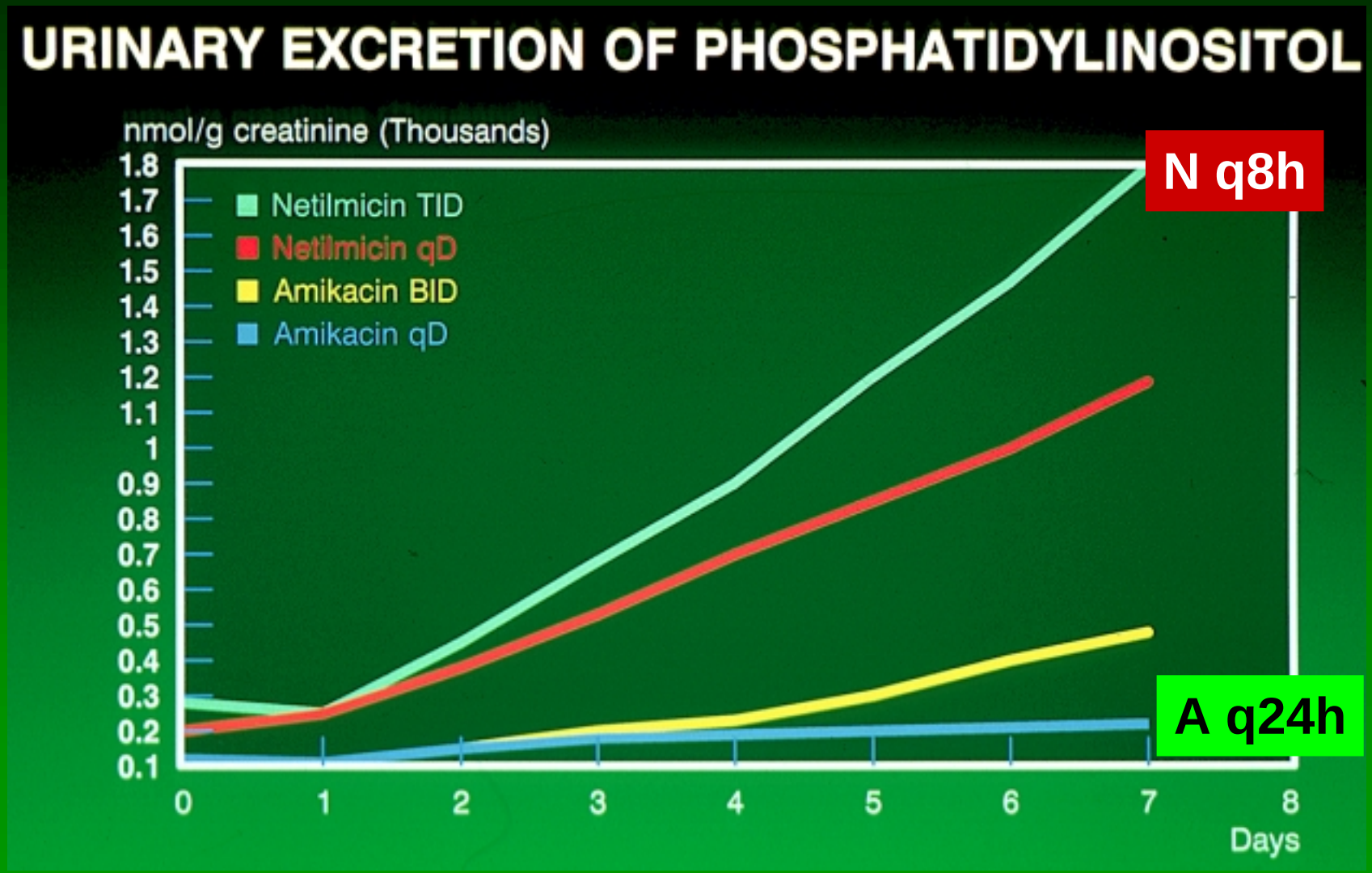
[1] daily dose = 15 mg/kg (1 x 15 mg/kg *vs* 2 x 7.5 mg/kg per 24h)

[2] daily dose = 6.6 mg/kg (1 x 6.6 mg/kg vs 2 x 3.3 mg/kg per 24h)

Phospholipiduria (1)



Phospholipiduria (2)



Phospholipiduria: statistical comment ...

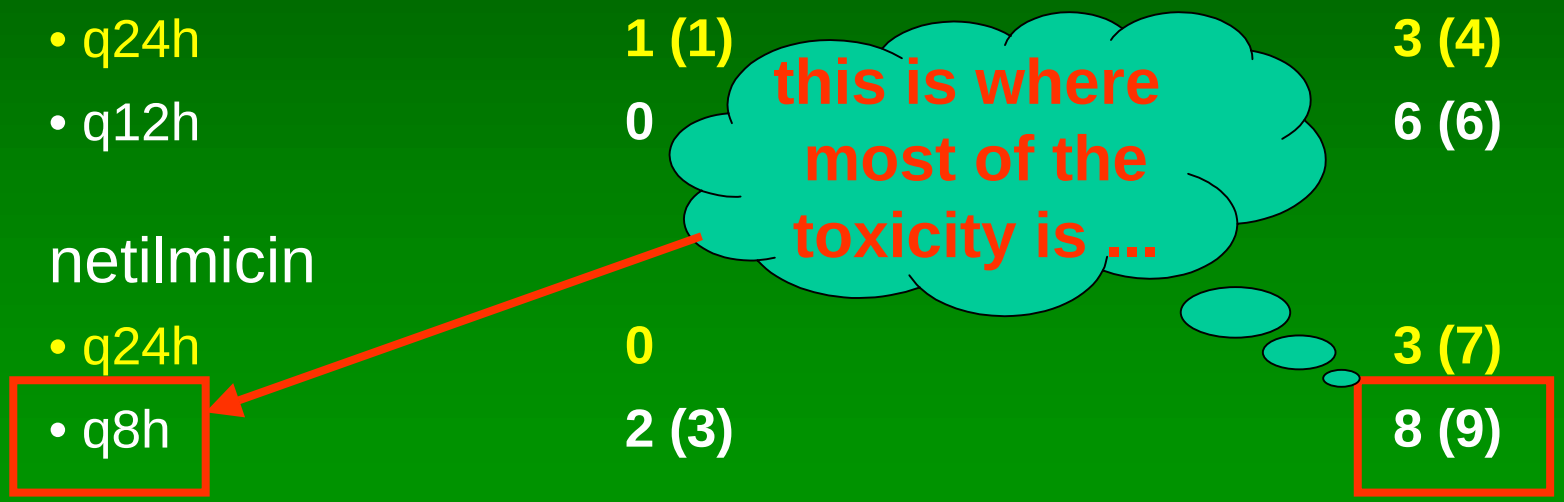
- There is a highly significant difference between the two medications (A < N)
- For each variable, there is a highly significant time effect
- The interaction between medication and time is highly significant. The effect of time, however, is not the same for the two medications (N > A)
- **The increase, when it occurs, is always faster for the multiple doses schedule (q8h / q12h) than for the once-a-day (q24h) groups**

Nephrotoxicity will not be suppressed but <u>delayed</u>
… which is what has been found in most subsequent clinical trials

Auditory alterations

no. of patients [over 20 in each group] with lesions* and total no. of frequencies affected

	low tone (0.25-8 kHz)	high tone (10-18 kHz)
amikacin		
• q24h	**1 (1)**	**3 (4)**
• q12h	**0**	**6 (6)**
netilmicin		
• q24h	**0**	**3 (7)**
• q8h	**2 (3)**	**8 (9)**



* loss of 15dB or more over baseline(max. loss recorded: 30 dB)

General conclusions of the first clinical trials … *

	amikacin	*vs*	netilmicin
	q24h *vs* q12h		q24h *vs* q8h
efficacy	=	=	=
renal alterations[1]	<	<<*	<
auditory alterations[2]	=	=	<<*

* highly significant by repeated variance analysis

[1] phospholipiduria

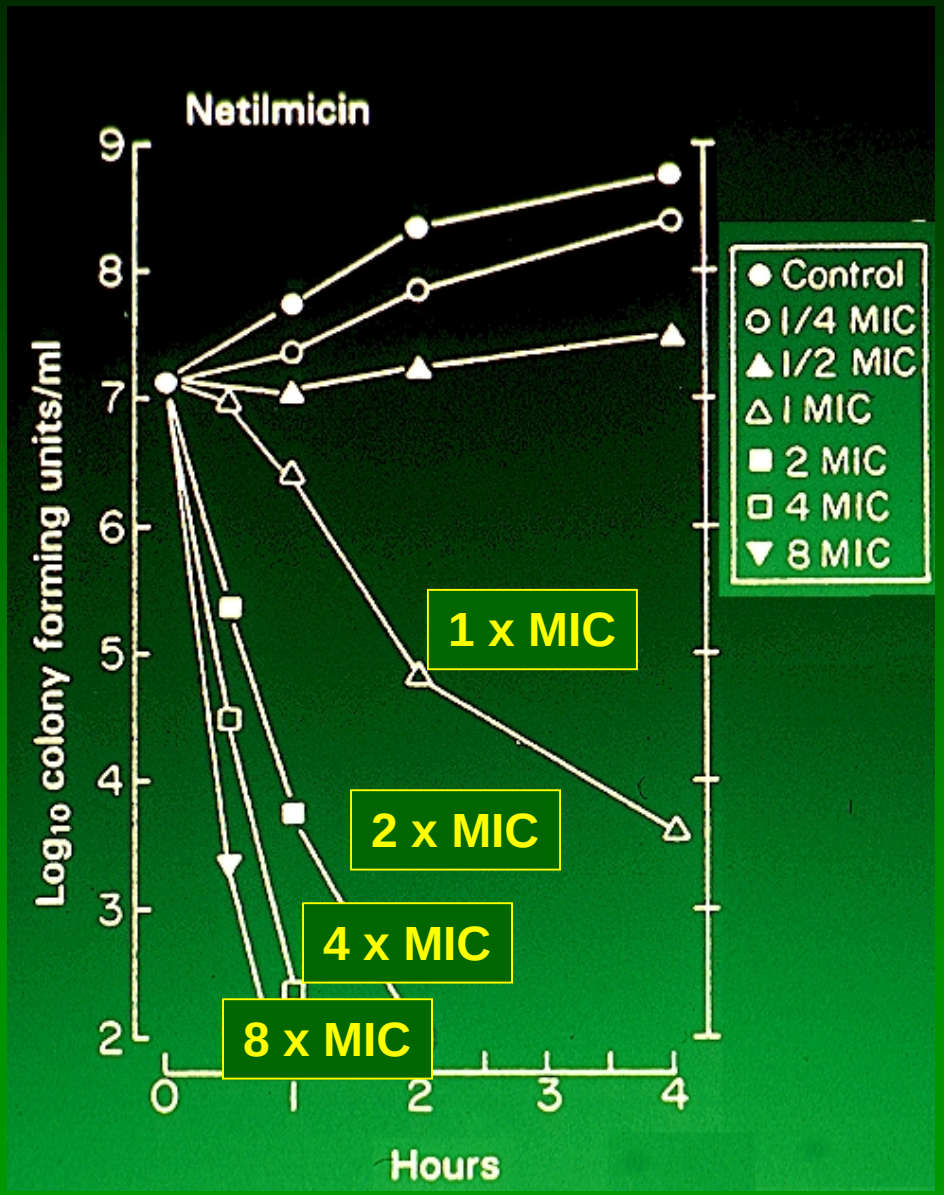
[2] high tone (10-18 kHz audiometry)

Isn't that what you want ?

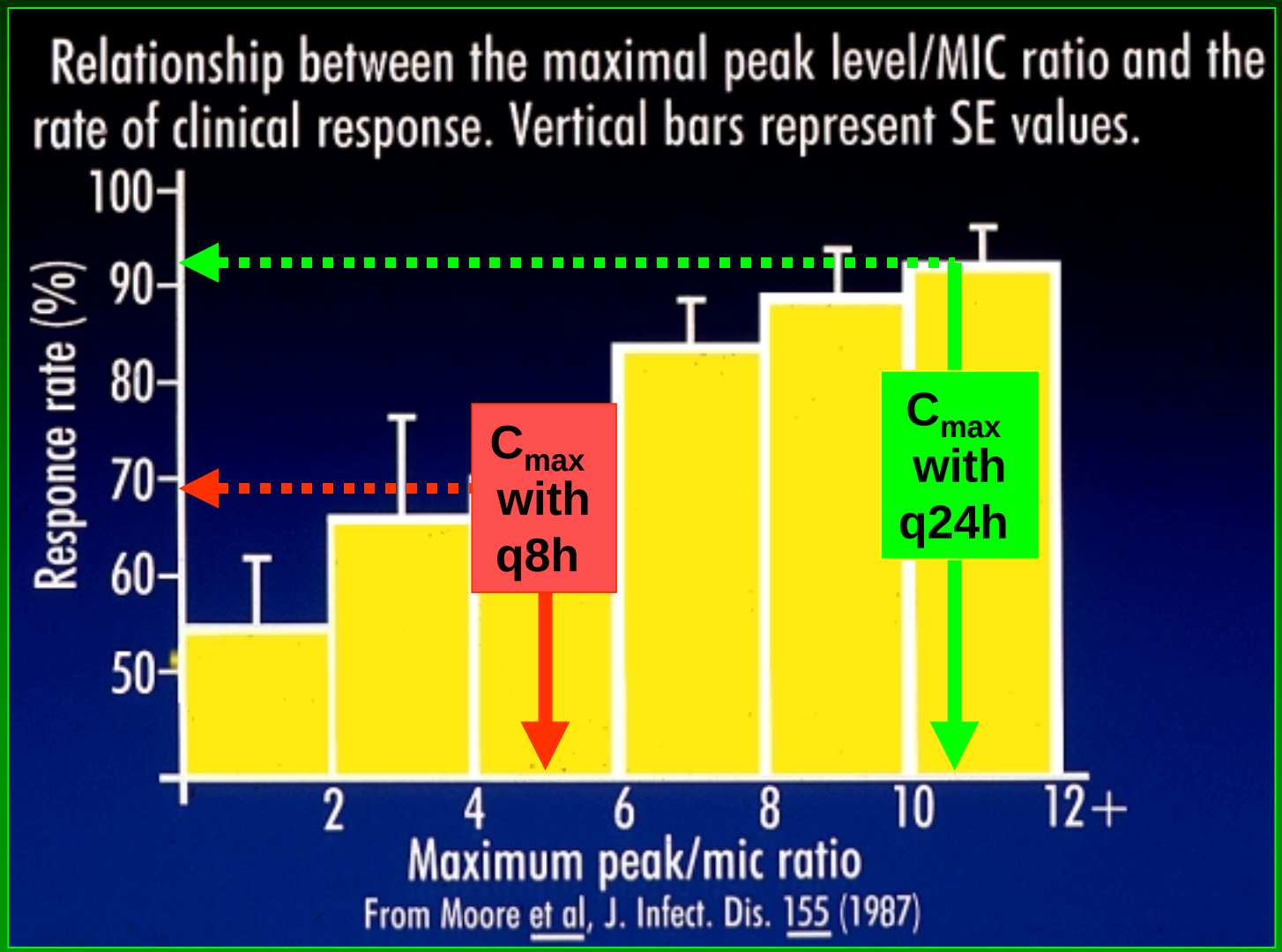
- Tulkens, Clerckc-Braune, et al. Safety and efficacy of aminoglycosides once-a-day: experimental data and randomized, controlled evaluation in patients suffering from pelvic inflammatory disease. J Drug Devel (1988) 1:71-82
- Van der Auwera Pet al., Pharmacodynamic parameters and toxicity of netilmicin (6 mg/kg.day) given once daily or in three divided doses to cancer patients with urinary tract infection., Antimicrob Agents Chemother (1991) 35:640-647
- Tulkens PM. Pharmacokinetic and toxicological evaluation of the once-daily regimen versus conventional schedules of netilmicin and amikacin. J. Antimicrob Chemother (1991) 27:49-61.

But, will once-a-day be effective ?

Aminoglycosides are concentration-dependent drugs...



Aminoglycosidepeak /MIC ratio is predictive of clinical efficacy



How are you going to show that patients will benefit of receiving aminoglycosides once-a-day ?

Proof of concept

moderately sick patients

Internal Medicine

success

Setting the limits

selected severe situations

neutropenic patients

success

How large can the benefit be ?

enlarged population

- **intensive care**
- **neonates**
- **nosocomial pneumonia,**
- **...**

The worldwide progress of the once-a-day made by clinicians ...

- 1989 - 1993: 14 comparative studies in all major indications showing = or > efficacy and = or < toxicity
  - ➔ one mini-review in AAC (Gilbert, 1991)
  - ➔ one ICAAC symposium
  - ➔ FDA petition
  - ➔ one re-registration (netilmicin)
- 1993 - 1999: 245 studies (≥ eff. ; ≤ tox) in almost every indication
  8 meta-analyses supporting the once-a-day
  - ➔ several editorials *
  - ➔ inclusion in textbooks **
  - ➔ isepamicin is developped and registered once-a-day

---

* Gilbert, CID, 1997: " there is no need of further studies…"
** In Mandell & assoc. (aminoglycoside chapter) as from 1995

Aminoglycosides in the last 2 years

- Is the once-a-day schedule used ?
- Is it good for all indications ?
- Do we understand AG toxicity ?
- Can we better prevent AG toxicity
- Other toxicities ...
- Do we still need aminoglycosides ?

Is the once-a-day schedule used ?

Clin Infect Dis 2000 Mar;30(3):433-9

National survey of extended-interval aminoglycoside dosing (EIAD).

Chuck SK, Raber SR, Rodvold KA, Areff D.

- **500 acute care hospitals in the United States**
- **EIAD adopted in 3 of every 4 acute care hospitals**
  - **4-fold increase since 1993**
  - **written guidelines for EIAD in 64% of all hospitals**
- **rationale**
  - **87.1% : equal or less toxicity (),**
  - **76.9% : equal efficacy**
  - **65.6% :cost-savings**
- **dose: > 5 mg/Kg**
- **47% used extended interval in case of decline in renal function (38% with Hartford nomogram)**

Is the once-a-day schedule good for all indications ?

Indications for which questions are still often raised:

- febrile neutropenia (what is the organism ?)
- cystic fibrosis (abnormal V_d and Cl)
- endocarditis (synergy)
- “special situations” (like peritoneal dialysis)
- ...

Once-a-day schedule in febrile neutropenia ...

J Antimicrob Chemother 2000 Mar;45(3):383-6

Once-daily versus multiple-daily gentamicin in empirical antibiotherapy of febrile neutropenia following intensive chemotherapy.

Bakri FE, Pallett A, Smith AG, Duncombe AS.

- **Gentamicin (7mg/kg per day qD *vs* multiple doses) + azlocillin**
- **52 episodes of febrile neutropenia in 28 patients (80.2 % with undocumented cause...)**
- **response rate 3 x higher in the qD group (p = 0.012)**
- **NS increase in toxicity**

In this clinical context once-daily gentamicin is more effective than a multiple-daily dosing regimen but may be more toxic...

Once-a-day schedule in cystic fibrosis ...

Cochrane Database Syst Rev 2000;(4):CD002009
Once daily versus multiple daily dosing with intravenous aminoglycosides for cystic fibrosis (Cochrane Review).
Tan K, Bunn H.

- **Two trials (n=70 patients) qD vs tid**
- **data on Forced Expiratory Volume at one second (FEV1), Forced Vital Capacity (FVC), nutritional status and side effects**
- **no significant difference in efficacy or in the incidence of ototoxicity and nephrotoxicity**

There is a need for an adequately-powered, multicentre, randomised controlled trial assessing qD vs md dosing of AG in cystic fibrosis.

Once-a-day schedule in endocarditis ...

Pharmacotherapy 2000 Sep;20(9):1116-9

Once-daily aminoglycoside in the treatment of Enterococcus faecalis endocarditis: case report and review.

Tam VH, Mckinnon PS, Levine DP, Brandel SM, Rybak MJ.

- **To date, no case reports or clinical trials have examined its utility in human enterococcal endocarditis.**
- **A patient with right-sided endocarditis caused by Enterococcus faecalis was succesfully treated by once-daily gentamicin.**
- **Clinical and bacteriologic cures of this patient raise questions as to whether enterococcal endocarditis should still be be regarded as contraindication to ODA.**

The clinical utility of ODA in this disease deserves further investigation.

Once-a-day schedule in peritoneal dialysis ...

Adv Perit Dial 2000;16:280-4

Use of bolus intraperitoneal aminoglycosides for treating peritonitis in end-stage renal disease patients receiving continuous ambulatory peritoneal dialysis and continuous cycling peritoneal dialysis.

Mars RL, Moles K, Pope K, Hargrove P.

- **6 patients -- 5 mg/kg tobramycin -- 6 continuous nightly cycles with daytime dwell**
- **$t_{1/2}$ = 29.3 ± 3.5 h (therapeutic blood levels persisted for 72-96 hours)**
- **no change in audiograms at 17 days**

- **no clinical oto/vestibular toxicity,**
- **cost-effective,**
- **convenient strategy for patients and nursing staff.**

Do we understand aminoglycoside nephro- and oto-toxicity and its relation to dosage ?

- apoptosis ...
  - ➔ is this the cause of the toxicity at clinical doses ?
- impairment of Mrp2 et PgP efflux systems
  - ➔ does the cell get indirectly intoxicated ?
- interaction with NMDA receptor
  - ➔ can we dissociate activity and toxicity ?

Mimicking human clinical dose in animals

El Mouedden et al., 2000

TABLE 1. Experimental groups, conditions of treatments, and relevance to the clinical use of aminoglycosides

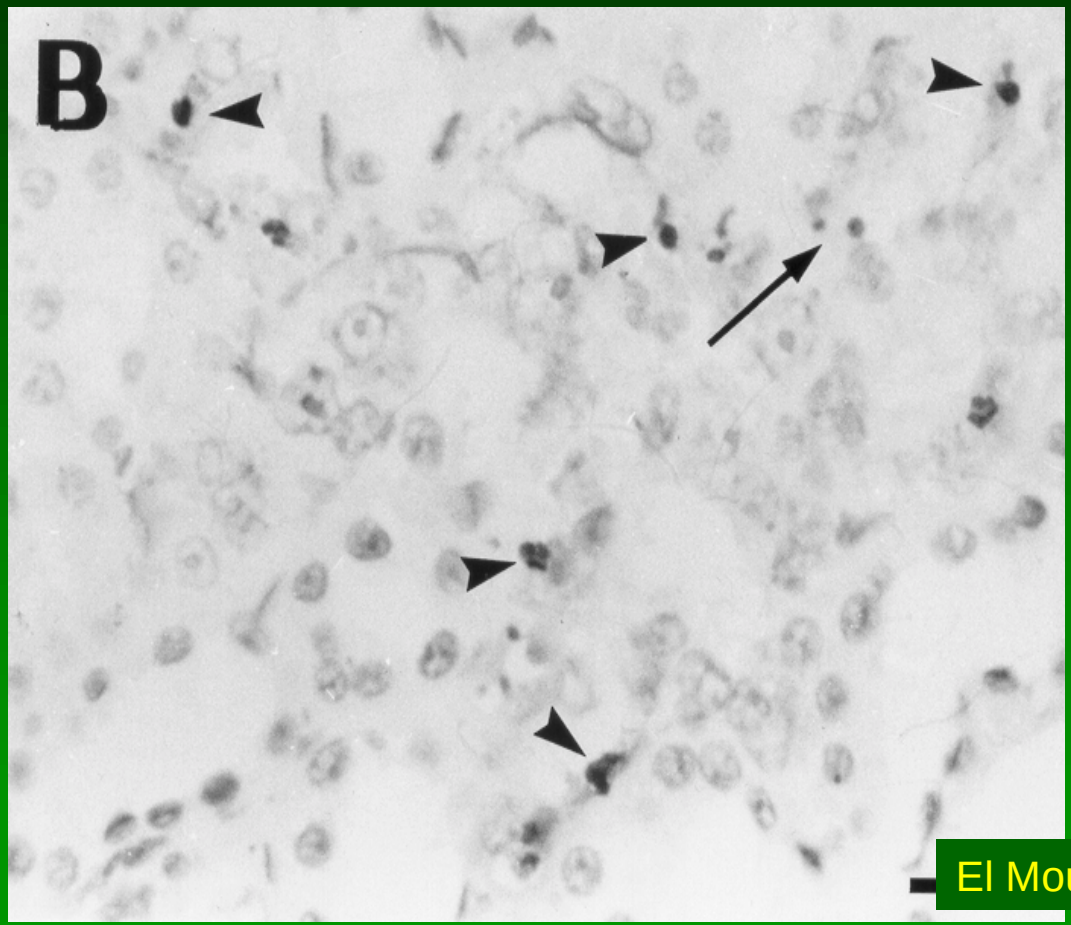
Drug	Dose (mg/kg)[a]	Duration (days)	Fold increase over:	
			Clinical dose[b]	Clinical daily drug exposure[c]
Gentamicin	10	4–10	~2	~0.5
	20	4–10	~4	~1
Netilmicin	10	4–10	~1.7	~0.4
	20	4–10	~3.3	~0.8
Amikacin	40	10	~2.7	~0.7
Isepamicin	40	10	~2.7	~0.7

[a] Twice-a-day schedule (daily dose split into two administrations at 12-h intervals). This schedule (or even a three-times-a-day schedule) was long considered mandatory for aminoglycosides but is known to increase toxicities at both low and high doses in animals (38, 52). Data for patients are less definite, even though a trend toward less toxicity is commonly observed with a once-a-day schedule (21, 48).

[b] Suggested maintenance doses for an adult patient with an estimated creatinine clearance of 90 ml/min (20) (gentamicin, 5.1; netilmicin, 6; and amikacin, 15 mg/kg, respectively) or based on the registered dosage in Belgium and many other countries for isepamicin.

[c] Based on estimated ratio of areas under the serum concentration-time curve, AUC ratio, using the dose ratio defined in footnote *b* and assuming apparent half-lives of ~30 min in rats and ~120 min in humans (β-elimination phases).

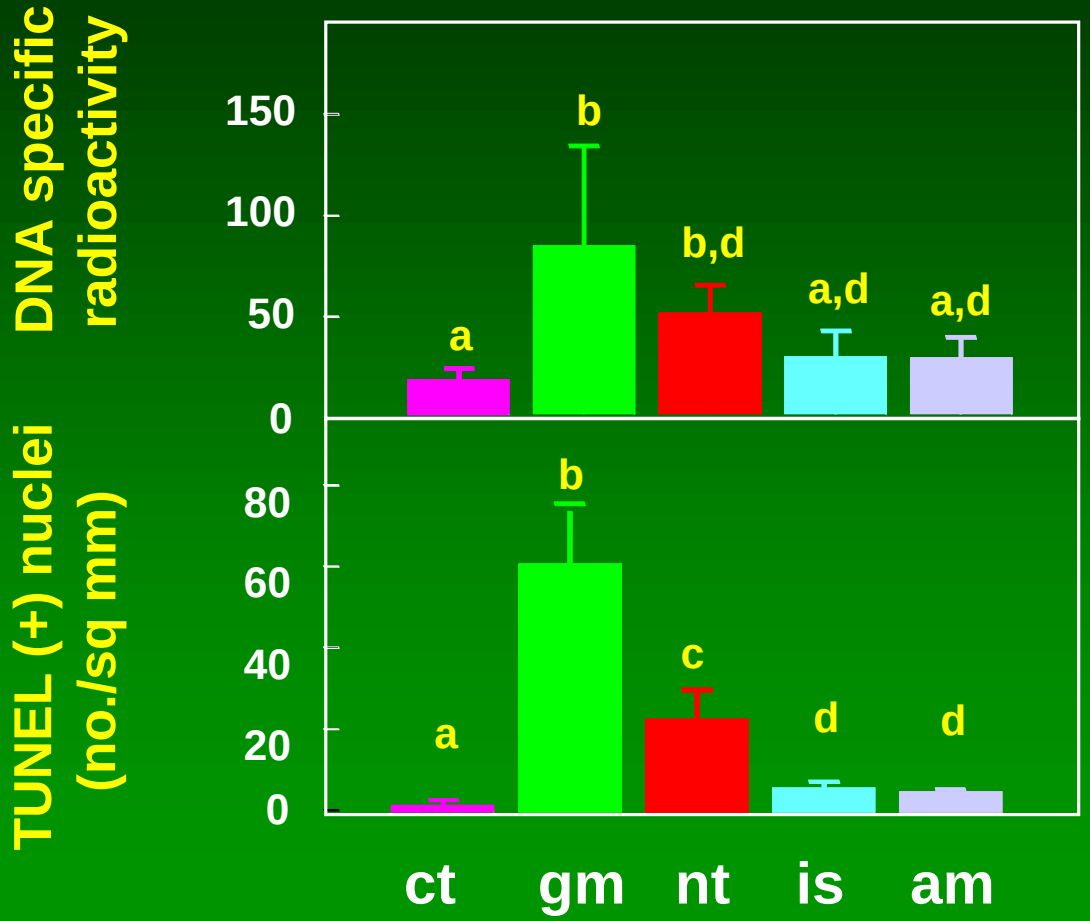
Evidence of apoptosis in proximal tubular cells: TUNEL staining



El Mouedden et al., 2000

gentamicin 10 mg/kg, 10 days

The severity of AG-induced regeneration (top) and apoptosis (bottom) at “clinical doses” varies among derivatives ...



El Mouedden et al., 2000

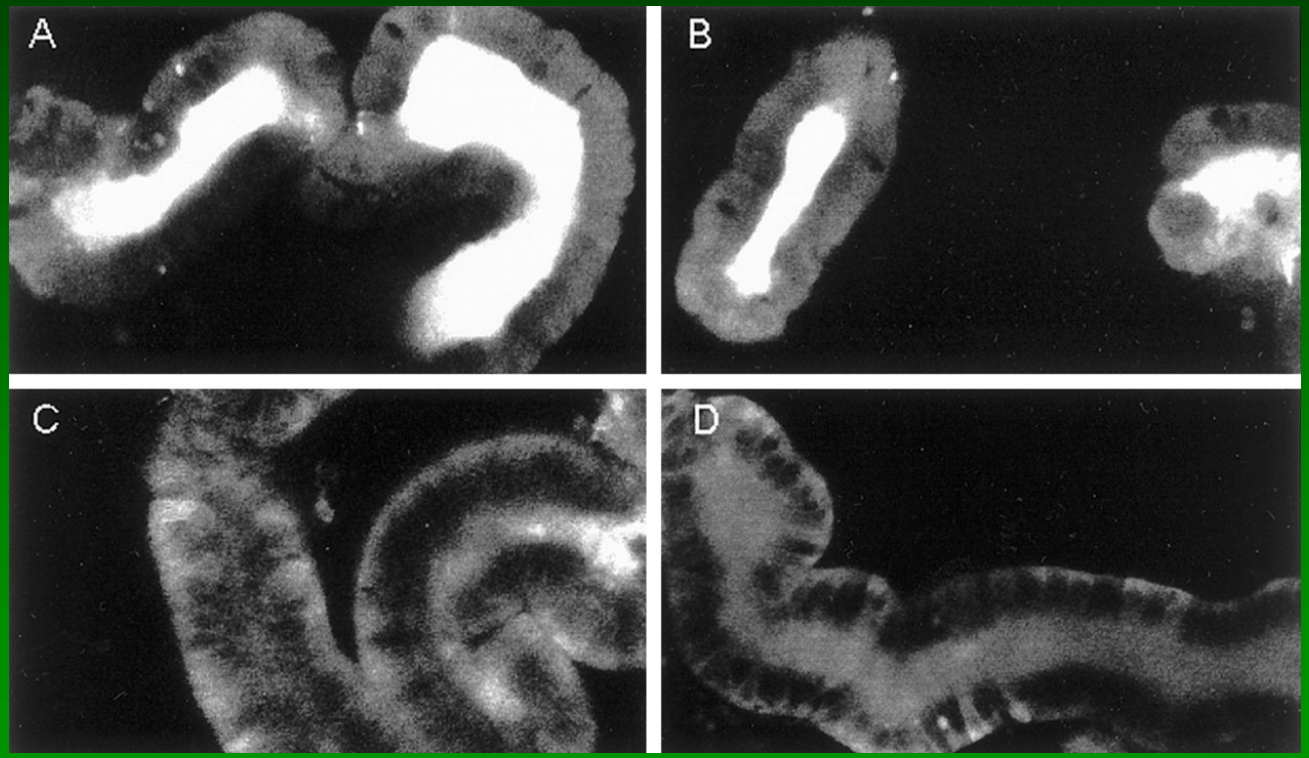
ct = control
gm = gentamicin (10mg)
nt = netilmicin (10 mg)
is = isepamicin (40 mg)
am = amikacin (40 mg)

Aminoglycosides inhibit Mrp2 and P-glycoprotein-mediated fluoresecin-labelled methotrexate transport in killifish proximal tubular cells

controls

amikacin
50 µM or ~ 25 mg/L

gentamicin
10 µM or ~ 5 mg/L

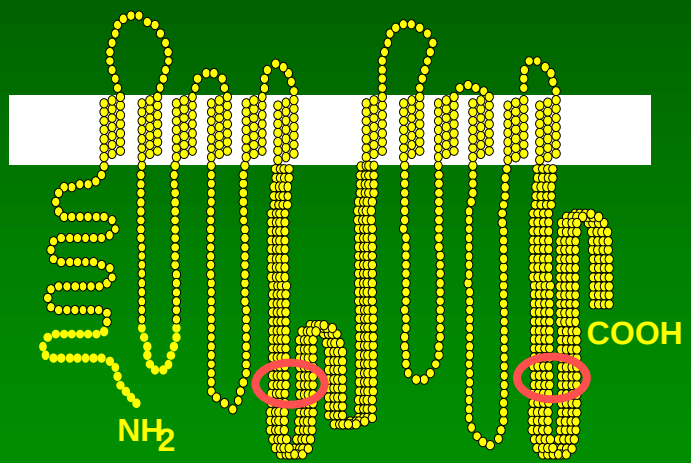


Terlouw et al., Mol. Pharmacol. 59:1433-1440, 2001

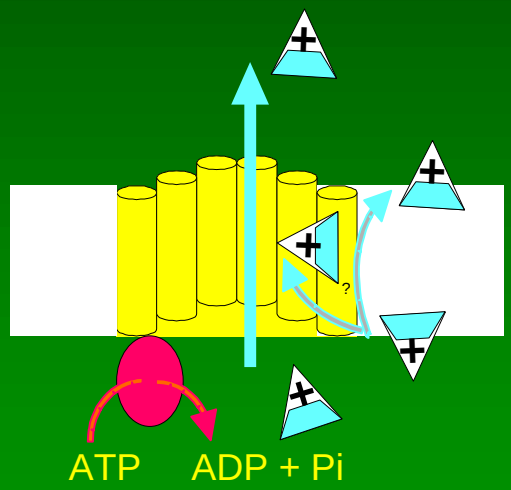
Most frequent antibiotic-pumps in eucaryotes (1/2)

Multiple Drug Resistance (MDR also known as PgP)

TOPOLOGY



MECHANISM



ANTIBIOTICS

tetracyclines
fluoroquinolones
erythromycin
lincosamides
rifampicin

chloramphenicol

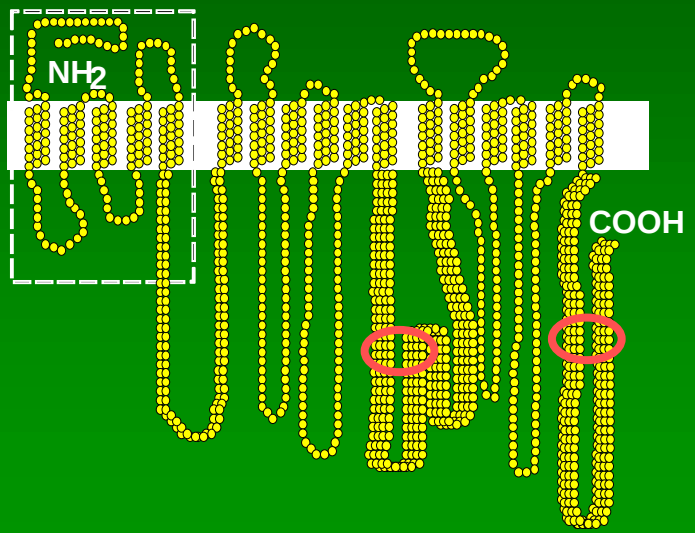
aminoglycosides

Van Bambeke et al.,Biochem. Pharmacol. 2000

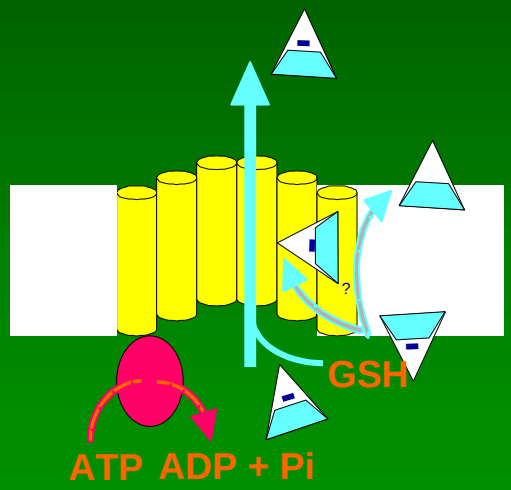
Most frequent antibiotic-pumps in eucaryotes (2/2)

Multidrug Resistance Proteins (Mrp1 - Mrp2)

TOPOLOGY



MECHANISM



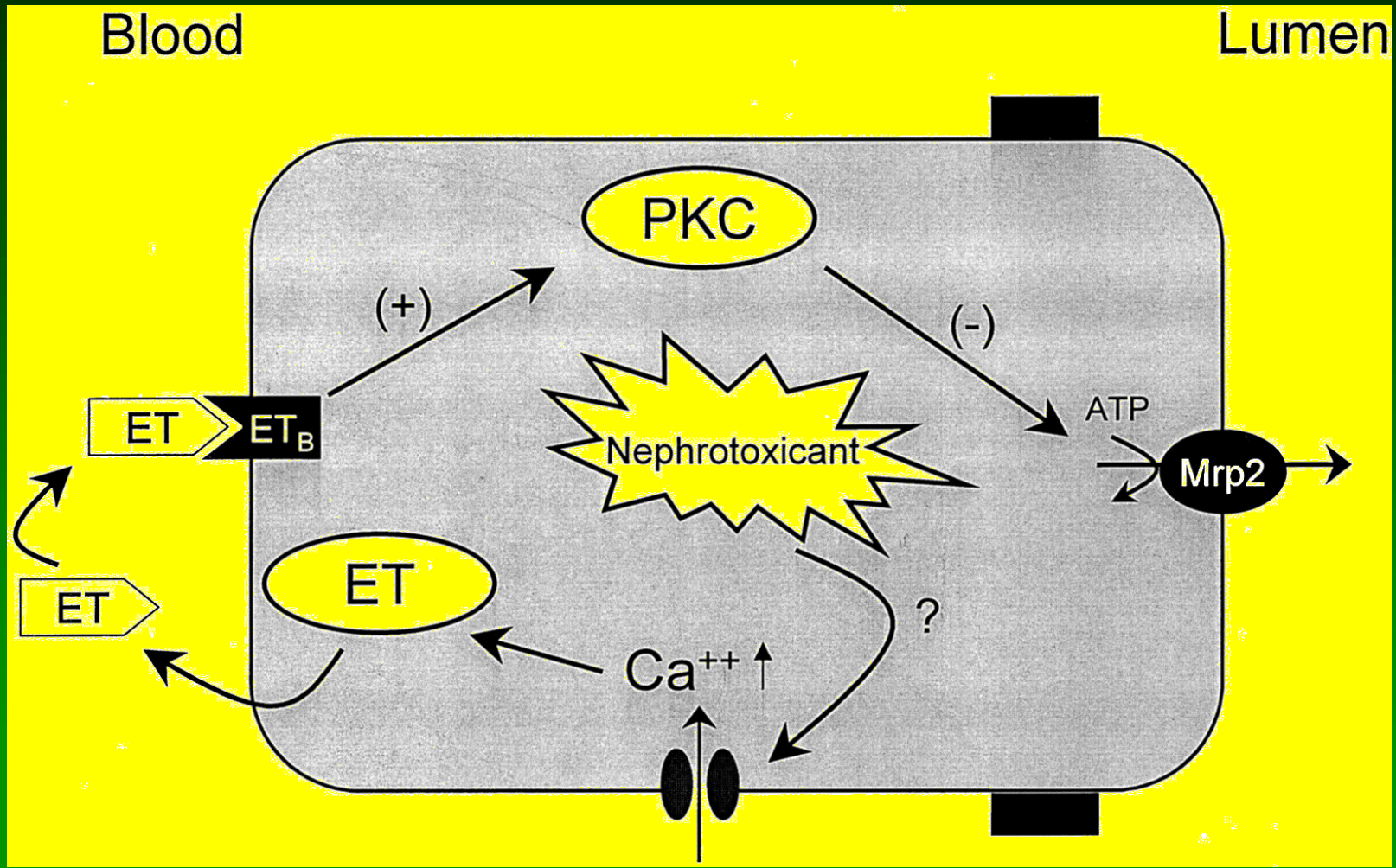
ANTIBIOTICS

fluoroquinolones
β-lactams

tetracyclines
macrolides

Van Bambeke et al.,Biochem. Pharmacol. 2000

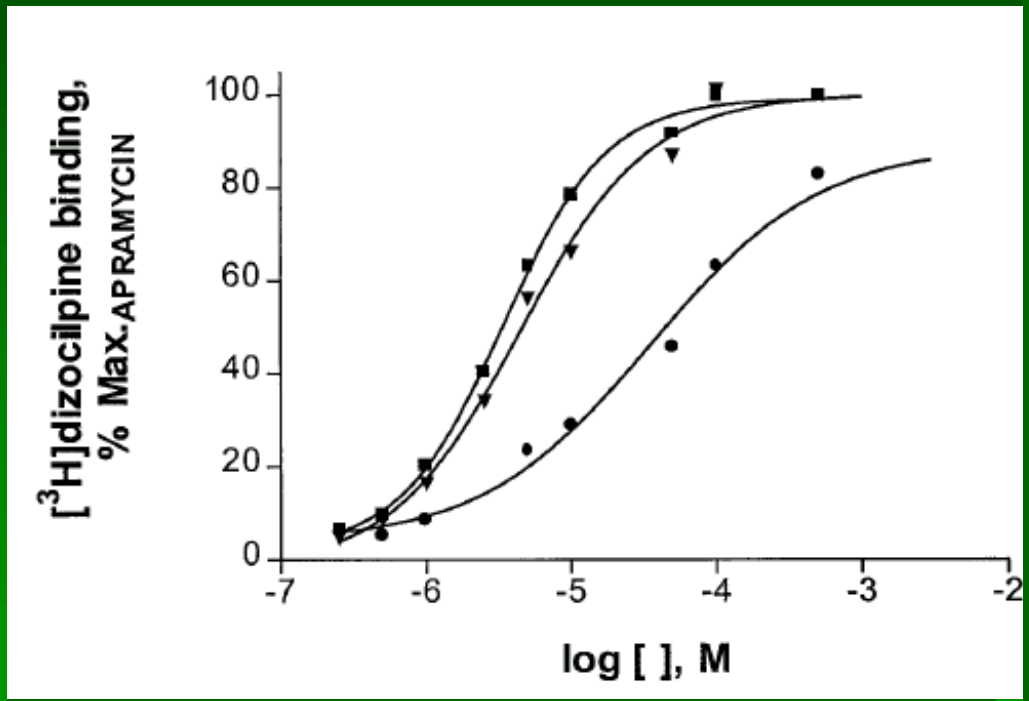
Mrp2 is inactivated by nephrotoxins throuh Ca^{2+}-induced endothelin release and PKC activation ...



Terlouw et al., Mol. Pharmacol. 59:1433-1440, 2001

AG and NMDA receptor ...

Polyamines → **Activation of the NMDA receptor** → **cochleo-toxicity**

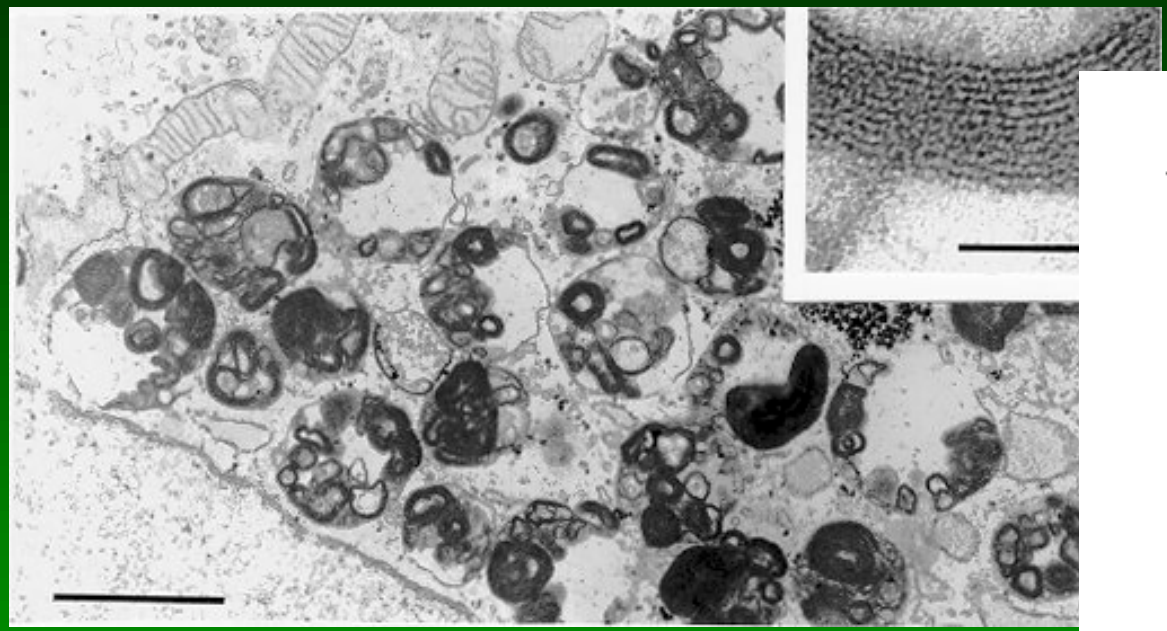


Activation of the NMDA receptor by apramycin (■) and phthalimidoapramycin (●)
Scott et al., Eur. J. Pharmacol. 387:1-7, 2000

	EC_{50} µM	MIC mg/L
N-ethyl-apramycin	3.2*	32
apramycin	3.9	4
cyclocarbonyl-apramycin	19	8

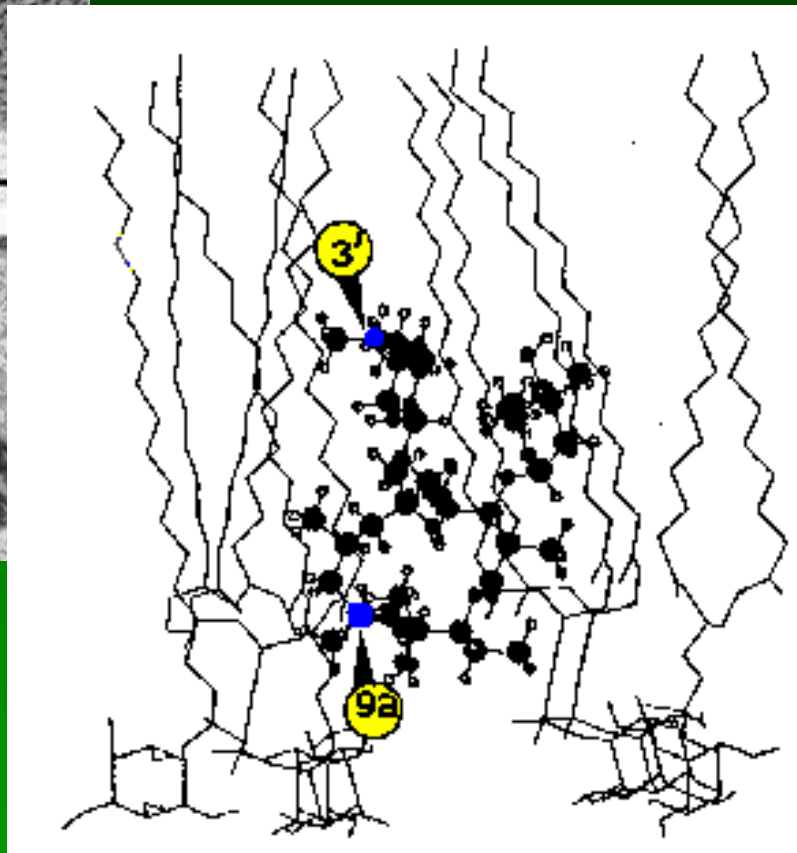
* ~ 2 mg/L

The macrolides in 5 slides...



azithromycin (10 mg/L) causes a phospholipidosis in cultured fibroblasts within 2-3 days

Van Bambeke et al., Eur. J. Pharmacol., 1996
Montenez et al. Tox. Appl. Pharmacol. 1999

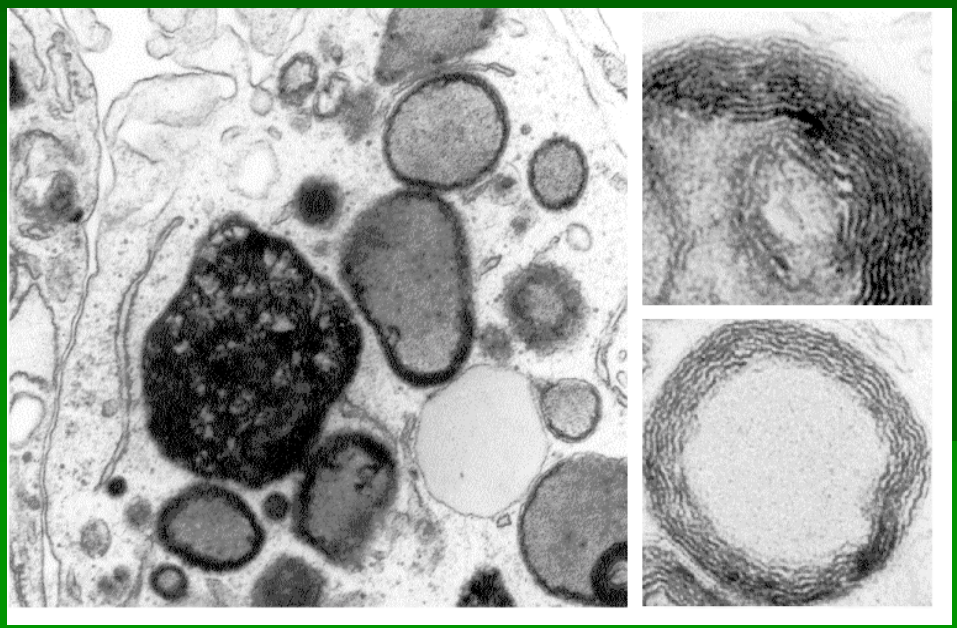


… because it interacts with phospholipids

Phospholipidosis induced by macrolides… Implication for drug early evaluation ?

Long-term (7 days culture) exposure to low doses (0.03 to 10 mg/l) of azithromycin ...

Morphology at 0.1 mg/ml:



Biochemistry:

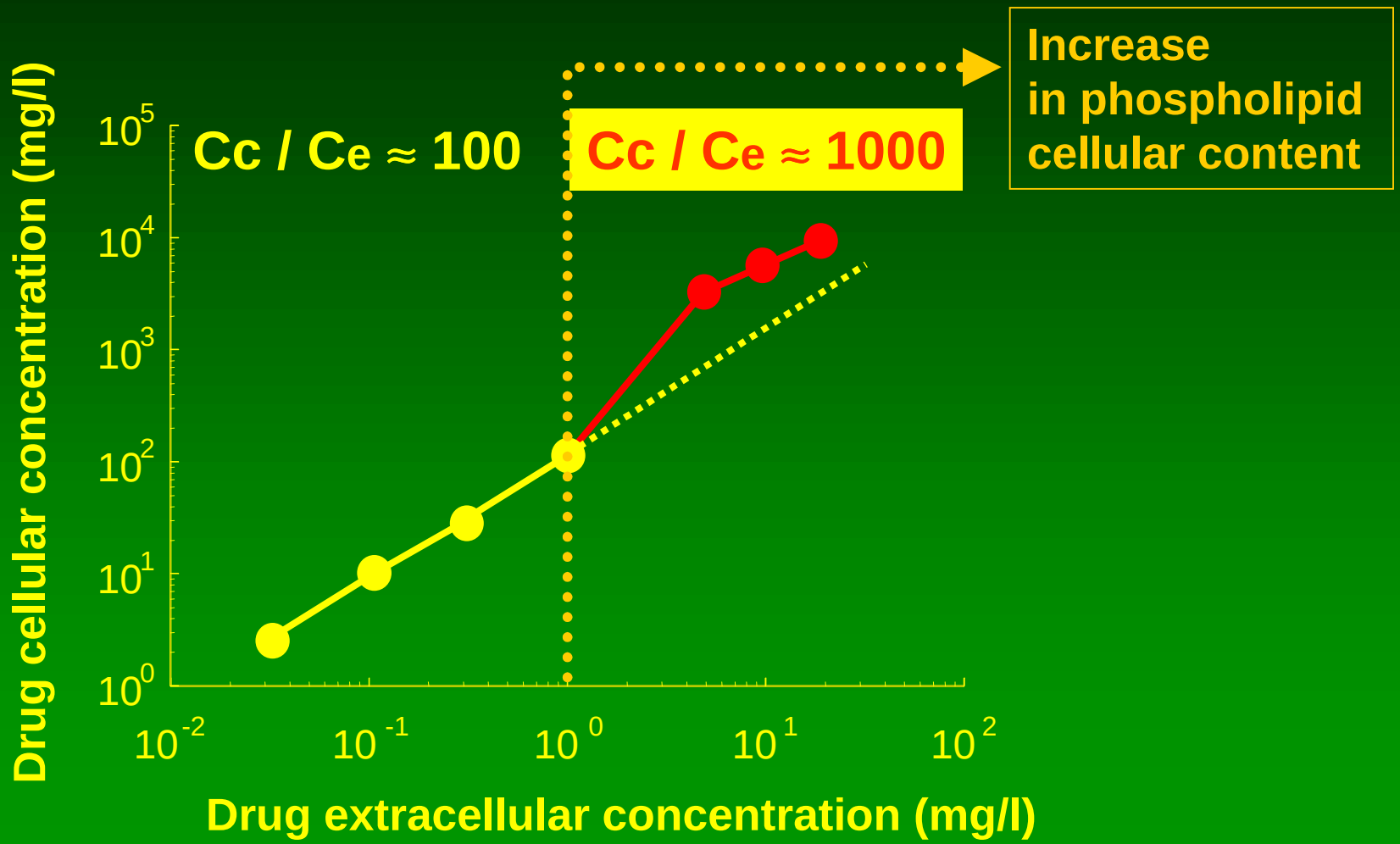
Cathepsin B activity ↗ > 1 mg/l

Phospholipid content ↗ > 5 mg/l

Cholesterol content ↗ > 10 mg/l

Van Bambeke *et al*, JAC,1998

Phospholipidosis induced by macrolides… Implication for drug early evaluation ?

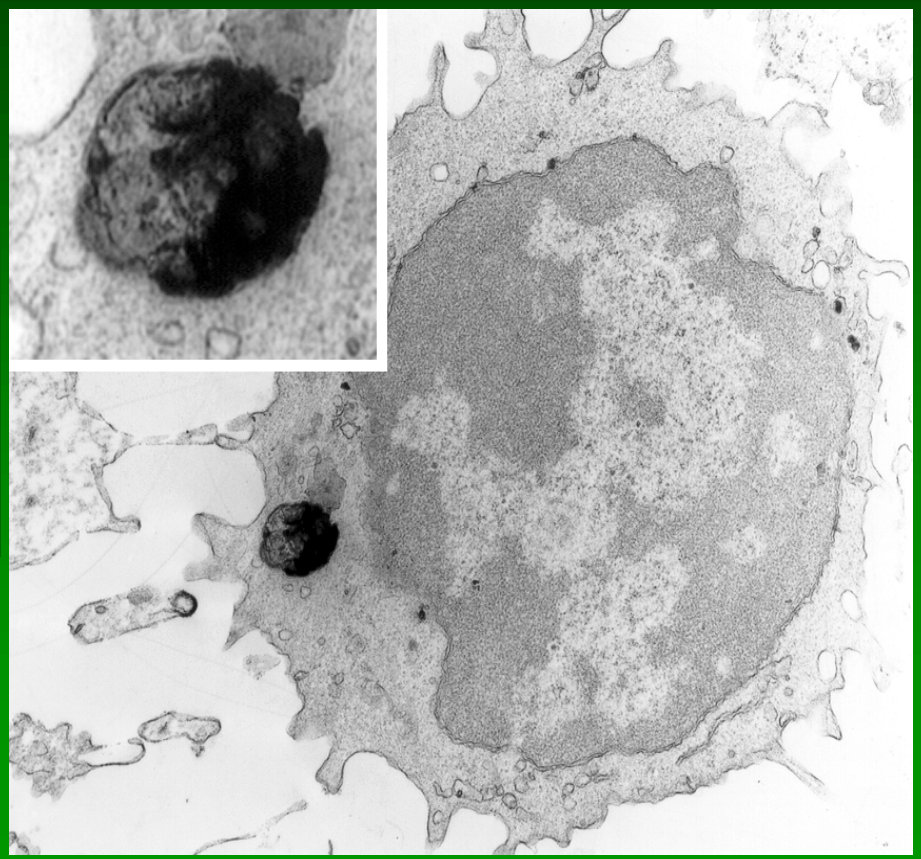


Van Bambeke *et al*, 1998

Toxicodynamic models for the discovery of cellular alterations induced by macrolides

Long-term therapy with azithromycin ...

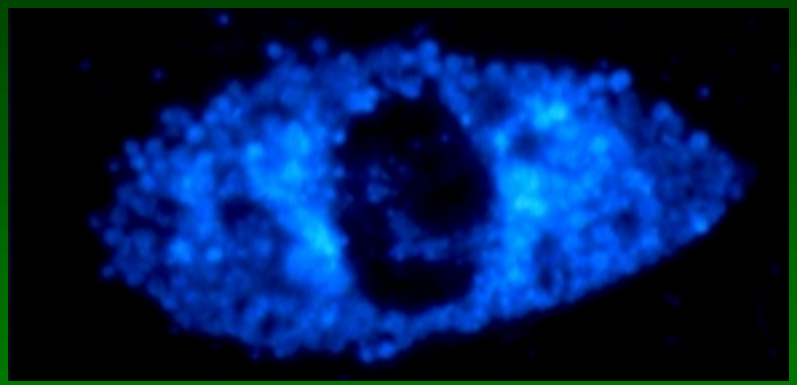
lymphocyte of a patient treated with azithromycin 1200 mg once-a-week during several weeks



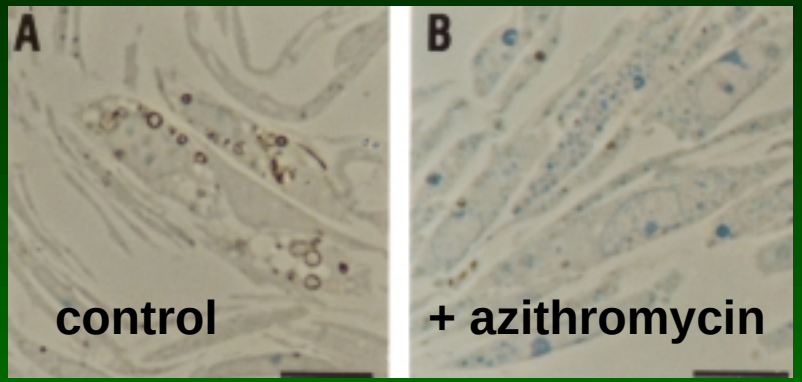
Y. Van Laeyhem & F. Van Bambeke, unpublished

Toxicodynamic models for the discovery of cellular alterations induced by macrolides

Unsuspected effects ....

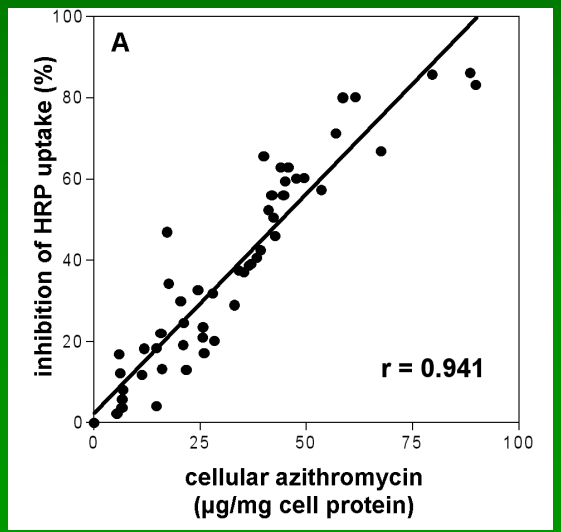


Accumulation of cholesterol…
(filippin staining)



Impairment of endocytosis…
(horseradish peroxidase uptake)

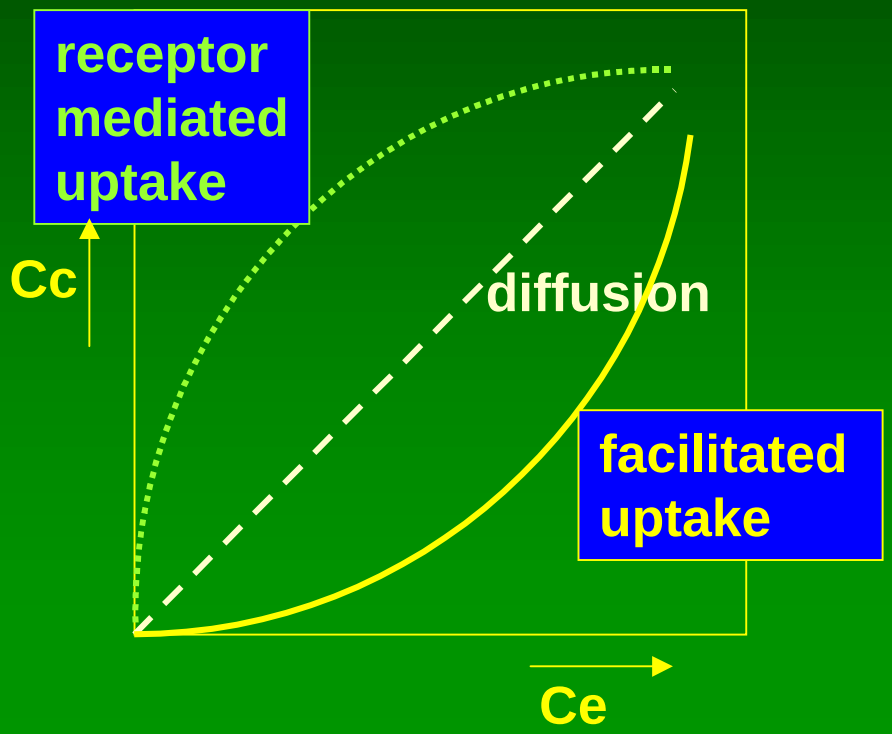
… in relation with azithromycin accumulation

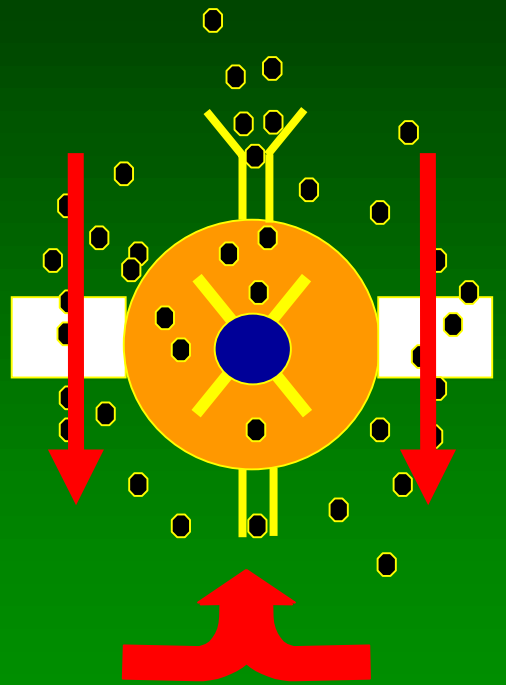


Tyteca et al., Eur. J. Cell Biol., in press

The fluoroquinolones in 3 slides ... or evidencing efflux

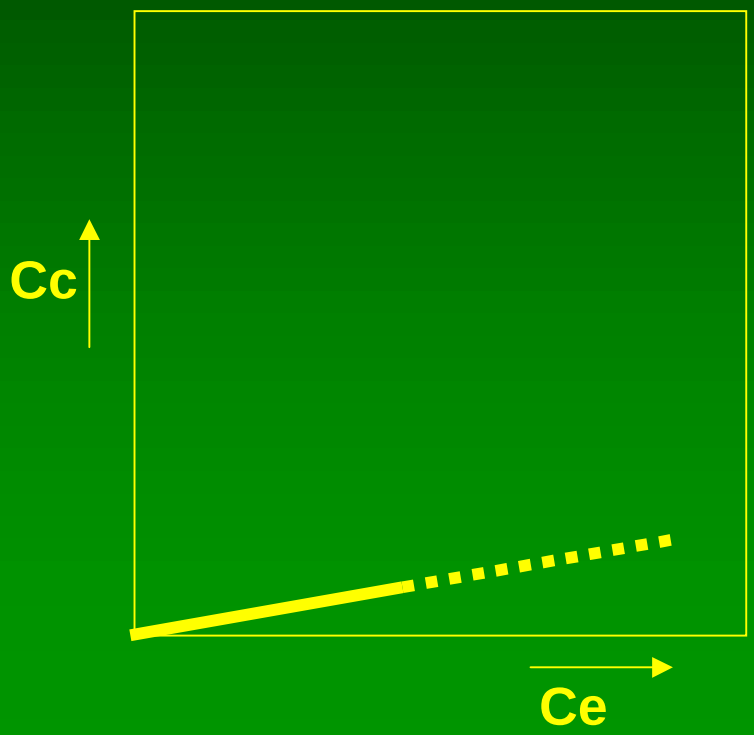
non linear accumulation kinetics ...

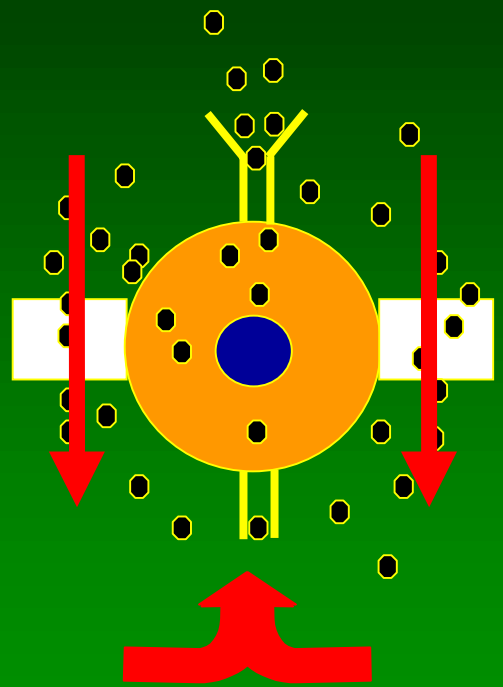




Evidencing active efflux ...

accumulation à low concentration

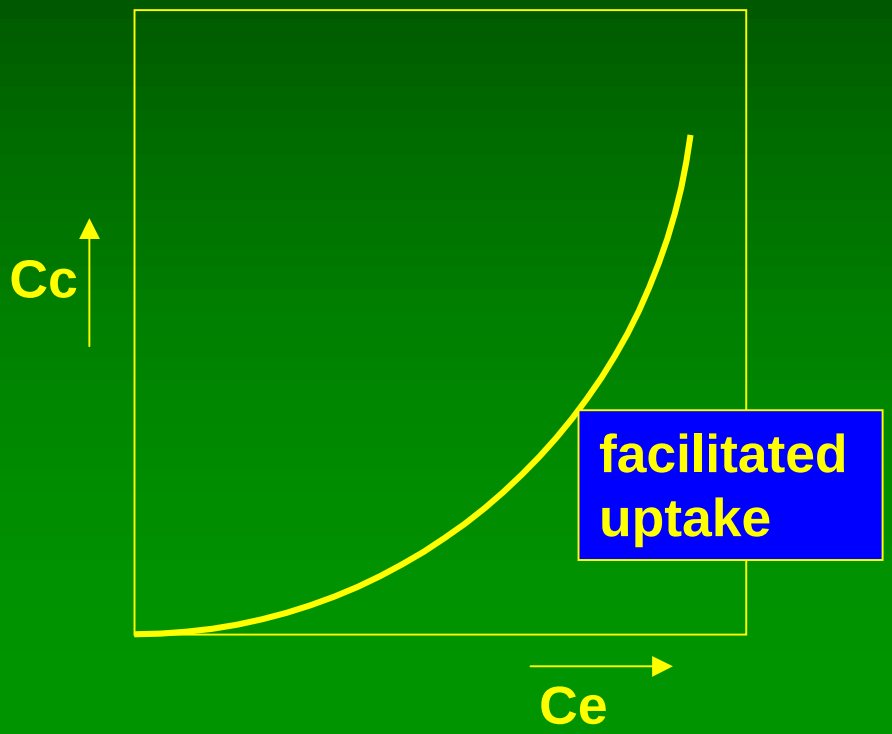


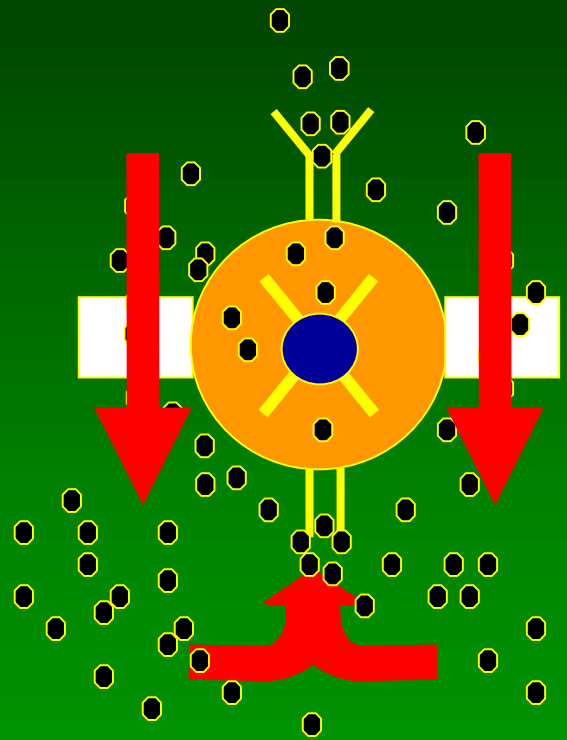


uptake is defeated by active efflux

Evidencing active efflux ...

accumulation at large concentrations ...



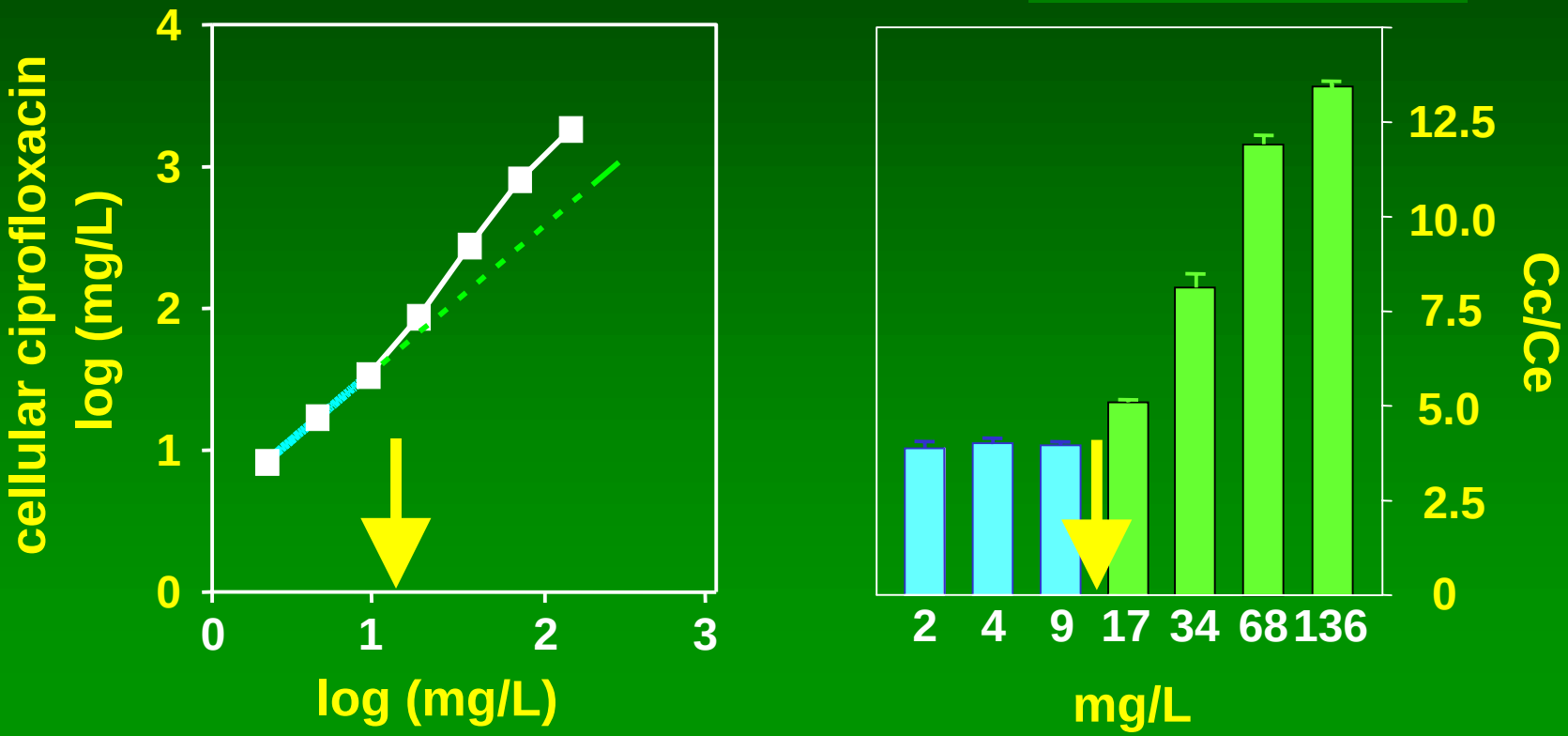


saturation of efflux !

Active efflux of ciprofloxacin

Ciprofloxacin accumulation is facilitated upon increase of its extracellular concentration

Michot et al., ICAAC 2000



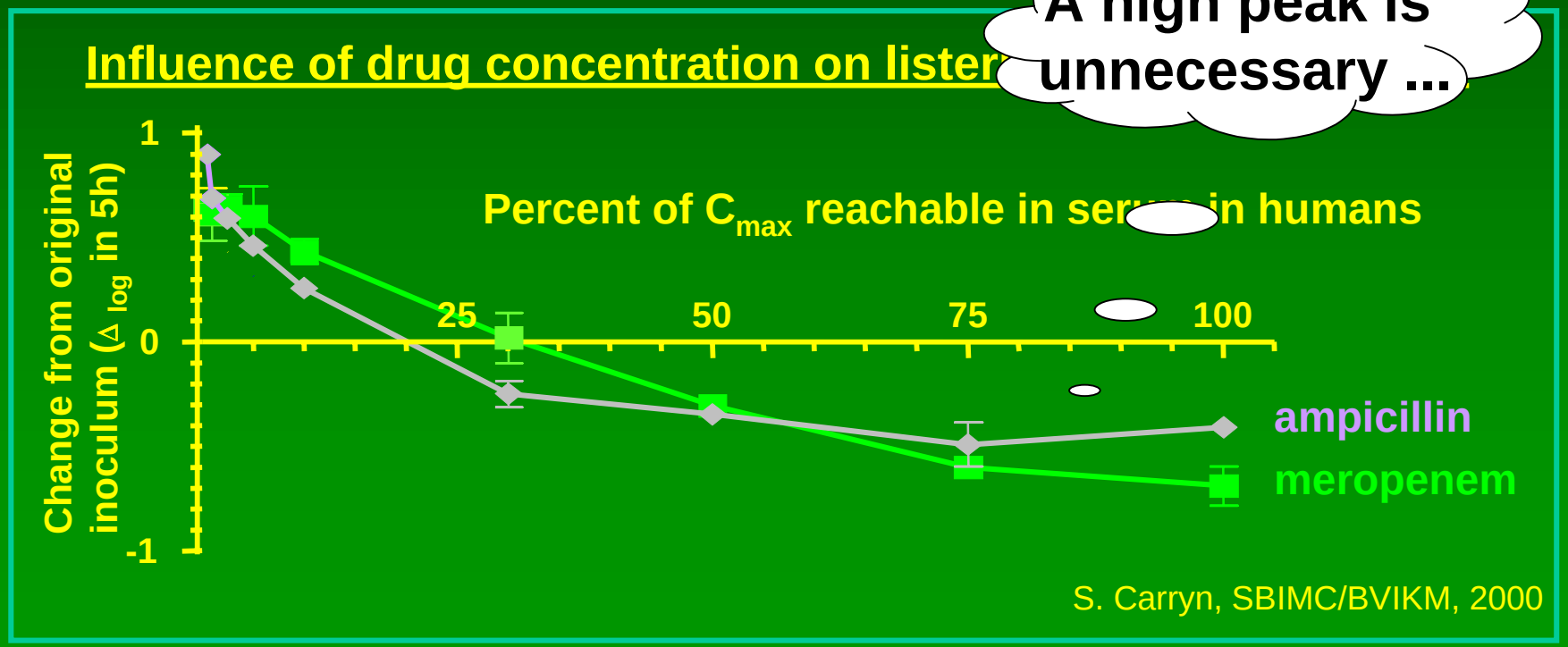
extracellular [ciprofloxacin] - 2h incubation at 37°C

Now, the β-lactar

Why wouldn't you try a continuous infusion ?

- time-dependent antibiotics
- little or no influence of the concentration once above a treshold (4 x the MIC for most organisms)

A high peak is unnecessary ...



Continuous infusion of ceftazidime in ICU (3 g/day)

	Intermittent *(n=17)*	*Continuous* *(n=17)*
C max (mg/ml)	106.5 (34.6)	18.2 (6.5)
C min (mg/ml)	10.3 (16.0)	16.5 (5.7)
C mean (mg/ml)		17.4 (6.1)
T½ (h)	3.2 (2.5)	
AUC0-24h	777.4 (474.6)	419.7 (141.5)
Cl (ml/min)	142.5 (58.7)	133.2 (37.0)

Pharmacokinetocs and Pharmacodynamics of continuous and intermittent ceftazidime during the treatment of nosocomial pneumonia. D.P. Nicolau et al. *Clin Drug Invest 1999:18(2):133-139.*

PK / PD in action …
continuous infusion of β-lactams:
the case of ceftazidime (4g / day) in Intensive Care Units

$C_{ss} = K_o / Cl$

serum concentration

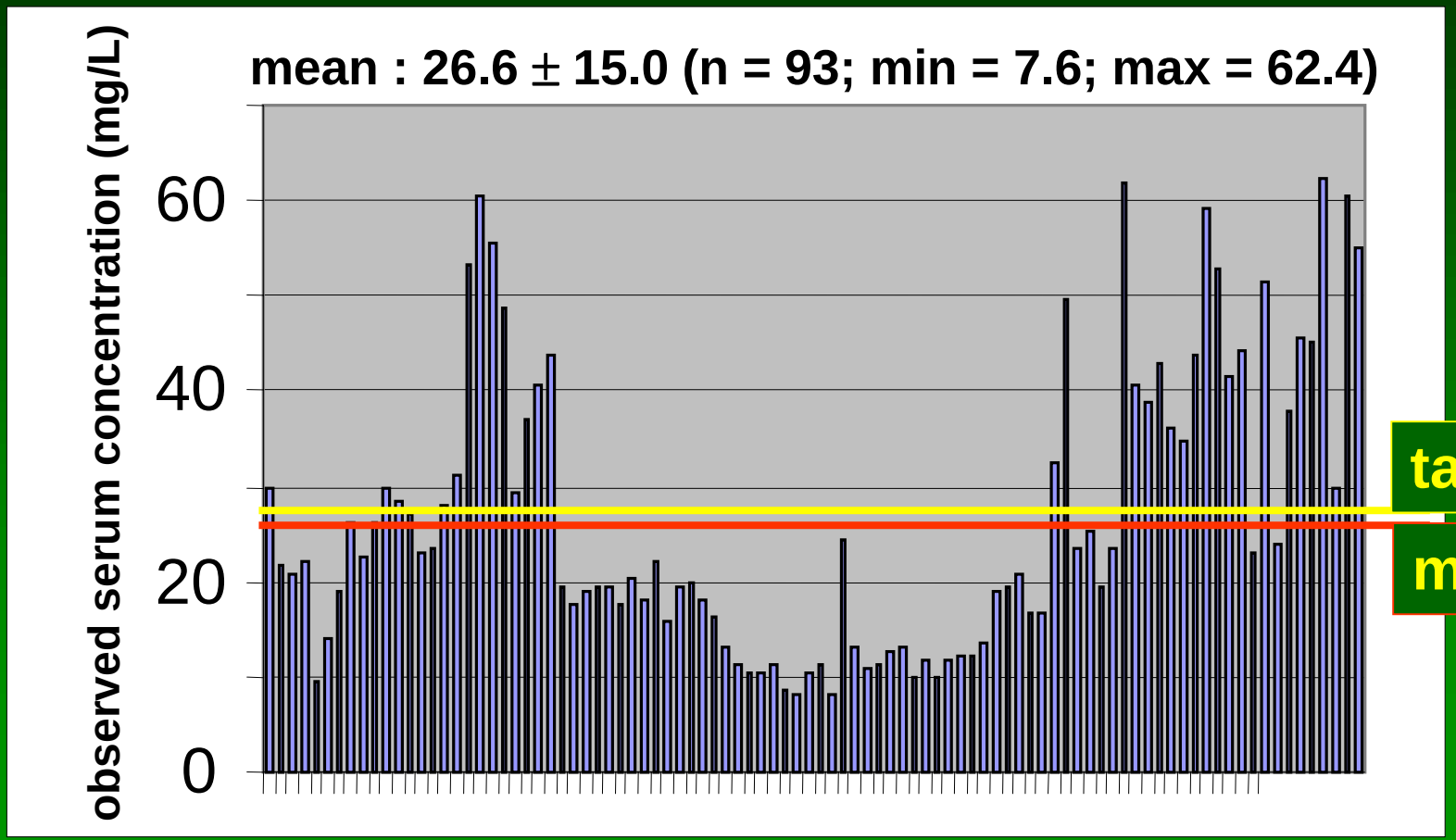
Clearance *

Infusion rate

27 [µg/ml] = { 2.77 [mg/min] / 102 [ml/min] } x 10^3

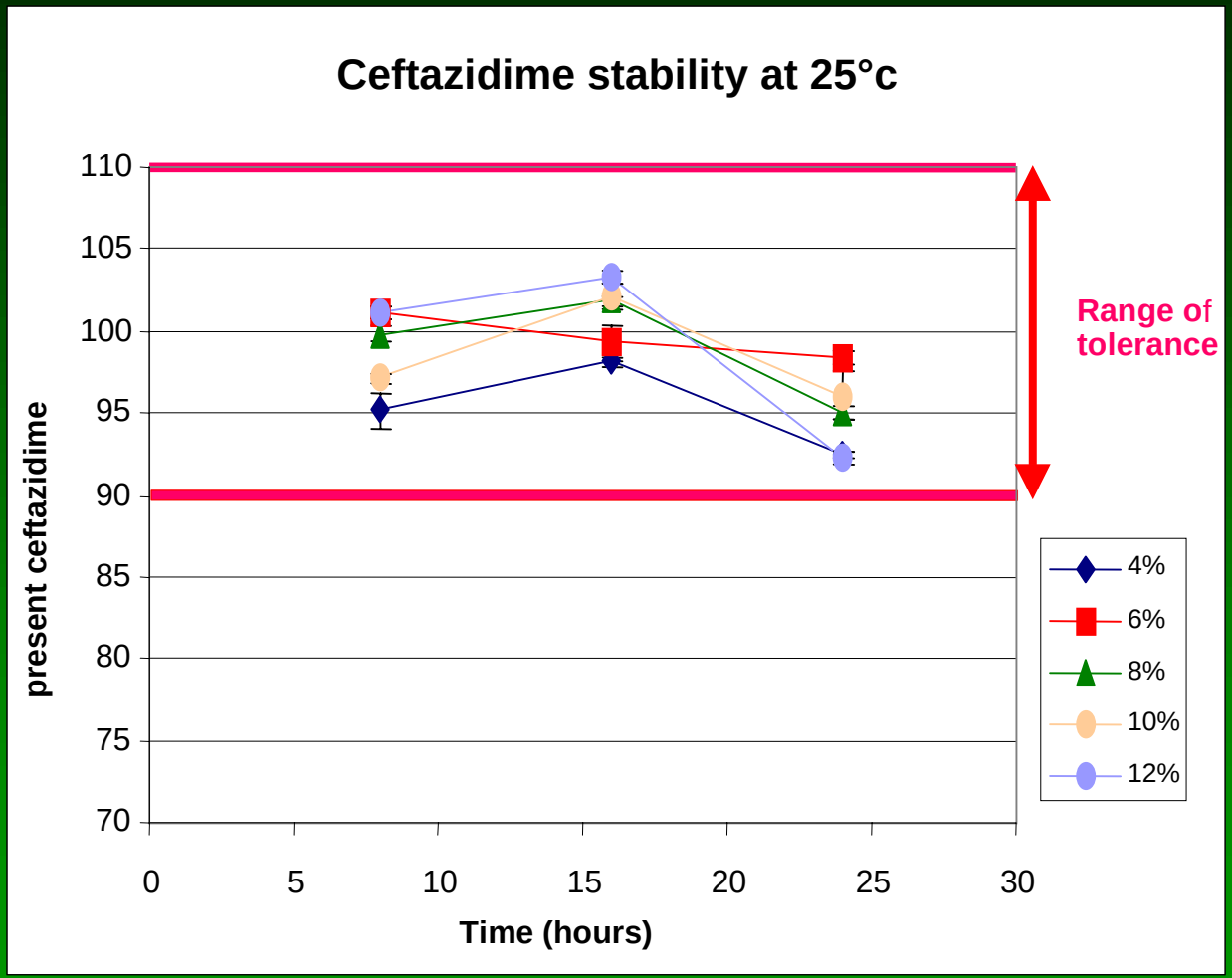
Targeted level for MIC's up to 6-8 mg/L …

PK / PD in action …
continuous infusion of β-lactams:
the case of ceftazidime (4g / day) in Intensive Care Units



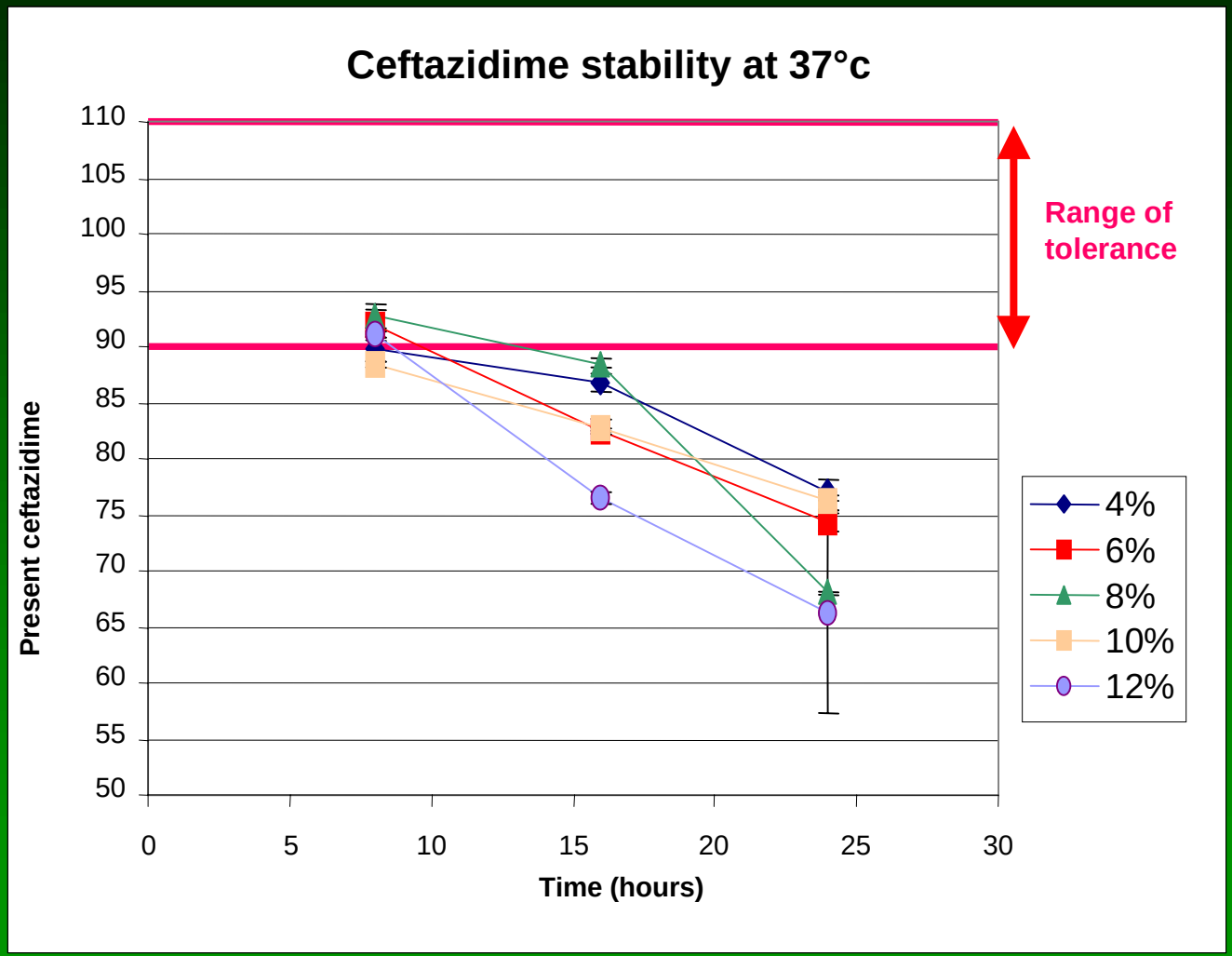
Servais, Laterre & Tulkens, unpublished

But is it safe ?
Ceftazidime stability studies … 25°C



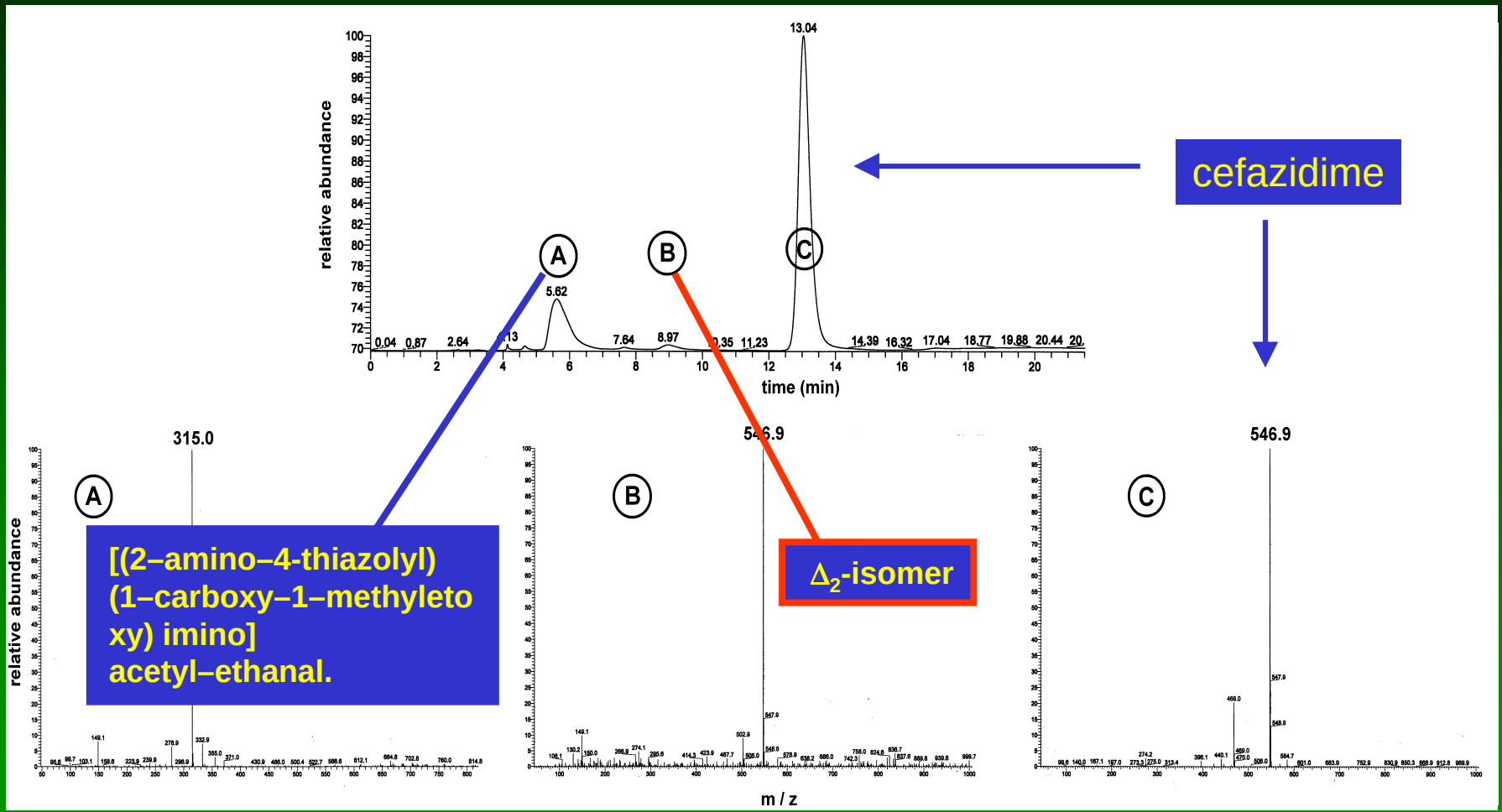
Servais & Tulkens, AAC, in press

But is it safe ?
Ceftazidime stability studies … 37°C ...



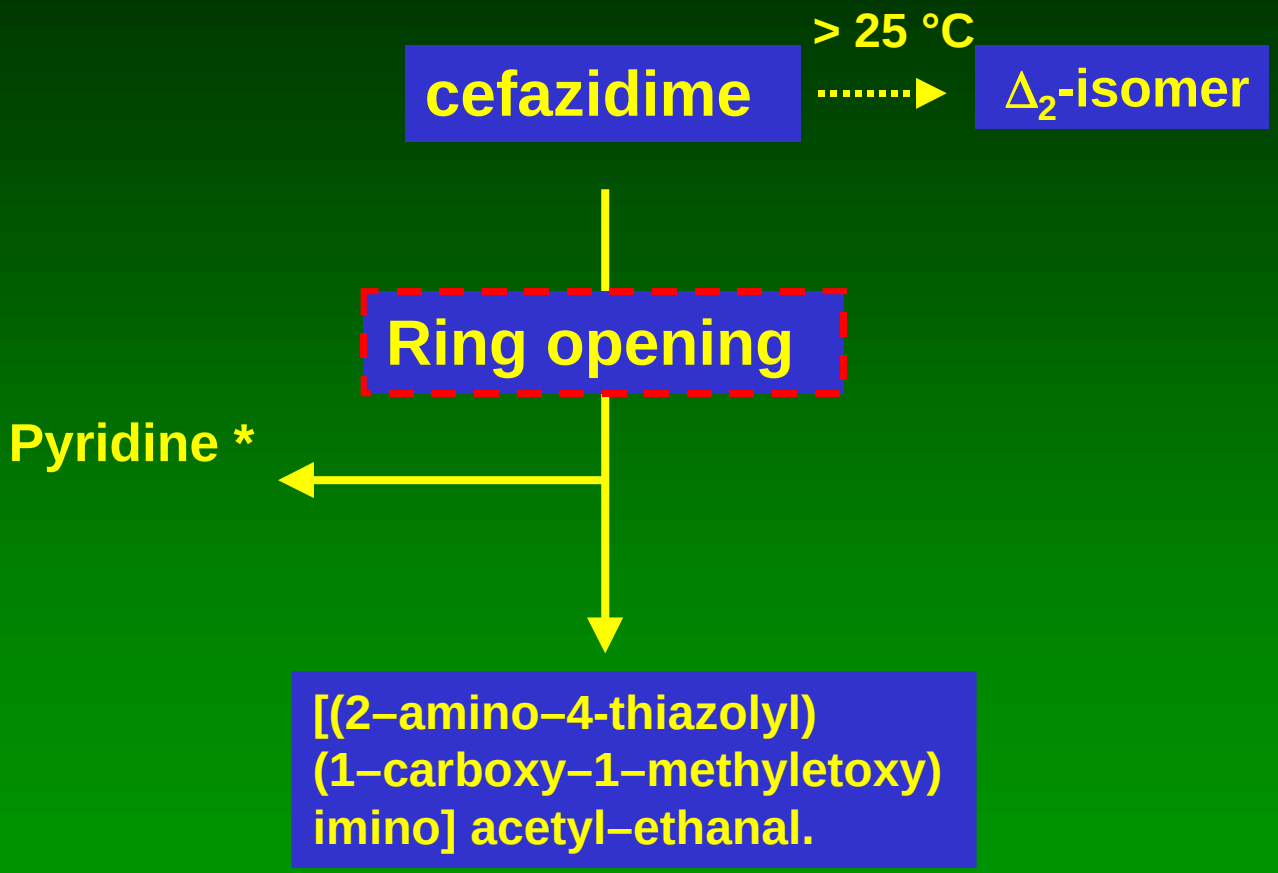
Servais & Tulkens, AAC, in press

Degradation products of ceftazidime



Servais & Tulkens, 11th ECCMID, 2001

Degradation pathways of ceftazidime
(24h in aqueous media)



* < 50 mg from an amount of 4 g in 24h at temp < 25°C

Servais & Tulkens, AAC, in press

Pharmacodynamics ...

It ‘s a brilliant idea....

But don’t forget toxicity...

Toxicodynamics ...

There is still MUCH work...

Novel antibiotics

Intracellular infections

Efflux modulators
- **in bacteria**
- **in eucaryotes**

Thanking people … *

Research is a lonely exercise but its true value is directly related to the collaborative activities it leads to...

Aminoglycosides...

Starting very basically in the early 80's ...

G. Laurent
M.B. Carlier
R. Brasseur
J.M. Ruysschaert

Aminoglycosides...
The once-a-day story...

In the late 80's ...

S. Ibrahim
P. Maldague
L. Giurgea
F. Renoird
M.C. Cambier
G. Laurent
D. Beauchamp

and

F. Clerckx-Braun * (FATC)
J. Donnez (St Luc)
M.P. Mingeot *
P. Lambricht
R. Wagner
B. Rollmann (CHAM)
P. Herman (SP-Belg.)
M.E. De Broe (UZ-UIA)
G. Verpooten (UZ-UIA)
A. Giuliano (UZ-UIA)
B. Kaufman (VUB)
B. Derde * (VUB)





The β-lactams, the macrolides, the fluoroquinolones, etc...

C. Renard
M. Leto *
C. Bruno
F. Van Bambeke *
S. Burton
C. Dupriez
J.M. Michot *
H. Chanteux *
Y. Ouadrhiri
H. Servais *
S. Carryn *
E. Viaene
….

I. Dab (UZ-VUB)
B. Byl (ULB-Erasme)
P.F. Laterre (St-Luc)
...





But ISAP made it all possible … when we were still youngs and serious...

population pharmacokinetics

tissue concentrations

efficacy/toxicity ratios

postantibiotic effect...

* AUIC

intracellular pharmacodynamics and toxicity

ISAP International Society of Anti-Infective Pharmacology
Founded in 1991

http://www.isap.org

And also when as young but less serious...

toxicity isn’t that bad...

http://www.isap.org

And now, en route to the future ...

To a bright future...