De la pharmacologie spéciale à la pharmacothérapie et la pharmacie clinique

Leçon inaugurale:

L'exemple des aminoglycosides ou des Sciences de base vers le patient

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http://www.facm.ucl.ac.be
http://www.farm.ucl.ac.be/cfcl
http://www.uclouvain.be/en-ldri.html

Service de Biochimie humaine
Faculté de Médecine et de Pharmacie
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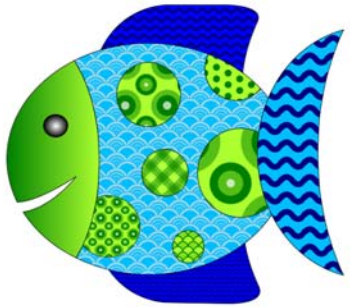
Chaire Francqui au titre belge

Université libre de Bruxelles

Fondation Francqui-Stichting
Fondation d'Utilité Publique - Stichting van Openbaar Nut

Le 1er avril dernier, la moitié des hopitaux belges ont "reçu" un pharmacien clinicien ...

Non, ce n'est pas un



- 1999-2002: démarrage de la pharmacie clinique en Belgique... Premiers projets pilotes
- 2005: premières Thèses en Pharmacie clinique et grands projets hospitaliers universitaires ...
- 2007: lancement des projets au niveau national (24 hôpitaux)
- 2010: élargissement à près de 65 hôpitaux...

Mais qu'est-ce que la pharmacie clinique ?

- **Pharmacologie:**
  discipline scientifique du vivant, subdivision de la biologie, qui étudie les mécanismes d'interactions entre une substance active et l'organisme dans lequel il évolue, de façon à pouvoir **ensuite** utiliser ces résultats à des fins thérapeutiques

- **Pharmacie:**
  La pharmacie (du grec φάρμακον/pharmakôn signifiant drogue, venin ou poison) est la science s'intéressant à la conception, au mode d'action, à la préparation et à la **dispensation** des médicaments.

- **Pharmacie clinique:**
  La pharmacie clinique est une pratique pharmaceutique **centrée sur le patient**, pour
  - assurer un usage aussi efficace et aussi sûr que possible des médicaments tels que prescrits et/ou existant
  - assurer une optimisation de l'usage des médicaments (actuels ou nouveaux) susceptible d'en augmenter l'efficacité, d'en diminuer les effect indésirables, et, diminuer le coût global.

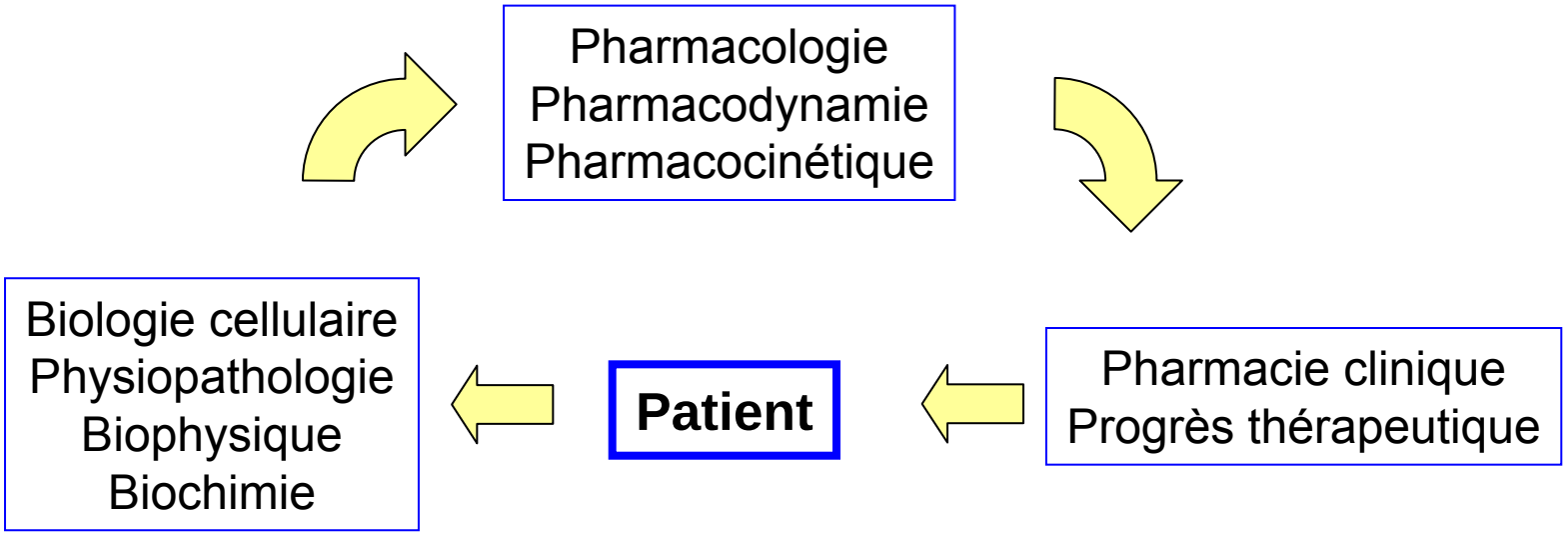
A quoi s'engage le pharmacien clinicien ?

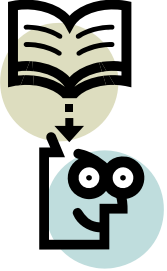
- En apportant ses "soins pharmaceutiques", le pharmacien s'engage à assumer envers les patients la responsabilité de l'atteinte clinique des objectifs préventifs, curatifs ou palliatifs de la pharmacothérapie mise en place par (ou en concertation étroite) avec le médecin

- Cet engagement peut s'exercer vis-à-vis d'un patient ou d'un groupe de patients précis, aussi bien en milieu ambulatoire qu'hospitalier. Il peut aussi s'envisager dans un cadre sociétal immédiat ou de progrès futur

Différents modèles de pharmacie clinique ?

1er modèle (qui sera utilisé aujourd'hui)





Résumé de la présentation

- Du patient vers le médicament:
  Le besoin thérapeutique
- Défense et illustration des sciences de base:
  Comment acquérir les connaissances nécessaires
- Le rôle de la pharmacologie
  Des modèles à la réalité biologique et thérapeutique
- De la pharmacologie vers la clinique
  Comment améliorer les traitements ?
- Le médicament optimisé pour le patient
  Intégration par le pharmacien clinicien

Autre modèles qui seront abordés dans les prochains exposés

- De la **demande médicale** à la découverte de cibles utiles:
  Les inhibiteurs de la synthèse et du transport du cholestérol

- De la **cible** au médicament **enregistré et mis à disposition**:
  Les nouveaux antibiotiques et les antiviraux

- De l'enregistrement aux **recommandations thérapeutiques**:
  La pneumonie communautaire et l'asthme

- Optimiser l'usage des médicaments - **une vue globale**
  Le rôle du pharmacien clinicien

Mais pour aujourd'hui, nous devons aborder un domaine …

- qui puisse nous servir d'exemple …
  si possible normatif * …

- que je connaisse suffisamment pour en parler
  … sans devoir lire mes notes …

- et qui soit un guide pour l'avenir …
  … ce qui implique qu'il aie été accepté en thérapeutique
  …

aminoglycosides ? vancomycine ?

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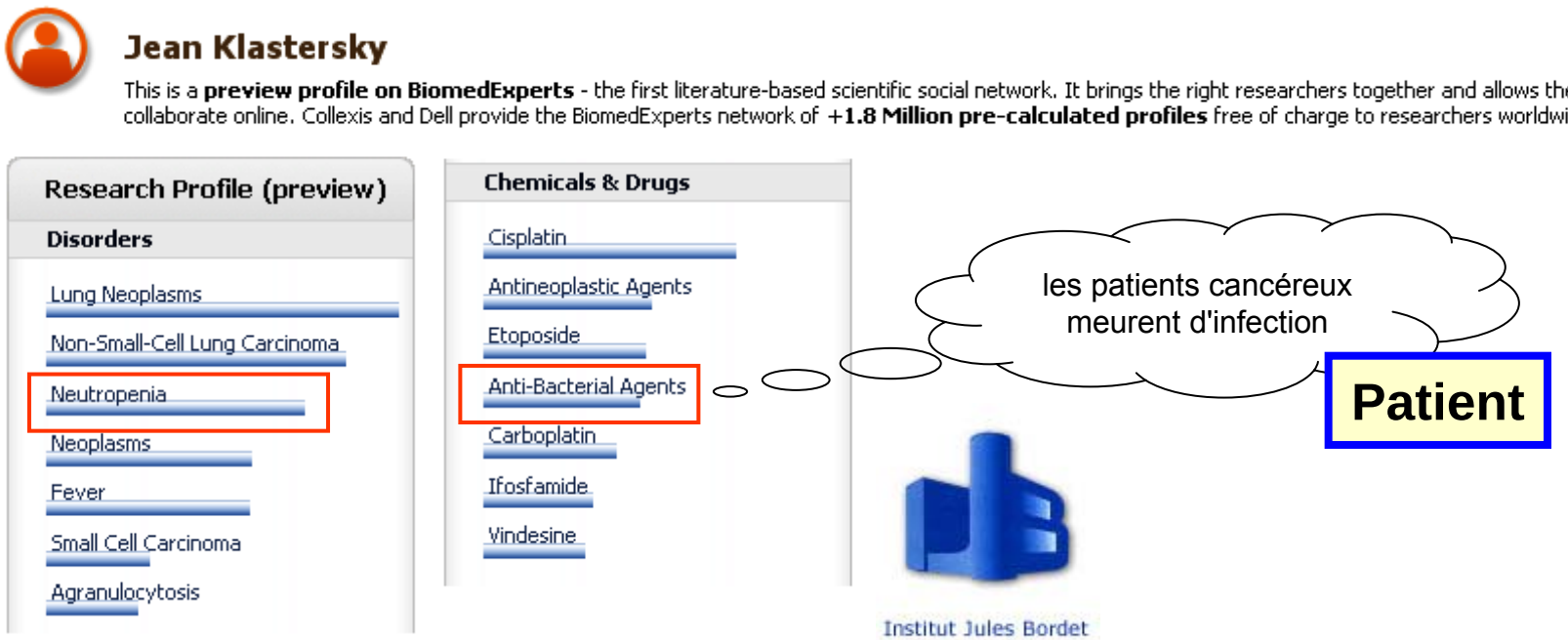
* A partir de quoi on établit une norme … (http://www.linternaute.com/dictionnaire/fr/definition/normatif/)
Normative theory: hypotheses or other statements about what is right and wrong, desirable or undesirable, just or unjust in society (A dictionary of Sociology - http://www.encyclopedia.com/doc/1O88-normativetheory.html)

Aminoglycosides

- Première grande classe d'antibiotiques actifs contre les bactéries Gram (-) …
- Quel est le problème médical ?



Aminoglycosides

- Les germes Gram (-) tuent les patients …

Que fait Jean Klastersky ?

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1974, p. 133–138

Vol. 5, No. 2
Printed in U.S.A.

Comparative Clinical Study of Tobramycin and Gentamicin

J. KLASTERSKY, C. HENSGENS, A. HENRI, AND D. DANEAU
Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, Brussels, Belgium

Received for publication 6 August 1973

Gentamicin and tobramycin have been compared in vitro and as single-drug therapy in patients with a serious infection caused by gram-negative rods. In vitro, a slight advantage of tobramycin over gentamicin has been found against *Pseudomonas aeruginosa*. Cross-resistance between gentamicin and tobramycin has been observed for gentamicin-resistant strains of *P. aeruginosa* and *Providence* but was not always present. The clinical effectiveness of gentamicin and tobramycin was similar: 14 (45.1%) out of the 31 patients in each series responded favorably. The clinical results were much better in urinary tract infections (66% of favorable responses) than in wound infections, pulmonary infections, septicemia, and meningitis (26% of favorable responses). The frequency of adverse reactions encountered in the present series was similar for both drugs.

Aminoglycosides

Mais encore ?

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1987, p. 1061–1068
0066-4804/87/071061-08$02.00/0

Vol. 31, No. 7

Amikacin (in 1987 …)

Serum Bactericidal Activity and Postantibiotic Effect in Serum of Patients with Urinary Tract Infection Receiving High-Dose Amikacin

P. VAN DER AUWERA* AND J. KLASTERSKY

Service de Médecine et Laboratoire d'Investigation Clinique H. J. Tagnon, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, 1000 Brussels, Belgium

Received 22 August 1986/Accepted 20 April 1987

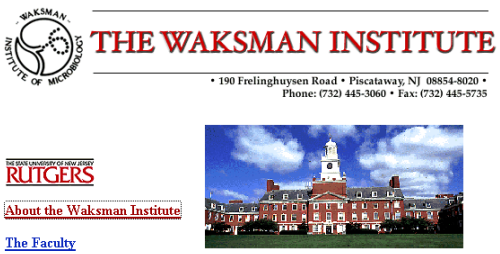
Et pas de problème avec une "haute dose" ?

Ten patients received a 30-min infusion of amikacin (30 mg/kg) on day 1 and 15 mg/kg on day 2. Mean serum creatinine was 1.1 ± 0.3 (standard deviation) mg/dl before and 1.0 ± 0.3 mg/dl 3 days after the second infusion. Mean serum amikacin concentrations before, at the end of infusion, and 1, 6, 12, and 24 h after 30 and 15 mg/kg were 0, 157, 79, 31, 16, 5, 5, 85, 51, 19, 12, and 5 mg/liter, respectively. Five strains each of *Staphylococcus aureus*, *Staphylococcus epidermidis* susceptible and resistant to oxacillin, *Streptococcus (Enterococcus) faecalis*, *Corynebacterium* sp. strain JK, *Listeria monocytogenes*, *Mycobacterium fortuitum* (three strains), *Klebsiella pneumoniae*, *Serratia marcescens*, *Acinetobacter calcoaceticus*, and *Pseudomonas aeruginosa* were tested. Serum bactericidal activities (SBAs) were ≥1:8 in ≥80% of the sera 1 and 6 h after 30 mg/kg and in ≥60% of the sera 1 and 6 h after 15 mg/kg against *Staphylococcus aureus* and *Staphylococcus epidermidis* susceptible to oxacillin, *A. calcoaceticus*, and *K. pneumoniae*. *L. monocytogenes*, *Serratia marcescens*, and *P. aeruginosa* had lower SBAs. Very low or no activity was observed against oxacillin-resistant staphylococci and *Streptococcus faecalis*. The study of the killing rate in serum confirmed these results. Postantibiotic effect was studied by incubating a strain from each species in serum samples obtained 1 and 6 h after both regimens for 0.5, 1, or 2 h. The duration of postantibiotic effect depended on the duration of contact and the concentration of amikacin for the following organisms: oxacillin-susceptible staphylococci, *L. monocytogenes*, *P. aeruginosa*, *A. calcoaceticus*, *K. pneumoniae*, and *Serratia marcescens*. *M. fortuitum* was killed after 30 min of contact. No postantibiotic effect was observed with *Streptococcus faecalis*, *Corynebacterium* sp. strain JK, or oxacillin-resistant staphylococci. Amikacin at 30 mg/kg provided high levels and SBAs against susceptible pathogens. Prolonged postantibiotic effects were observed. No signs of nephrotoxicity occurred.

La streptomycine (1er aminoglycoside): découverte par S. Waksman en 1943 par criblage systématique…

streptomyces grisaeus

Waksman and Fleming …



From the point of view of human benefit, never was a Nobel prize so justifiably awarded as was the award to Selman Waksman for the discovery of streptomycin and other antibiotics produced from *Streptomyces spp*. Waksman and his talented team (many of whom went on to make important antibiotic discoveries in their own right) developed the concept of **systematic screening** of microbial culture products for biological activity, a technology which has provided the foundation of the antibiotic industry, and for this alone his name should rank high in any pantheon of microbiology.

J. Davies: In Praise of Antibiotics, ASM News
http://www.asm.org/memonly/asmnews/may99/feature6.html

Aminoglycosides: mode d'action…

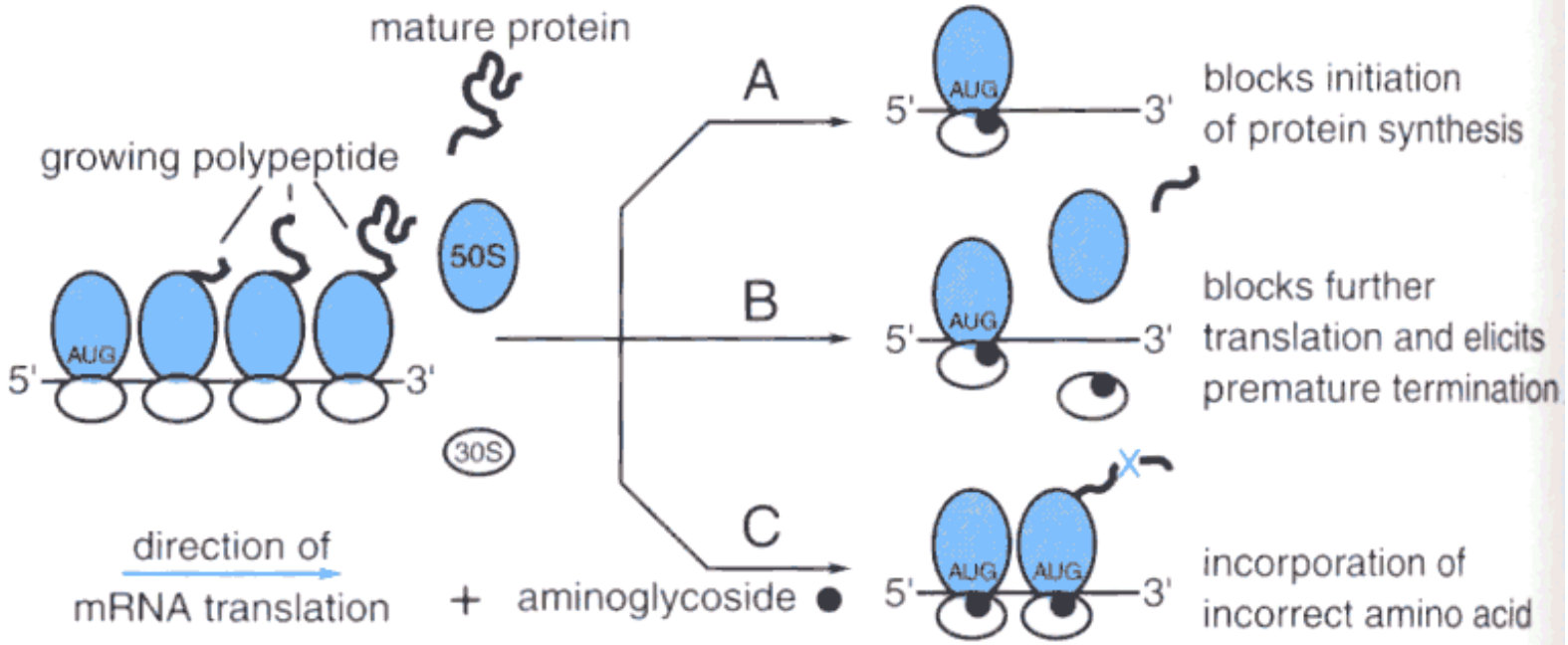


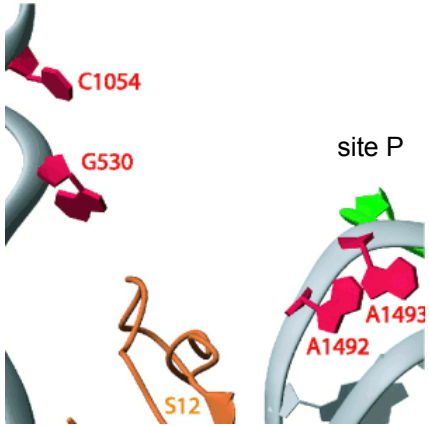
Figure 46–2. Effects of aminoglycosides on protein synthesis.

A. Aminoglycoside (represented by closed circles) binds to the 30 S ribosomal subunit and interferes with initiation of protein synthesis by fixing the 30 S–50 S ribosomal complex at the start codon (AUG) of mRNA. As 30 S–50 S complexes downstream complete translation of mRNA and detach, the abnormal initiation complexes, so-called streptomycin monosomes, accumulate, blocking further translation of message. Aminoglycoside binding to the 30 S subunit also causes misreading of mRNA, leading to ***B.*** premature termination of translation with detachment of the ribosomal complex and incompletely synthesized protein, or ***C.*** incorporation of incorrect amino acids (indicated by the "X"), resulting in the production of abnormal or nonfunctional proteins.

Goodman & Gilman's, 10th ed. p 1222

Les aminoglycosides perturbent le système de vérification du code génétique au niveau de la synthèse protéique …

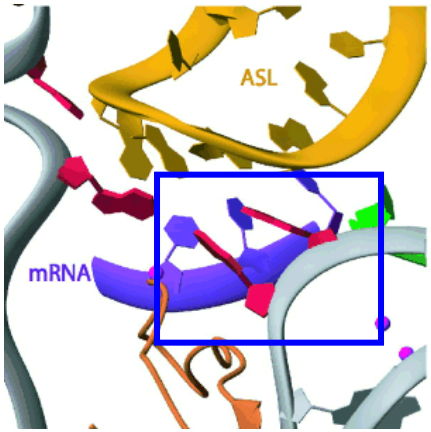
contrôle



déformation énergie-dépendante (GTP)

et protrusion de A1492 et A1493 uniquement si l'appariement mRNA – tRNA est correct

tRNA complémentaire



le code est confirmé !!

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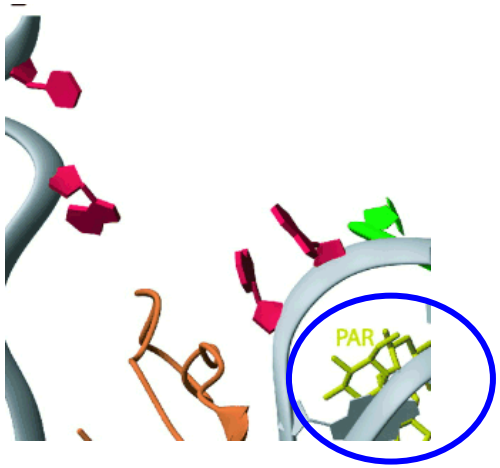
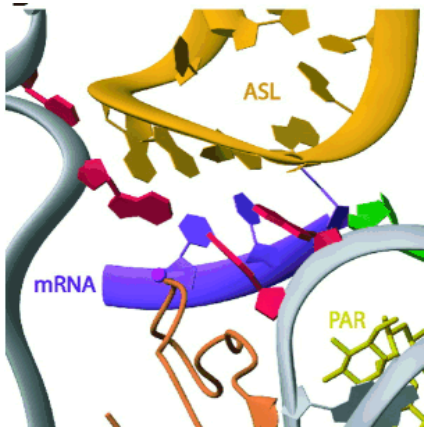
en présence d'un aminoglycoside



la liaison de l'aminoglycoside induit la même déformation et la protrusion de A1492 et A1493 sans besoin d'énergie

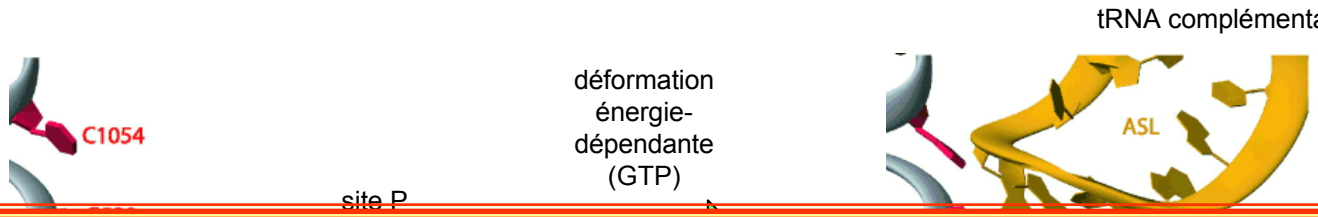
l'appariement sera toujours considéré comme correct



le code sera "confirmé" mais l'appariement ne sera pas nécessairement correct (erreur sur le tRNA…)

J. M. Ogle et al., Science 292, 897 -902 (2001)

Les aminoglycosides perturbent le système de vérification du code génétique au niveau de la synthèse protéique …



Ceci explique l'effet **bactéricide** intense des aminoglycosides
et donc leur effet thérapeutique important même chez des patients immunodéprimés

D'où l'intérêt de Jean Klasterky pour ces molécules !

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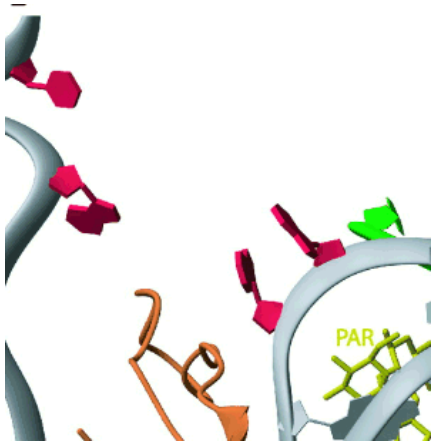
en présence d'un aminoglycoside



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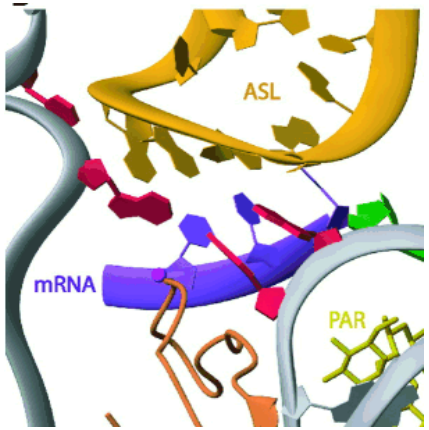
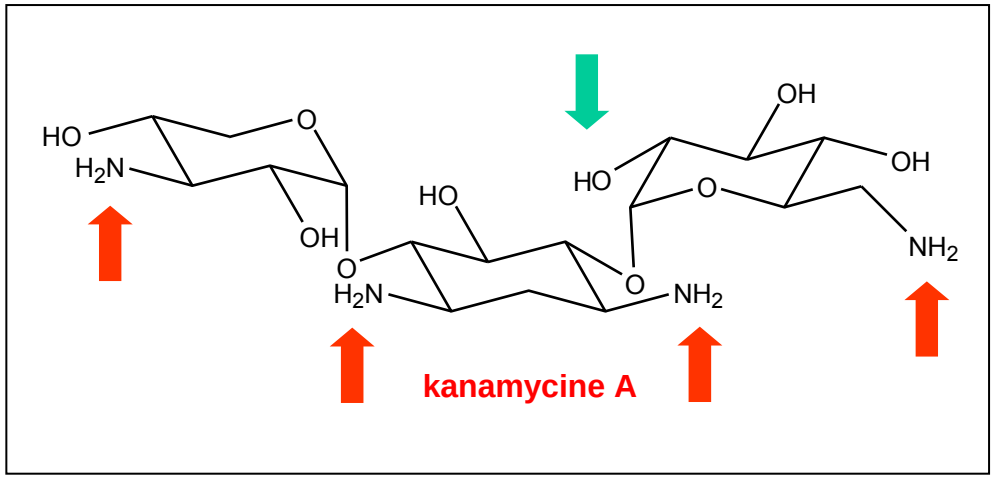


le code sera "confirmé" mais l'appariement ne sera pas nécessairement correct (erreur sur le tRNA…)

J. M. Ogle et al., Science 292, 897 -902 (2001)

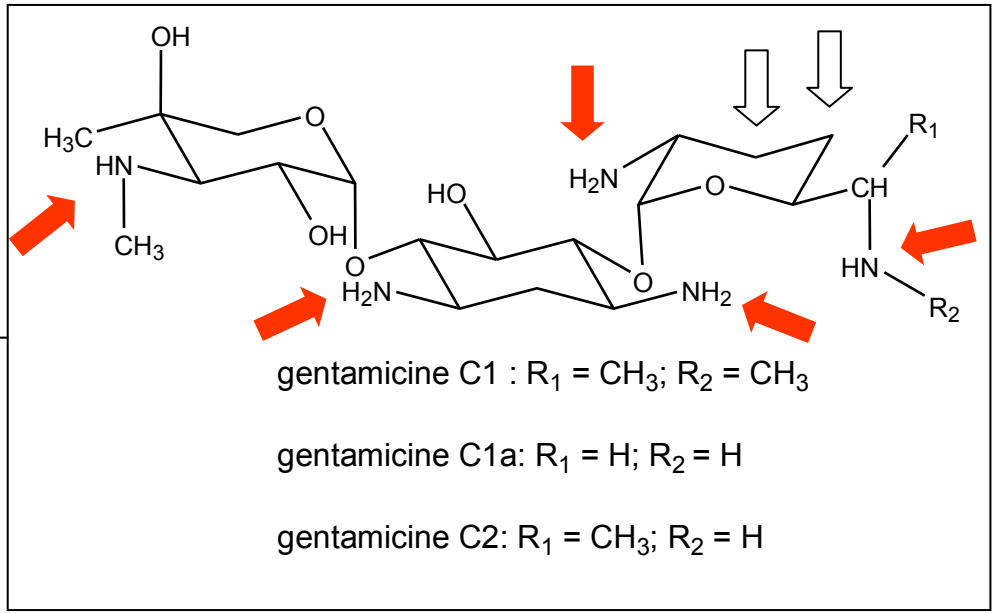
Les acteurs à partir des années '60 …



- activité raisonnable sur les Gram (-) SM-résistants
- toxicité modérée

➔succès clinique important (1960-1980),

grand succès clinique depuis 1965 !! "**gentamicine**" …

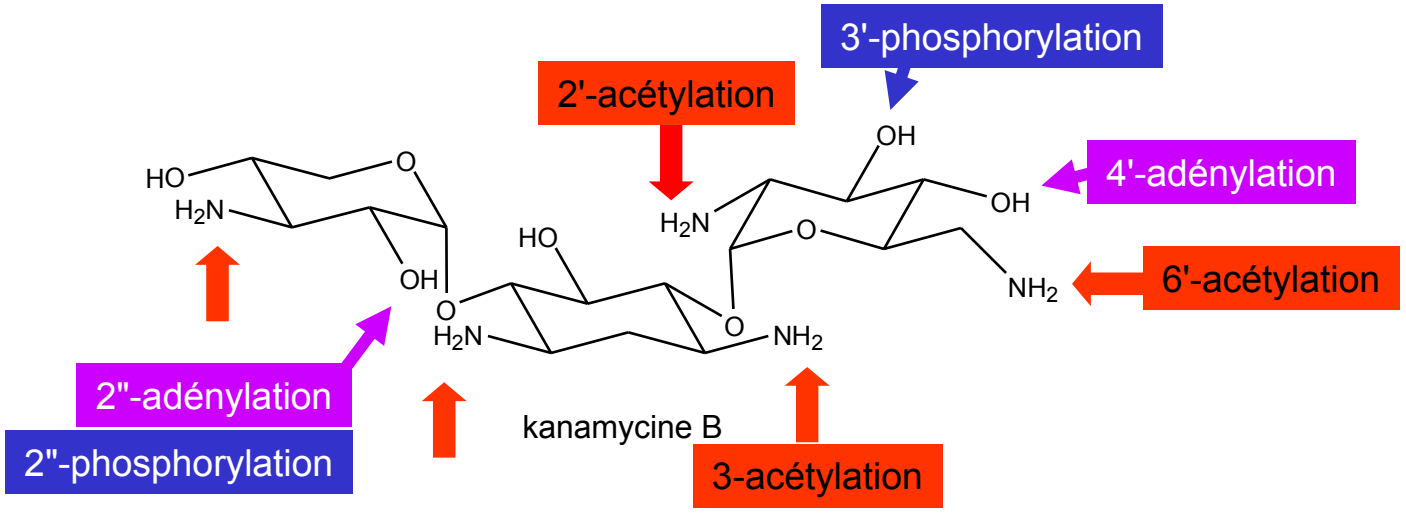


gentamicine C1 : $R_1 = CH_3$; $R_2 = CH_3$

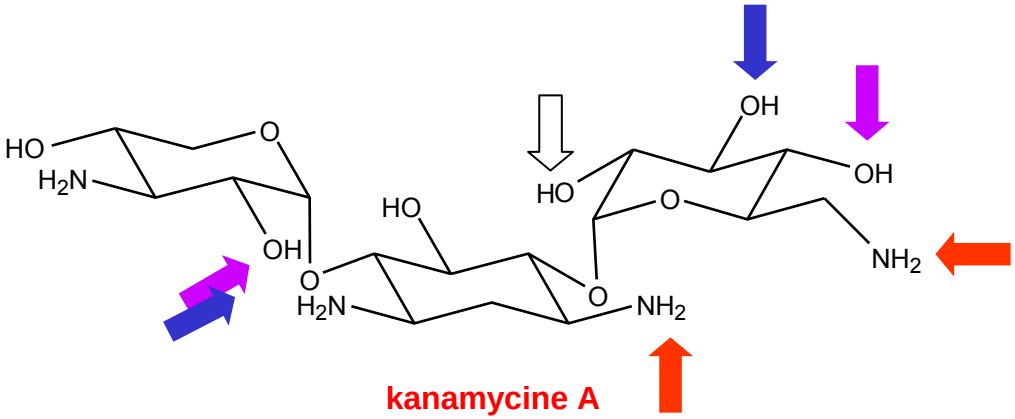
gentamicine C1a: $R_1 = H$; $R_2 = H$

gentamicine C2: $R_1 = CH_3$; $R_2 = H$

Mais … émergence rapide de résistance par inactivation enzymatique…

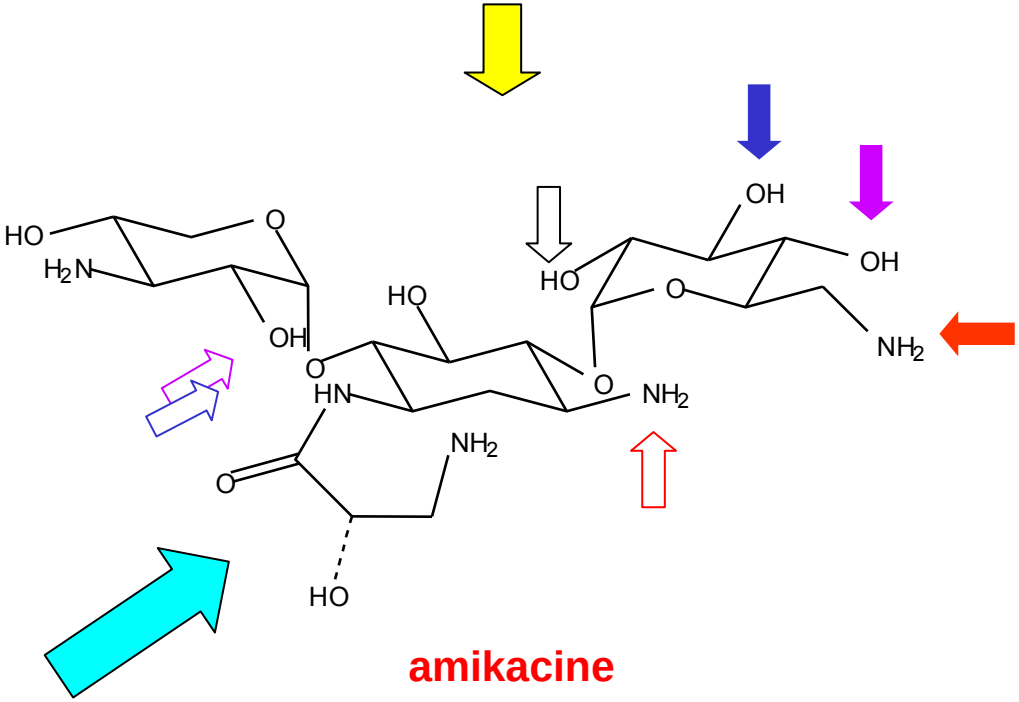


L'évolution…



kanamycine A

- activité raisonnable
- toxicité modérée

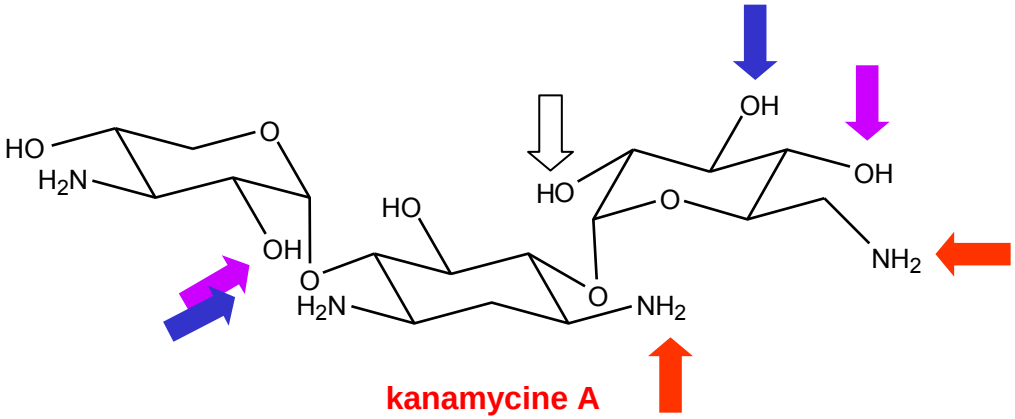


amikacine

- activité maintenue
- activité vis-à-vis des souches résistantes (2", 3; fréquentes) et insensible en 2' (fréquent)
- mais reste sensible en **3'**, **4'** et **6'**

➔néanmoins très grand succès clinique depuis les années 85

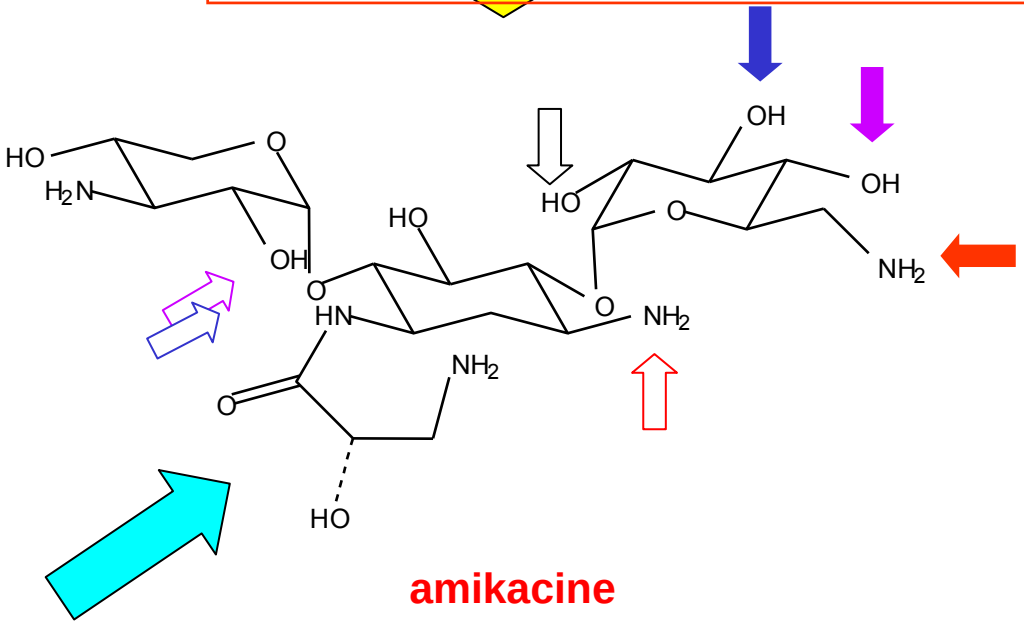
L'évolution…



kanamycine A

- activité raisonnable
- toxicité modérée

Voilà pourquoi Jean Klastersky s'intéressait à l'amikacine !



amikacine

- activité maintenue
- activité vis-à-vis des souches résistantes (2", 3; fréquentes) et insensible en 2' (fréquent)

➔très grand succès clinique depuis les années 85

Aminoglycosides et résistance …

nom-code de l'amikacine

Chemotherapy. 1975;21(1):45-51.

Comparison of the in vitro activities of BB-K8 and three other aminoglycosides against 215 strains of Pseudomonas and Enterobacteriaceae with variable sensitivity to kanamycin and gentamicin.

Yourassowsky E, Schoutens E, Vanderlinden MP.

étudié dès 1975 … à l'ULB

Abstract

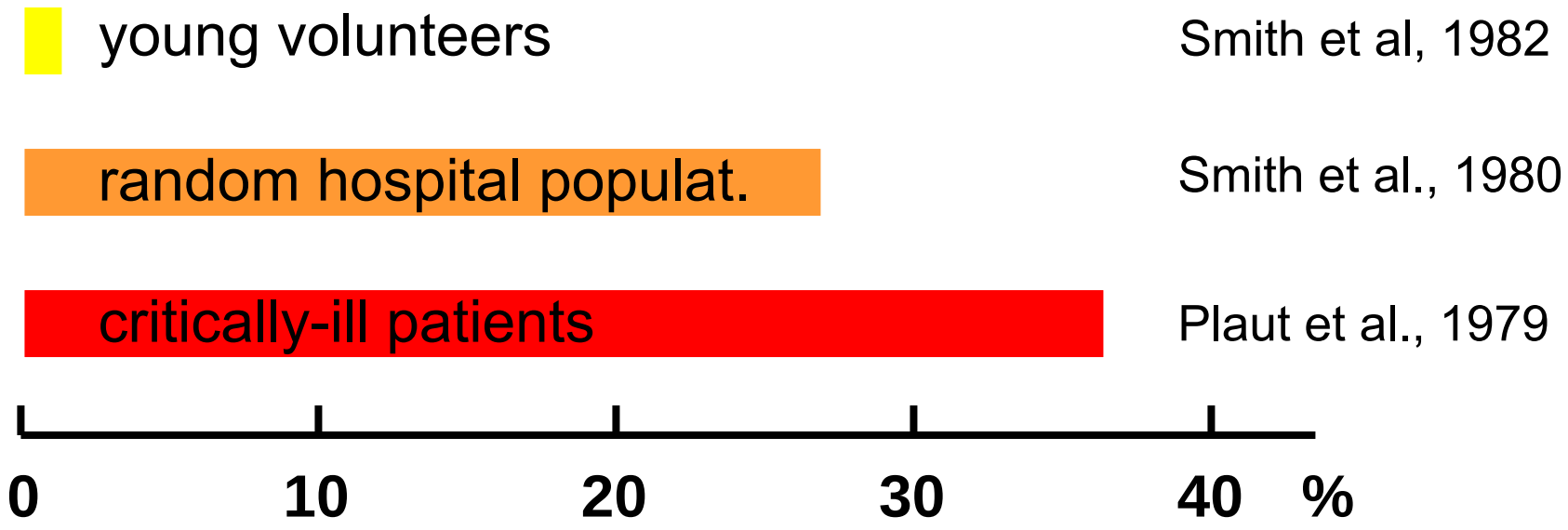
215 gram-negative bacilli isolated from clinical materials were tested in vitro against BB-K8 by means of disc diffusion and agar dilution tests; the strains included 40 isolates resistant to gentamicin. Approximately 90% of the strains were inhibited by 3.12 mug/ml or less BB-K8. This antibiotic exhibited a comparable activity, although somewhat inferior, to that of gentamicin, against organisms sensitive to gentamicin. It was considrably more active than gentamicin, and comparable to tobramycin, against the isolates of Klebsiella-Enterobacter-Serratia spp. resistant to gentamicin, but less active than tobramycin against 11 strains of Pseudomonas resistant to gentamicin.

à Brugmann…

Statue de George Brugmann
par Julien Dillens
(1849-1904)

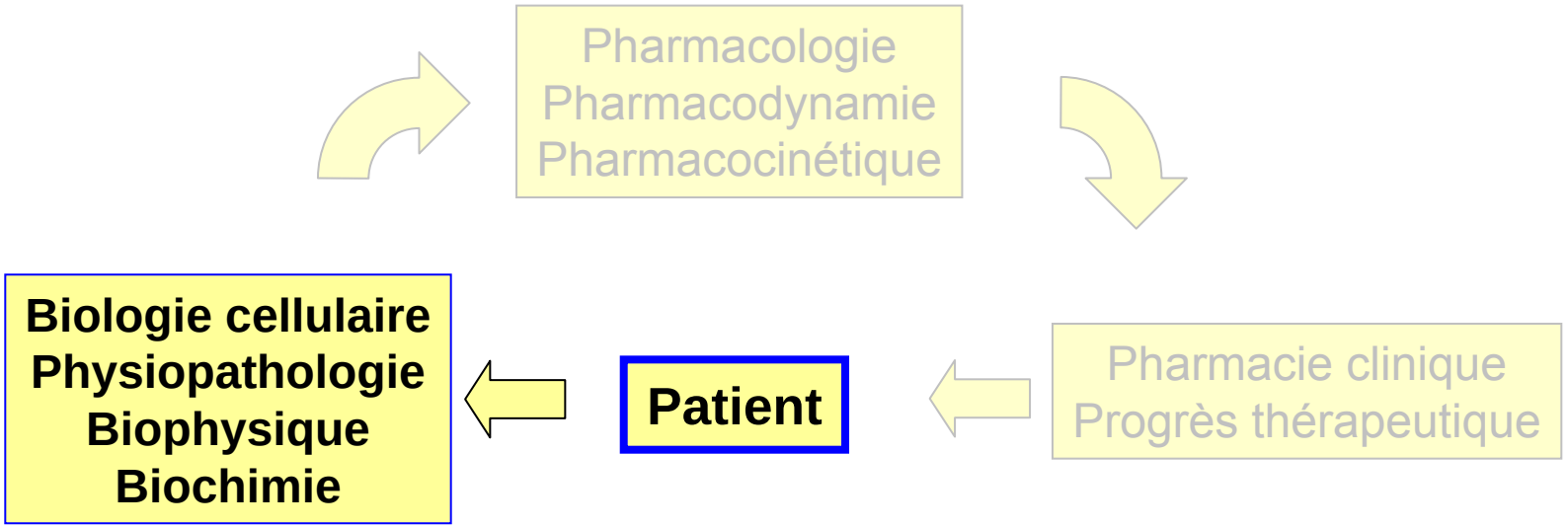
Aminoglycosides et toxicité …

Patients with nephrotoxic reaction after treatment with gentamicin



Progression dans le modèle ...

1er modèle (qui sera utilisé aujourd'hui)



Aminoglycosides cause precipitous renal necrosis, tubular dysfunction, and renal failure associated with regeneration

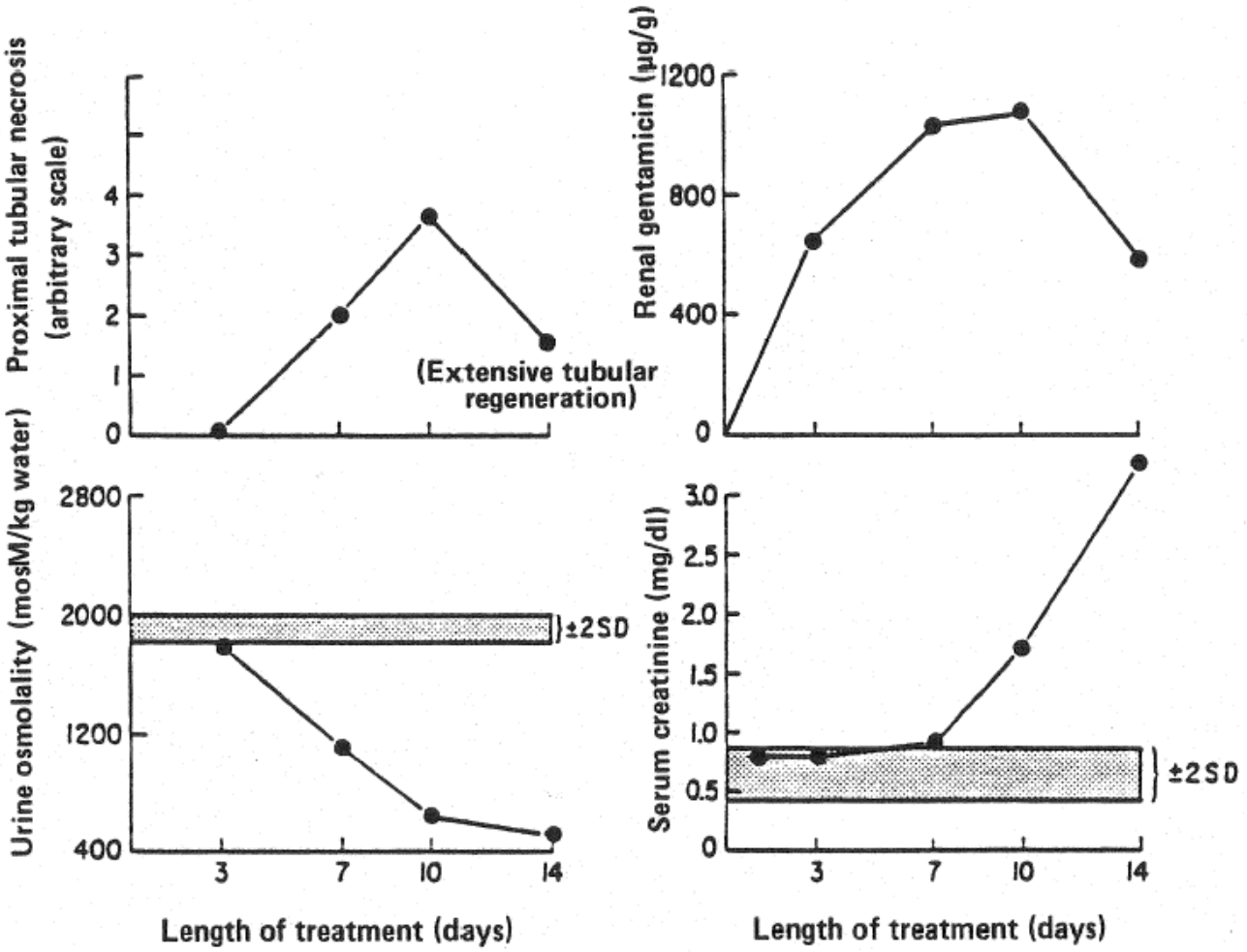
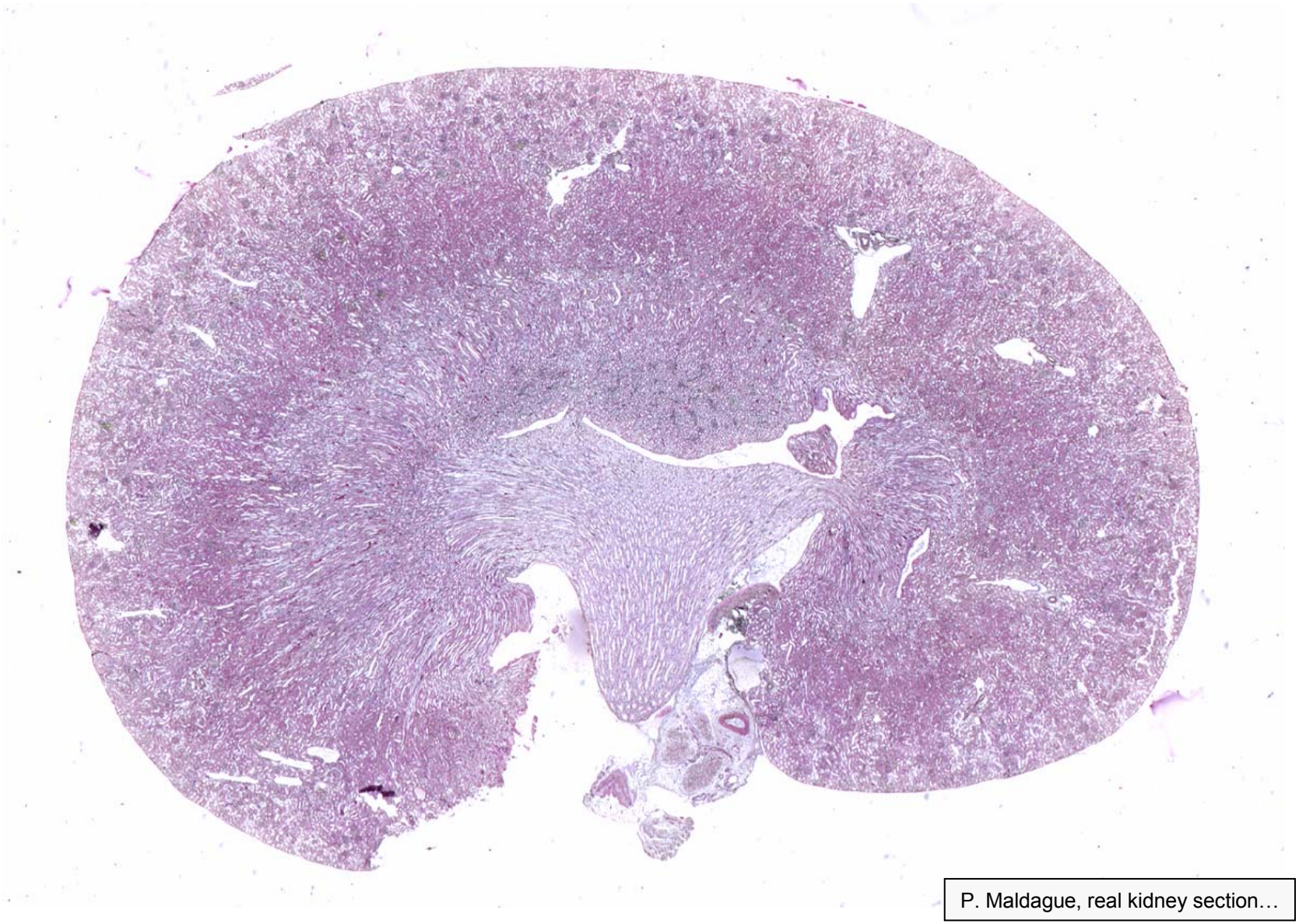


Fig. 1. Renal changes in Fischer 344 rats after gentamicin (40 mg/kg per day in two injections per day). From Ref. 13.

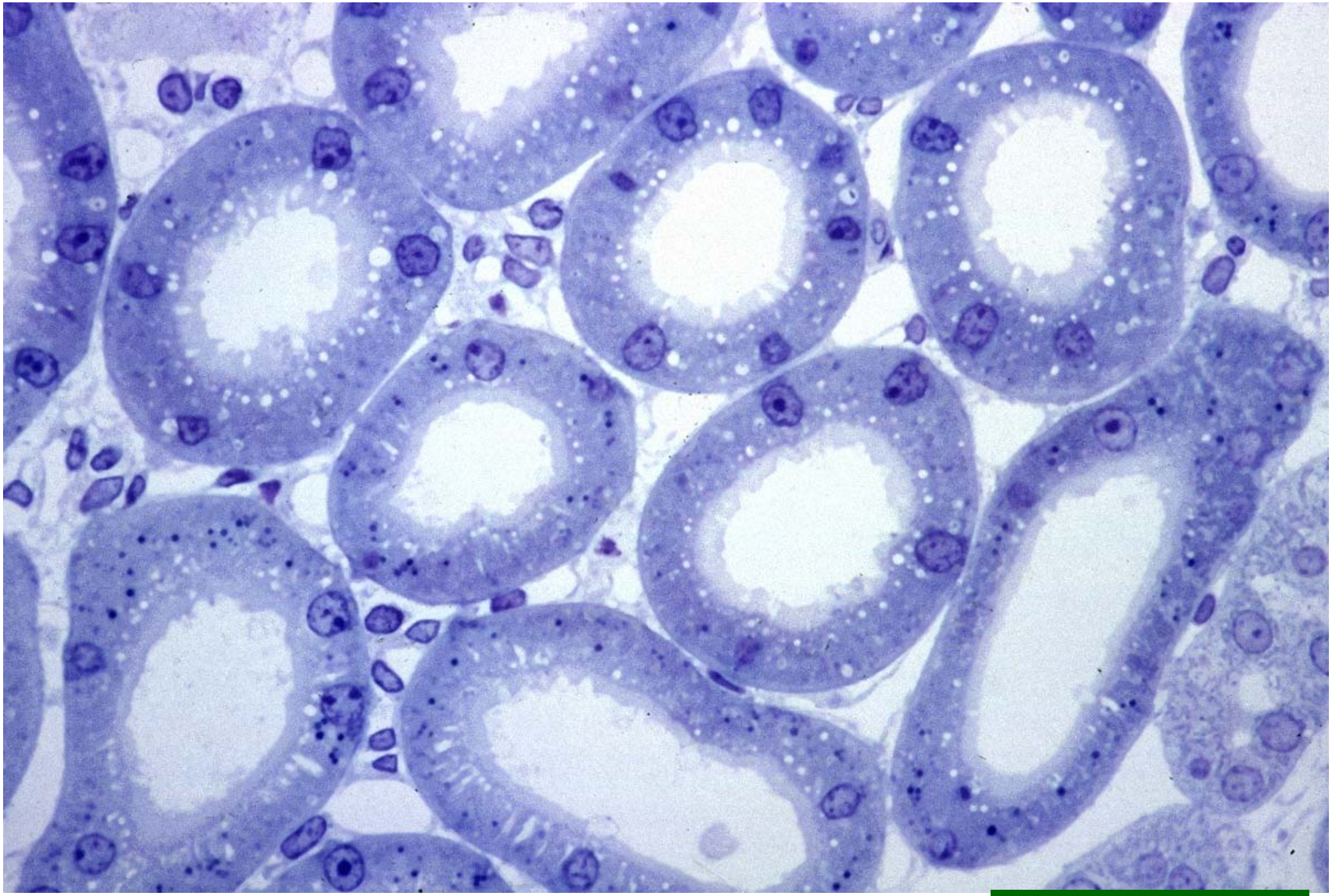
13 Parker, R.A., Bennett, W.H. and Porter, G.A. (1982) Animal models in the study of aminoglycoside nephrotoxicity. In: A. Whelton and H.C. Neu (Eds.), The Aminoglycosides: Microbiology, Clinical Use and Toxicology. Marcel Dekker, New York, pp. 235–267.

A look in the microscope in a rat treated at therapeutic doses … (10mg/kg – equivalent to human 4 mg/kg dose)



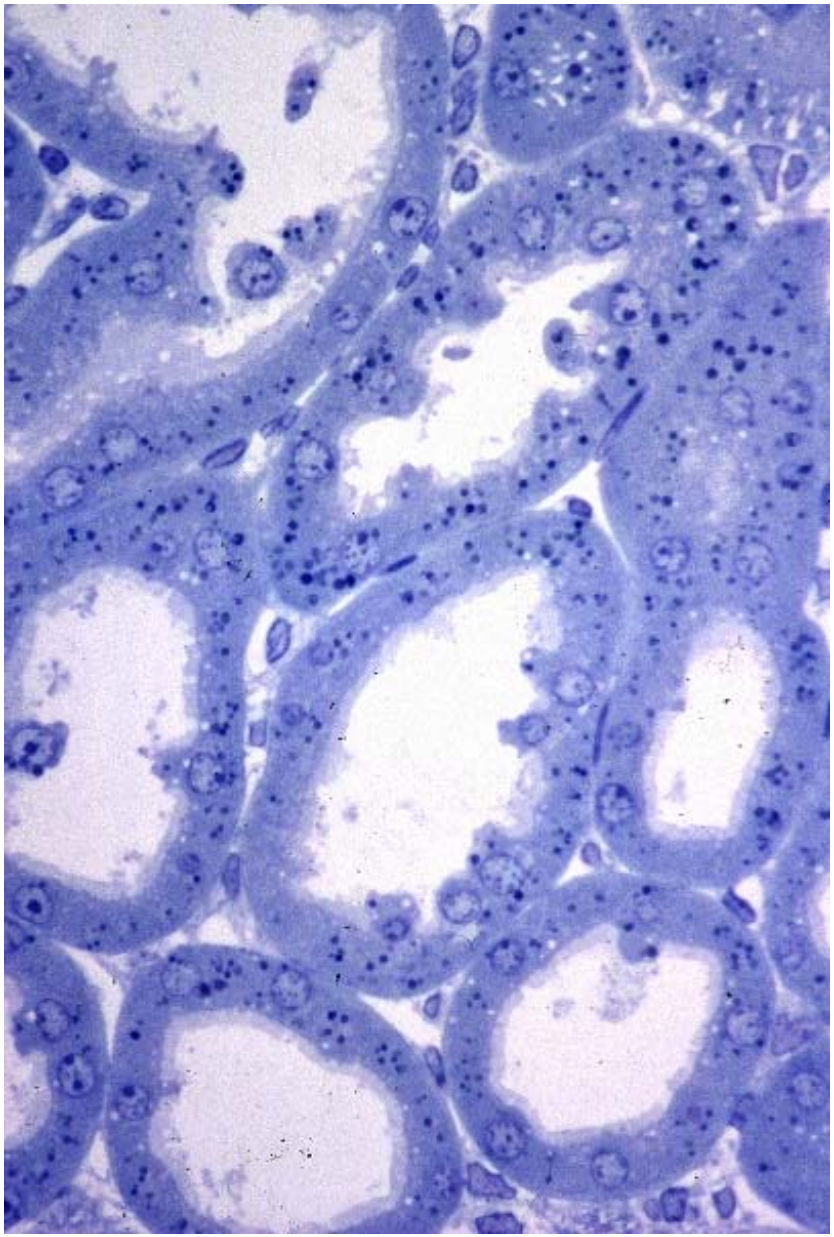
P. Maldague, real kidney section…

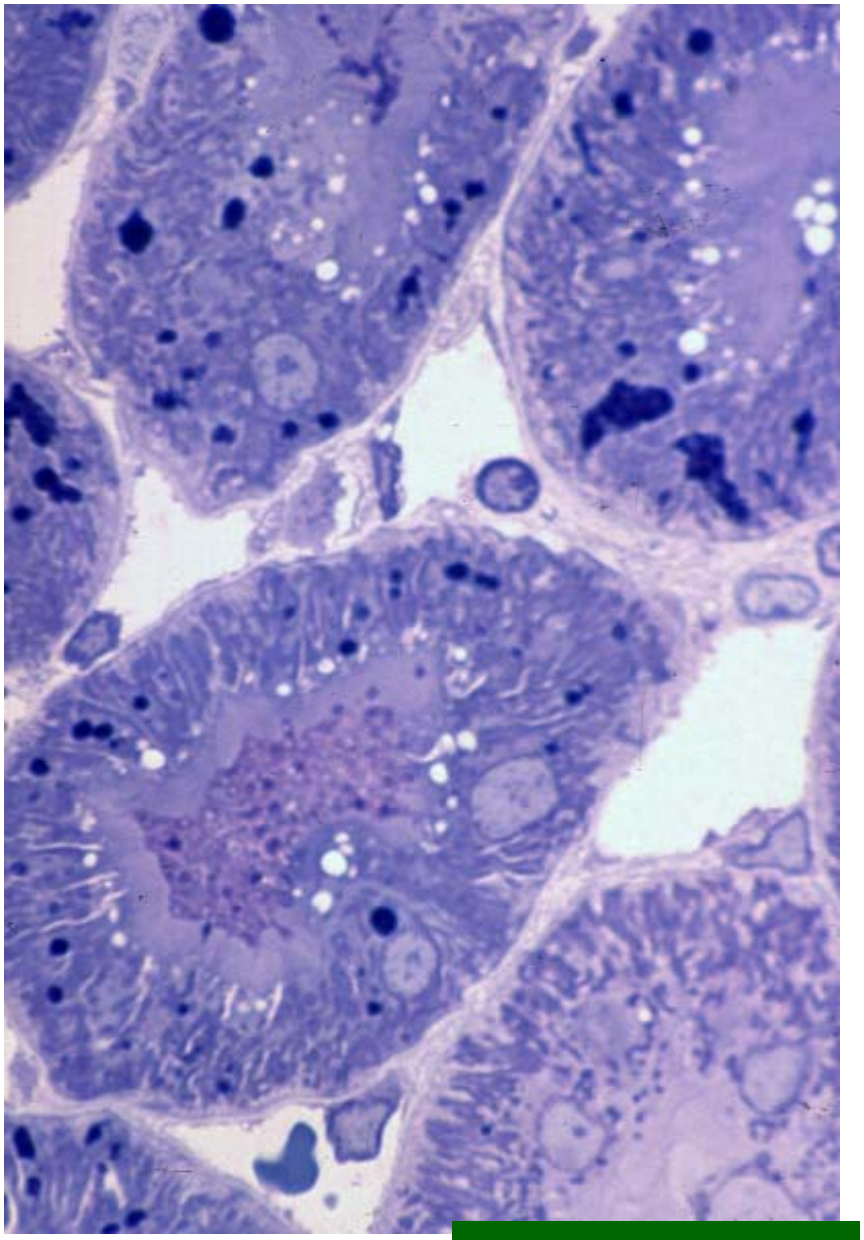
Somewhat closer in the control …



P. Maldague, unpublished

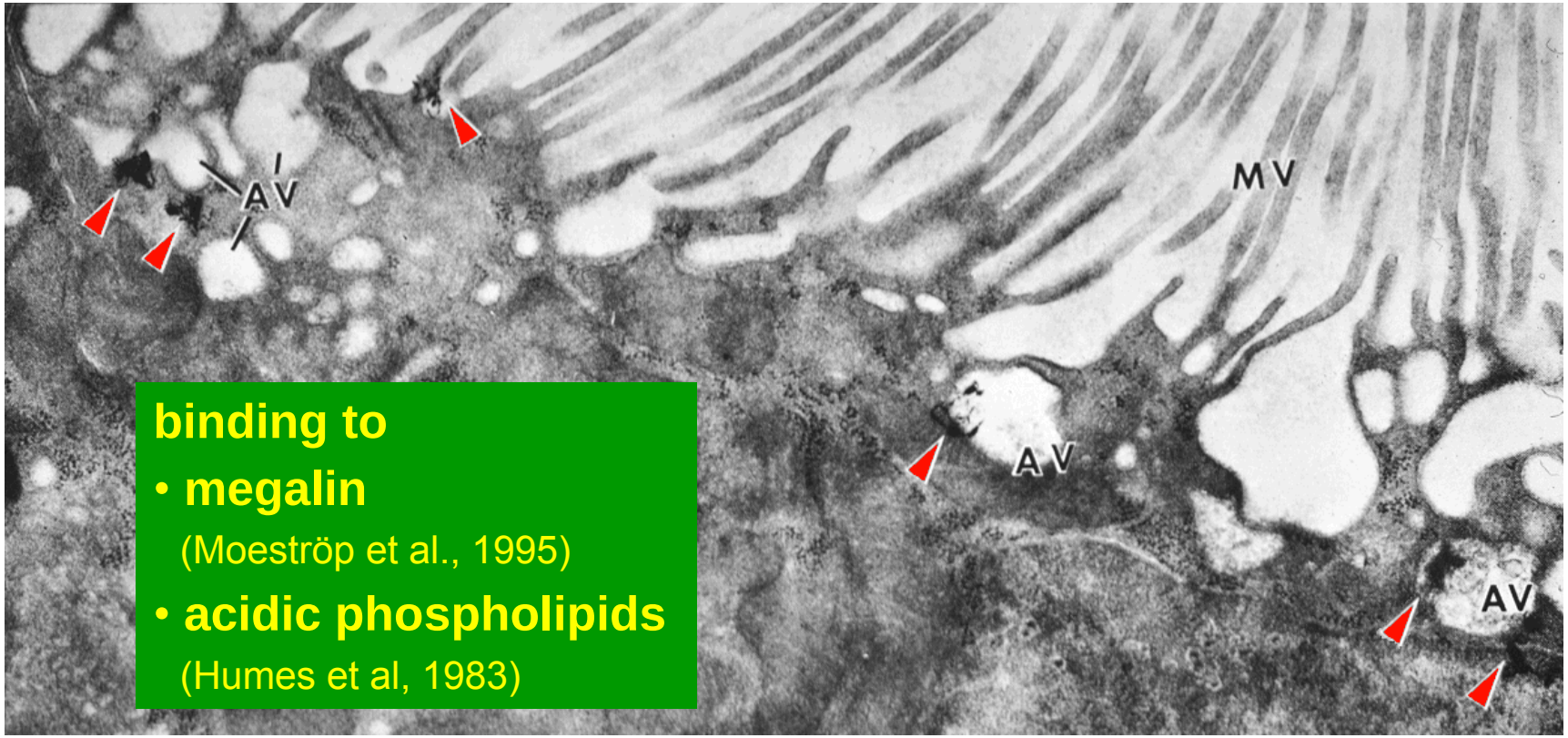
And examine …





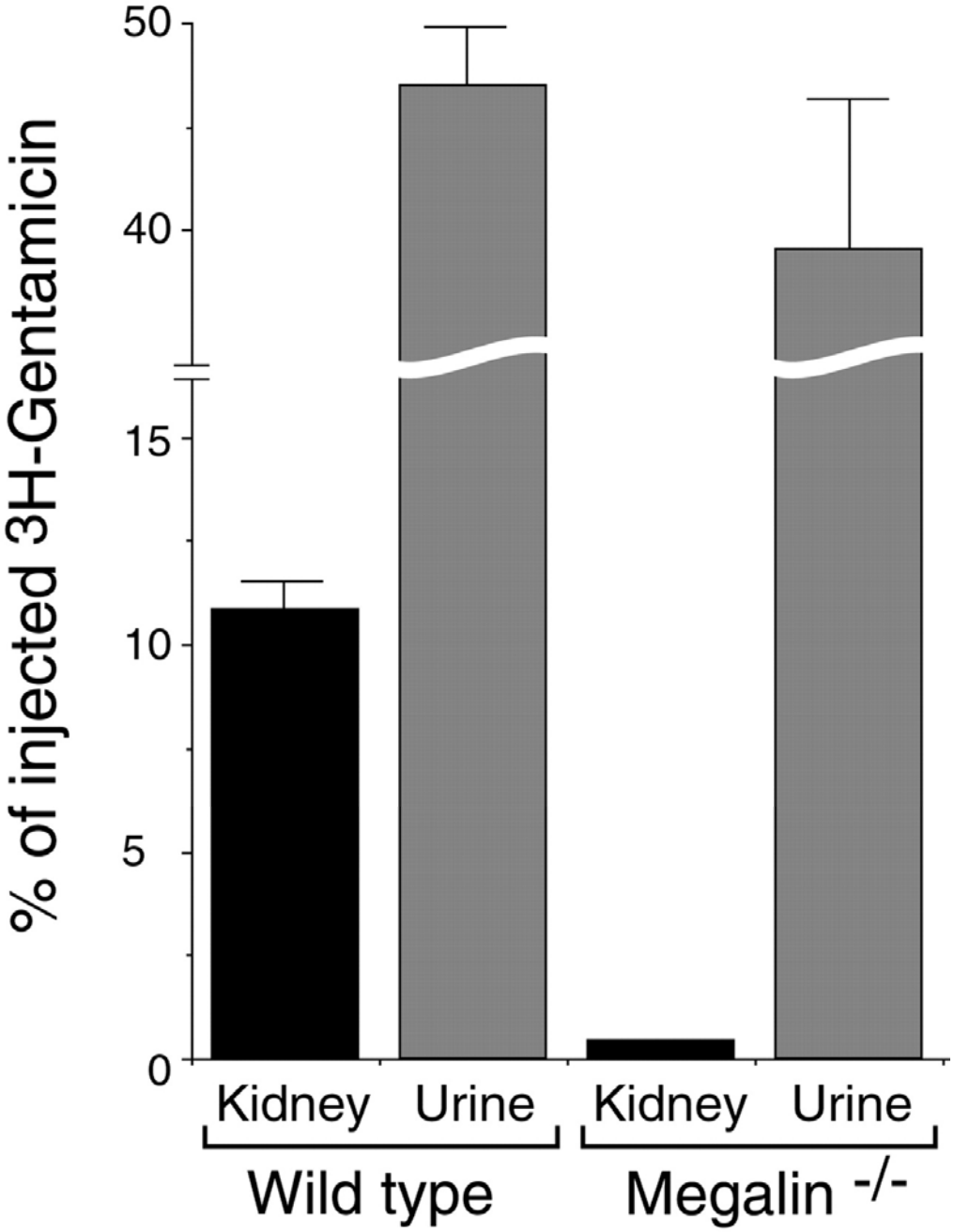
P. Maldague, unpublished

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



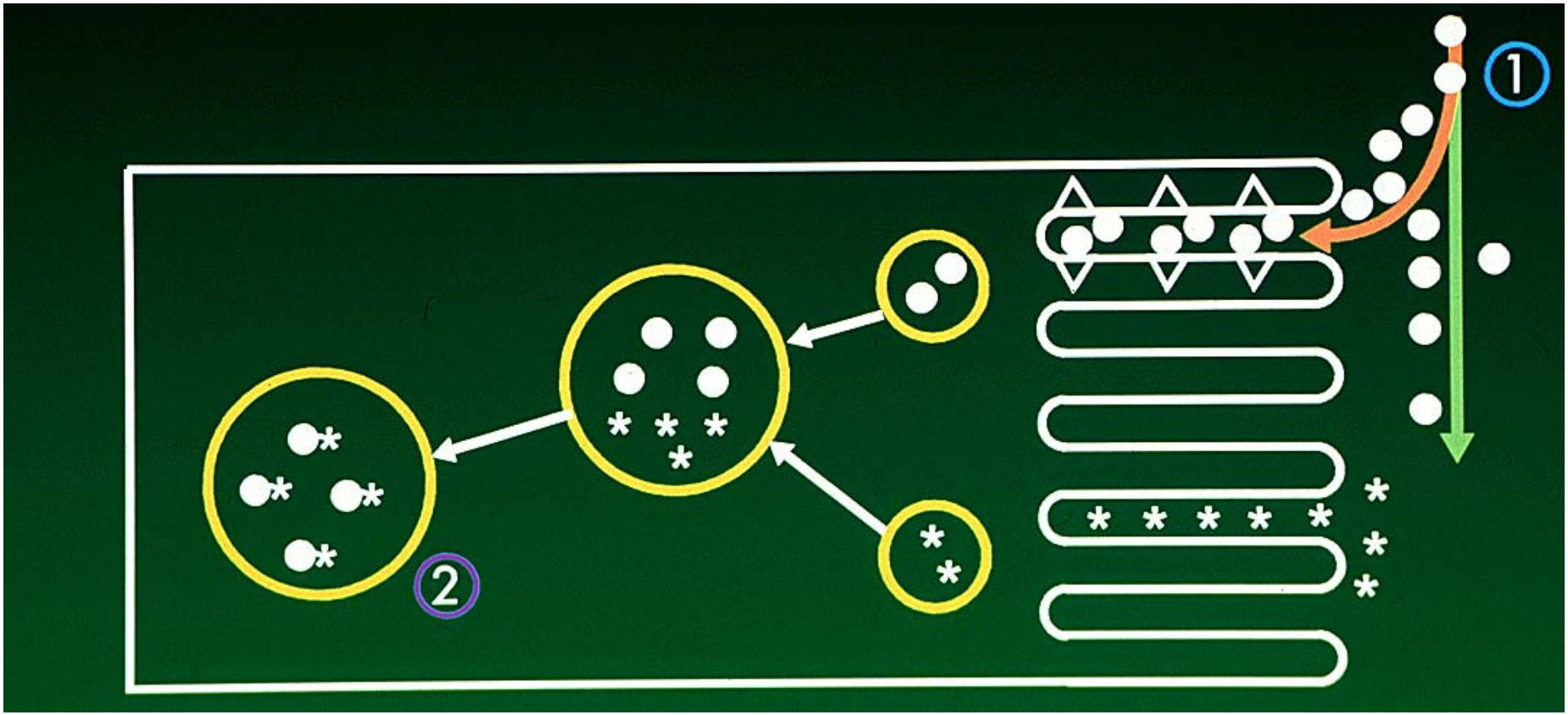
* Just *et al*, Naunym Schmied. Arch. Pharmacol, 1977
Silverblatt & Kuehen, Kidney Intern., 1979

Mice deficient in megalin do not accumulate gentamicin in kidney



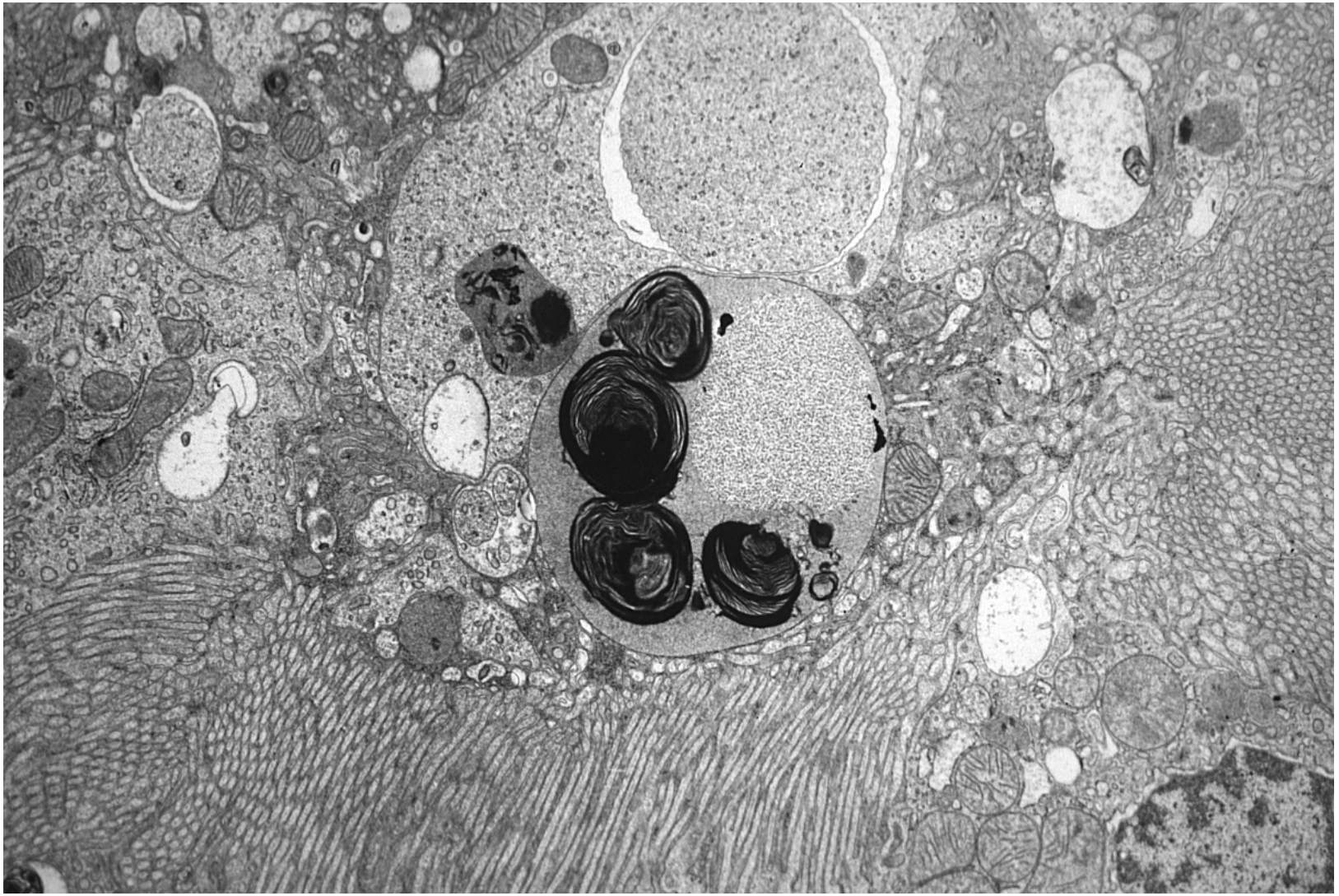
Schmitz et al., J. Biol. Chem. 277:618-622, 2002

Towards a mechanism …



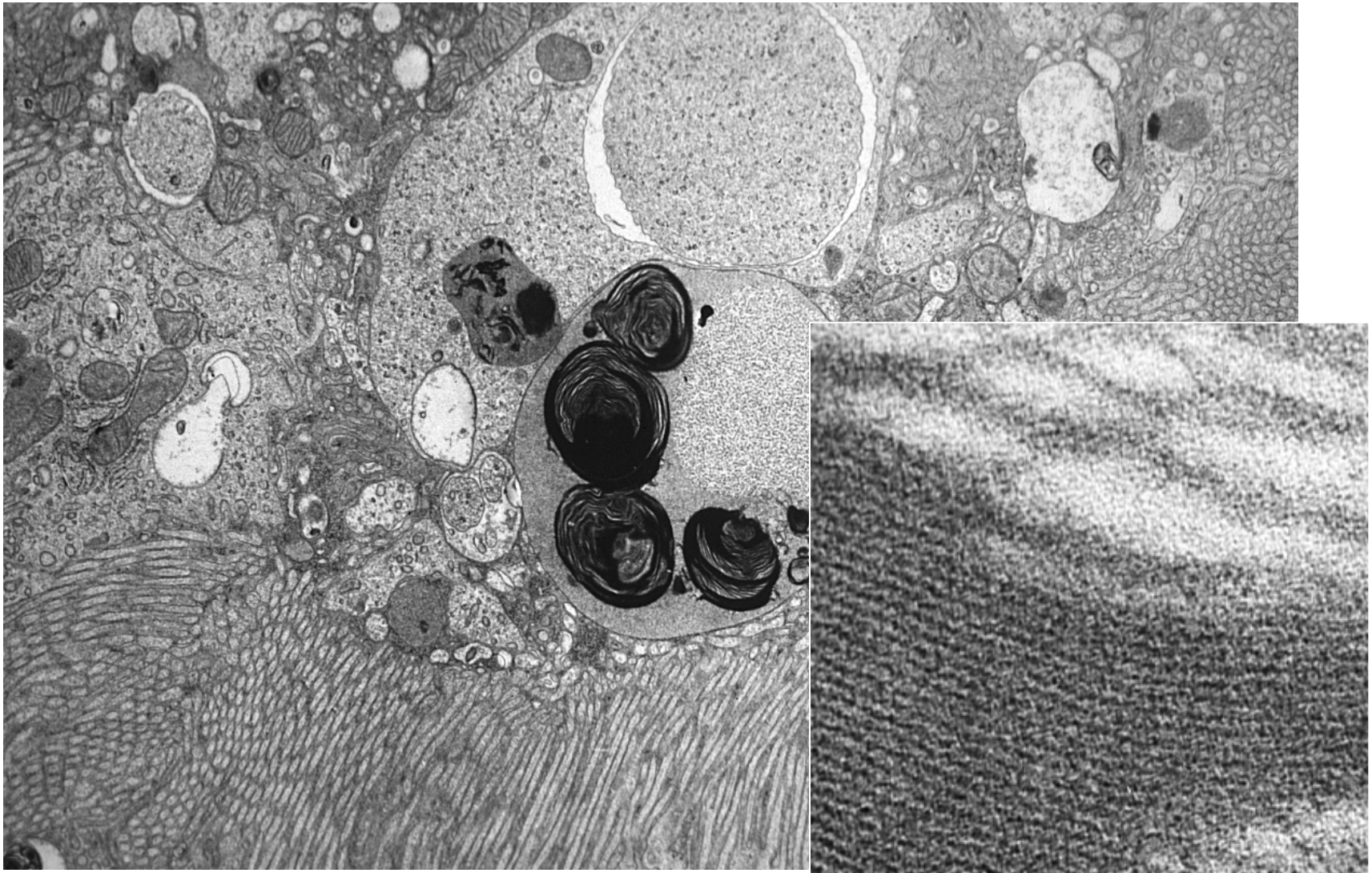
1. binding to brush border
2. accumulation in lysosomes

Intralysosomal gentamicin causes phospholipidosis



Tulkens, Am. J. Med. 80:105-114, 1986

Intralysosomal gentamicin binds to phospholipids and cause phospholipidosis



Tulkens, Am. J. Med. 80:105-114, 1986

Phospholipidosis is related to the binding of gentamicin to acidic phospholipids and subsequent inhibition of lysosomal phospholipases

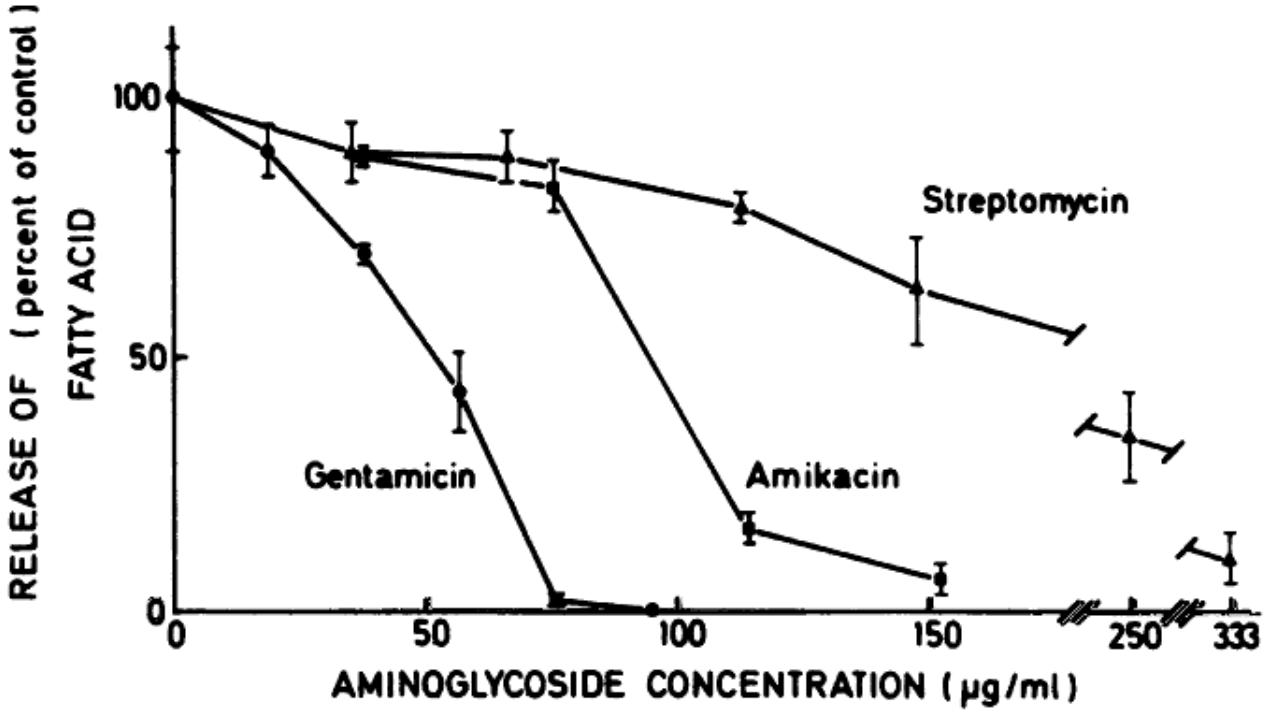
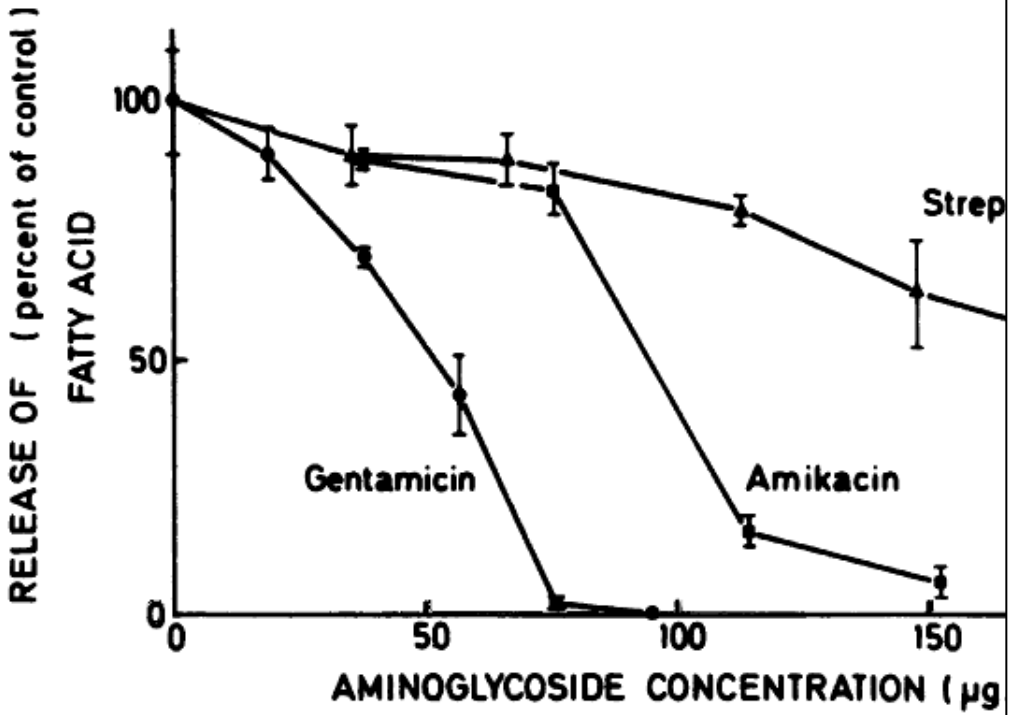


FIG. 3. Inhibition of the activities of phospholipase A_1 by gentamicin, amikacin, and streptomycin. The abscissa shows the concentration of aminoglycoside in micrograms of base per milliliter of assay mixture. The ordinate shows the amount of reaction product as a percentage of that measured in parallel experiments without antibiotic. Each symbol refers to the mean of three experiments ± the standard deviation (vertical bar).

Carlier *et al.* Antimicrob Agents Chemother 1983; 23:440-449

Phospholipidosis is related to the binding of g phospholipids and subsequent inhibition of lyso



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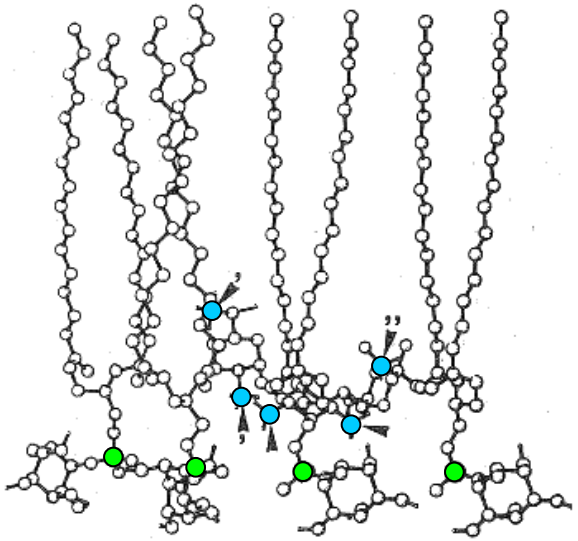
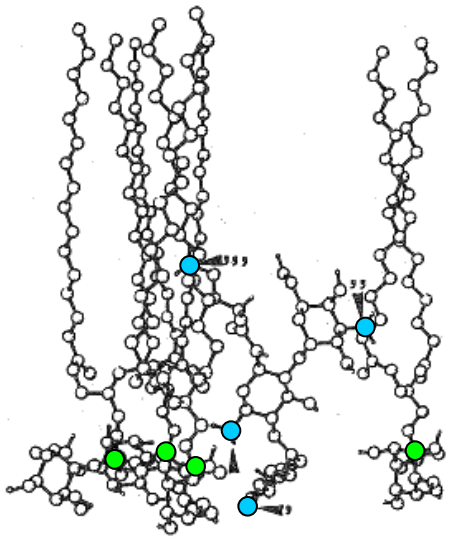
Carlier *et al.* Antimicrob Agents Chemother 1983; 23:440-449

Interactions of aminoglycosides with phospholipids



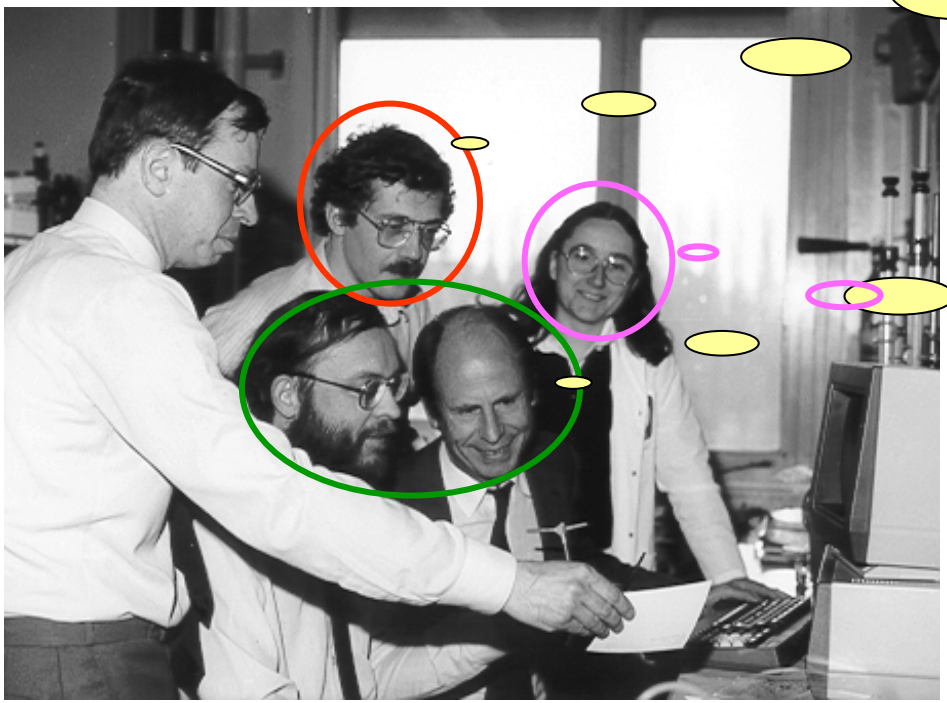
gentamicin



amikacin

Brasseur *et al.*, Biochem. Pharmacol.1984; 33:629-637

The encounter between biochemists and biophysicists with a semi-pharmacist...



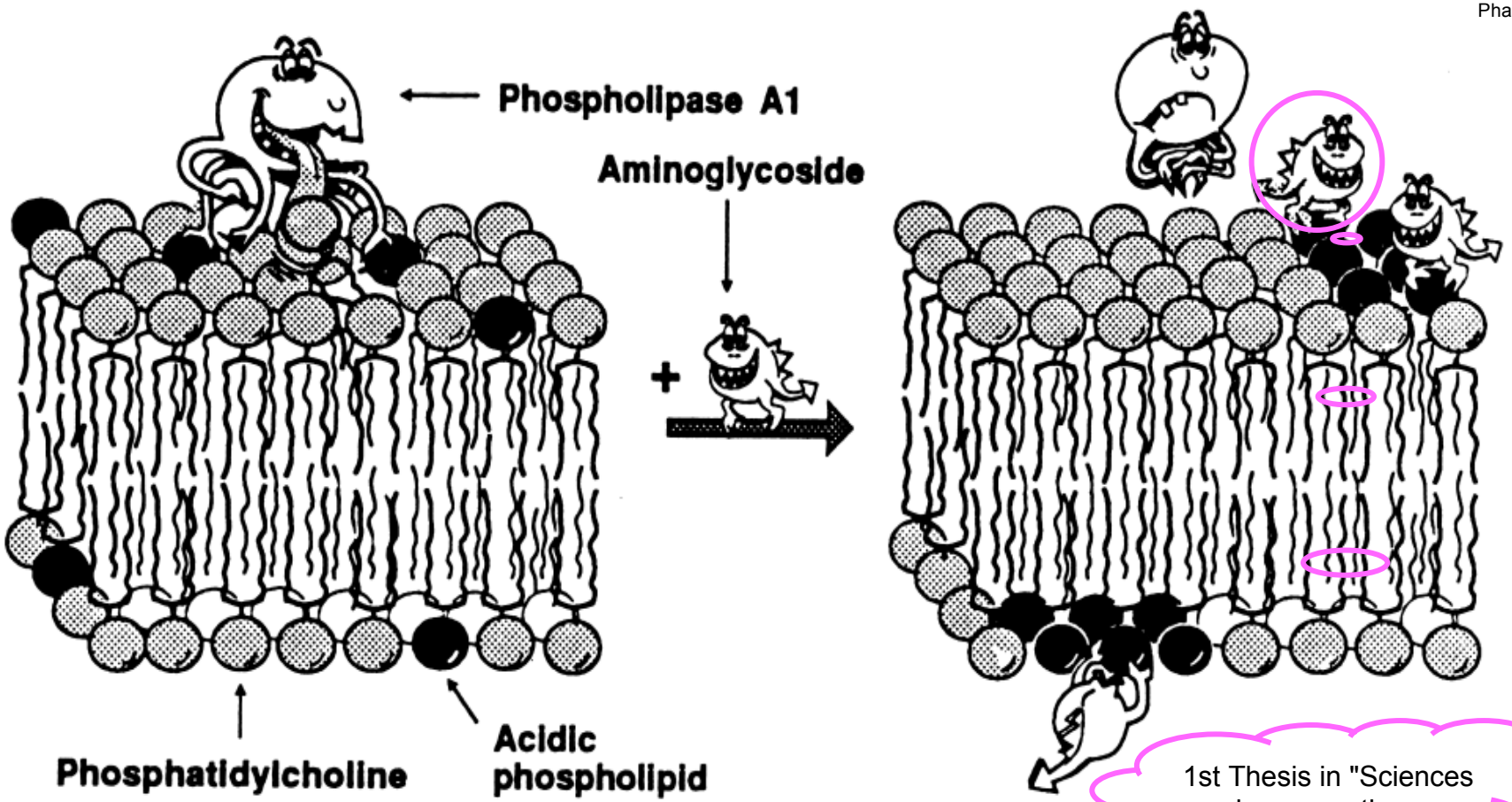
G. Laurent, coming from the Bordet Institute (biochemist)

R. Brasseur & J.M. Ruysschaet from ULB (biophysics)

B. Carlier, 1st Thesis in "Applications pharmaceutiques)

Et voici l'explication … biochimique apportée par une pharmacienne…

M.P. Minegot
PharmD



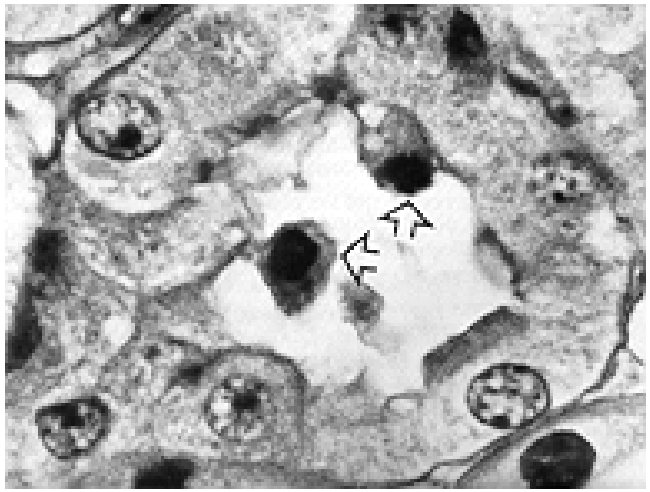
1st Thesis in "Sciences pharmaceutiques

Mingeot-Leclercq *et al.* Biochemical mechanism of aminoglycoside-induced inhibition of phosphatidylcholine hydrolysis by lysosomal phospholipases. Biochem Pharmacol (1988) 37:591-599.

But something more happens: Gentamicin causes apoptosis at low, therapeutically-relevant doses

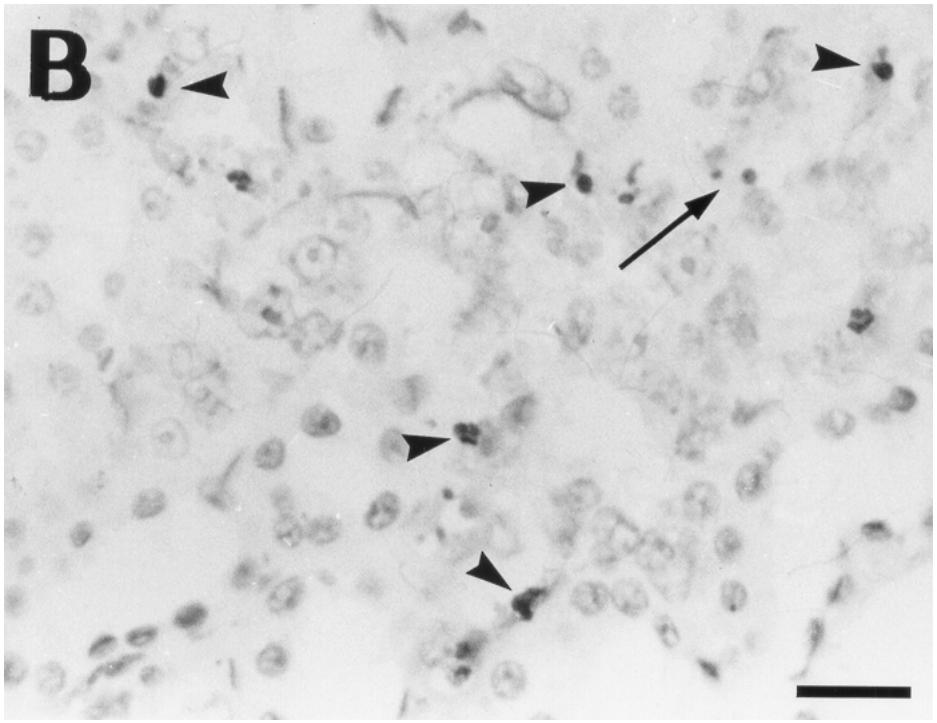
M. El Mouedden
PhD

Hematoxylin/eosin



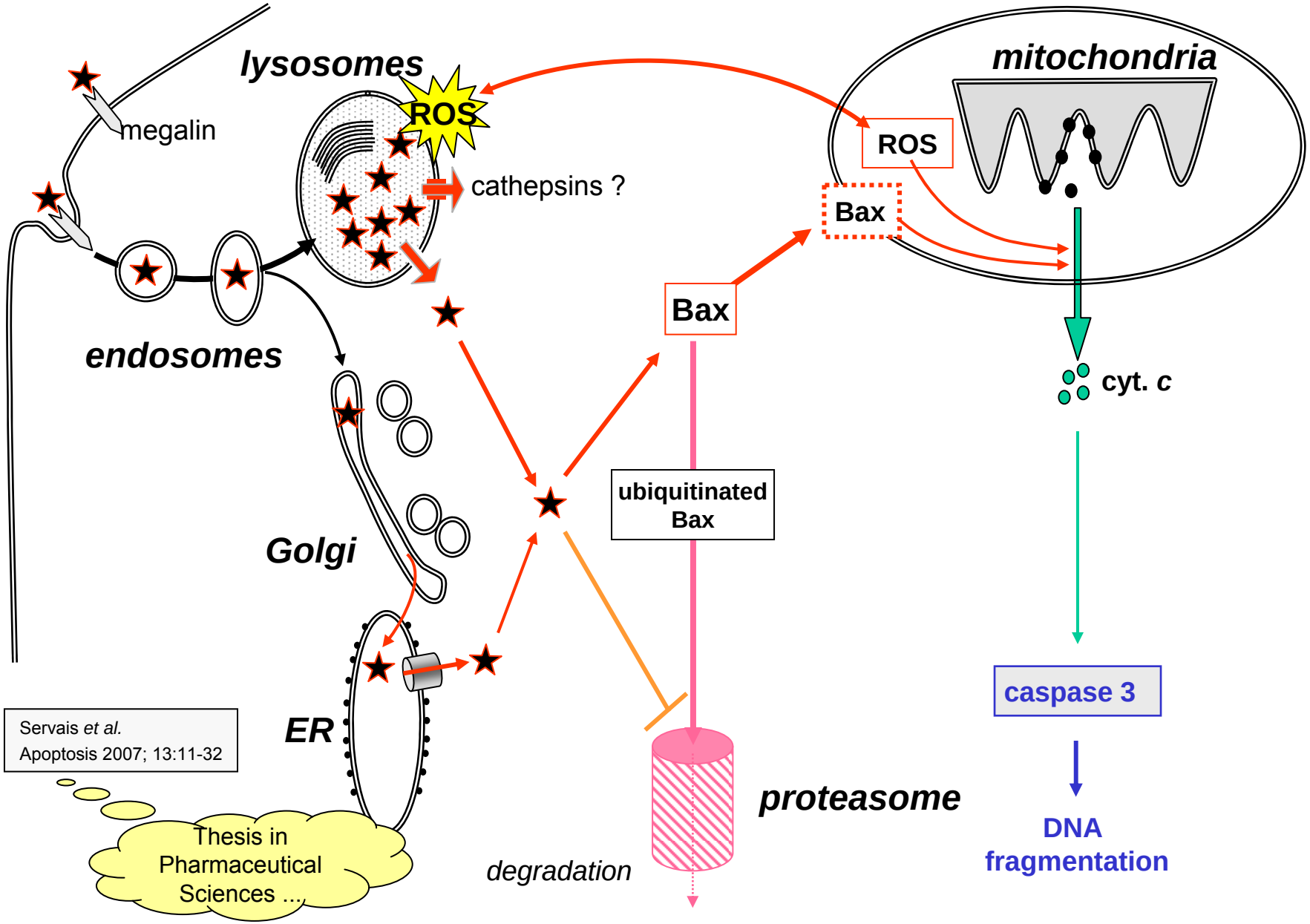
Laurent *et al.*,
Antimicrob. Agents Chemother.,
24:586-593, 1983

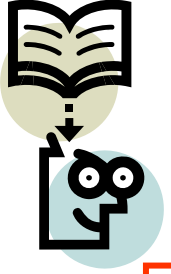
Tunel



El Mouedden *et al.*,
Antimicrob. Agents Chemother.,
44:665-675, 2000

Gentamicin and apoptosis: an overview by pharmacists...



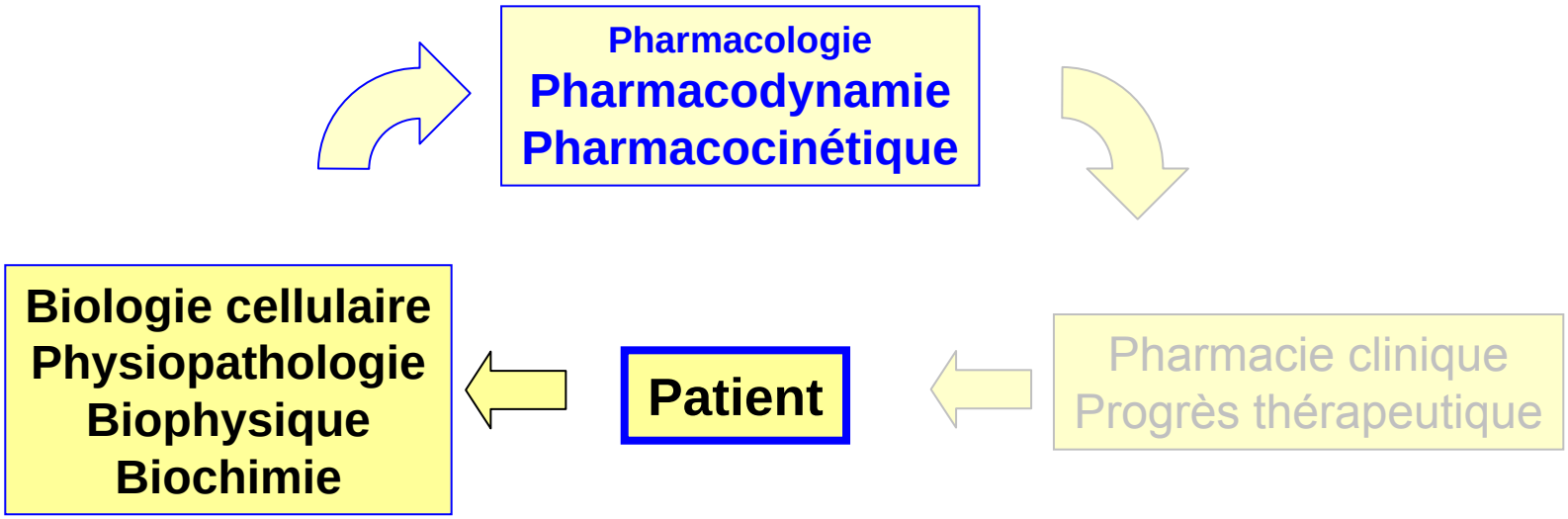


Résumé de la présentation

- Du patient vers le médicament:
  Le besoin thérapeutique
- Défense et illustration des sciences de base:
  Comment acquérir les connaissances nécessaires

- Le rôle de la pharmacologie
  Des modèles à la réalité biologique et thérapeutique
- De la pharmacologie vers la clinique
  Comment améliorer les traitements ?
- Le médicament optimisé pour le patient
  Intégration par le pharmacien clinicien

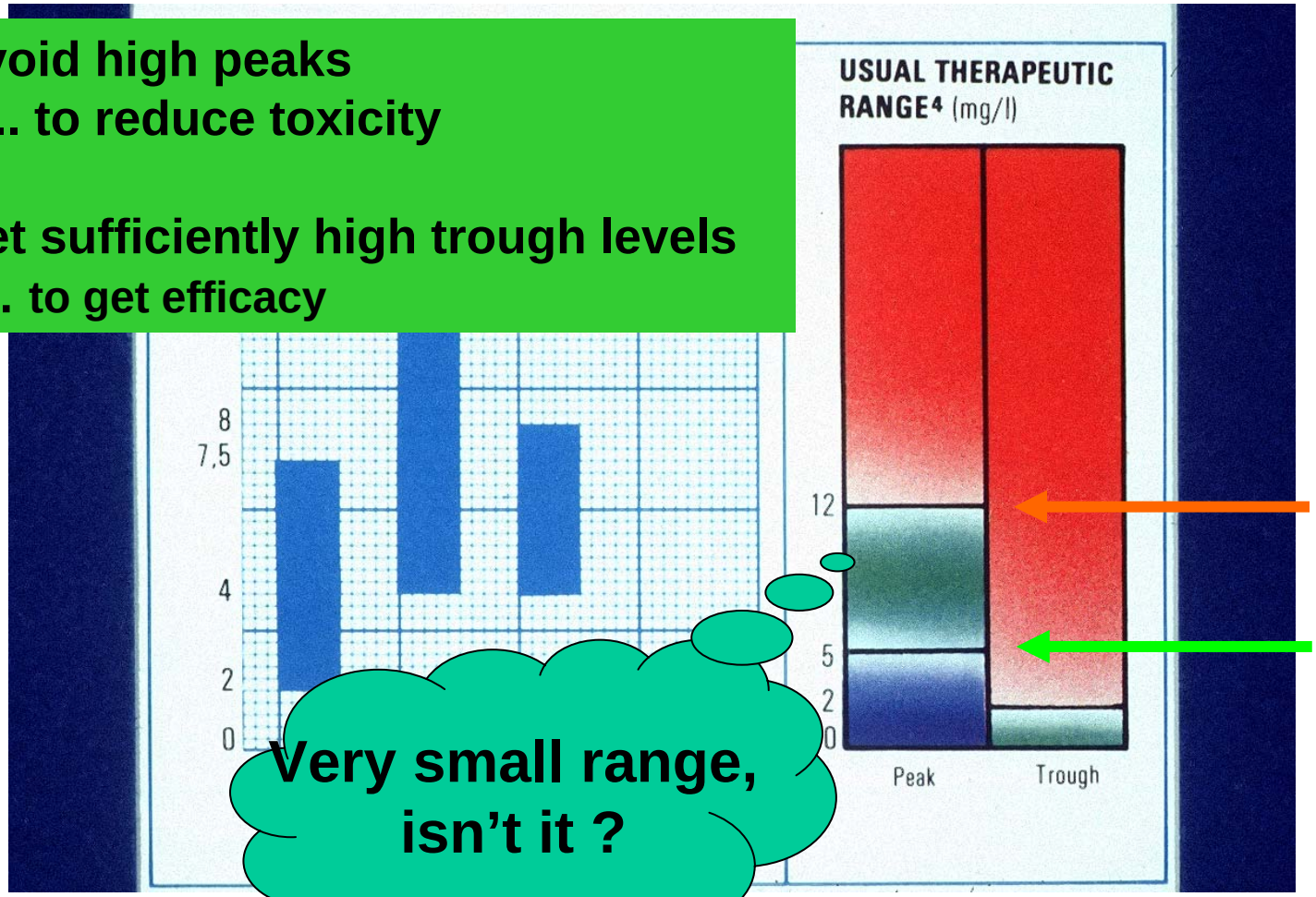
Progression dans le modèle ...



Aminoglycosides monitoring in the 80's ...

avoid high peaks
... to reduce toxicity

get sufficiently high trough levels
… to get efficacy



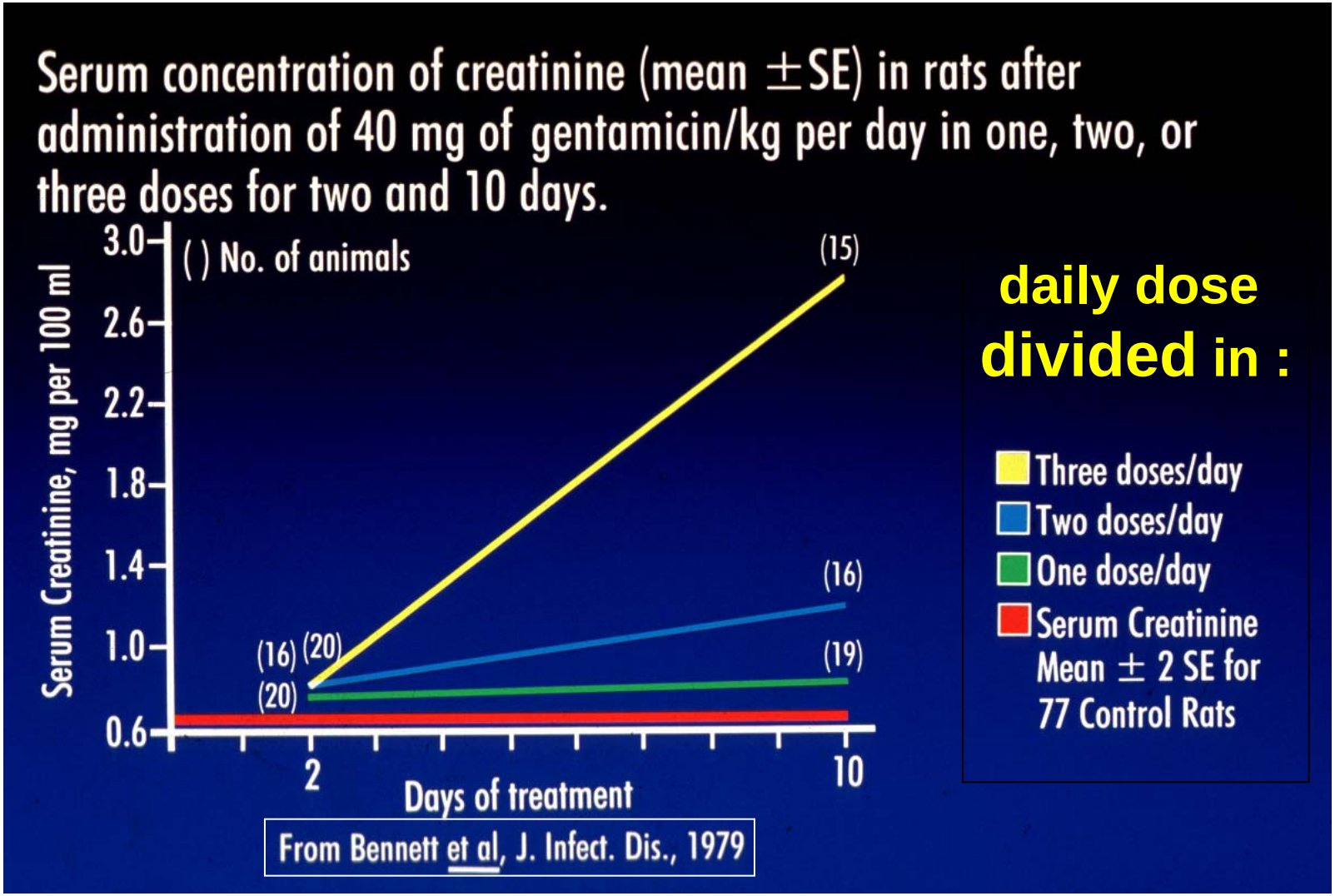
Patient

toxicity !!

lack of efficacy

Abott TdX manual, 1986

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



But toxicity is linked to renal accumulation ! …

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 1981, p. 147–152
0066-4804/81/010147-06$02.00/0

Vol. 19, No. 1

Amikacin and Gentamicin Accumulation Pharmacokinetics and Nephrotoxicity in Critically Ill Patients

MARGARET A. FRENCH,[1] FRANK B. CERRA,[2] MARTIN E. PLAUT,[3] AND JEROME J. SCHENTAG[1]*

Clinical Pharmacokinetics Laboratory,[1] Millard Fillmore Hospital, and the Departments of Medicine[3] and Surgery,[2] State University of New York at Buffalo, Buffalo, New York 14209

JJ Schentag, PharmD

But toxicity is linked to renal accumulation ! …

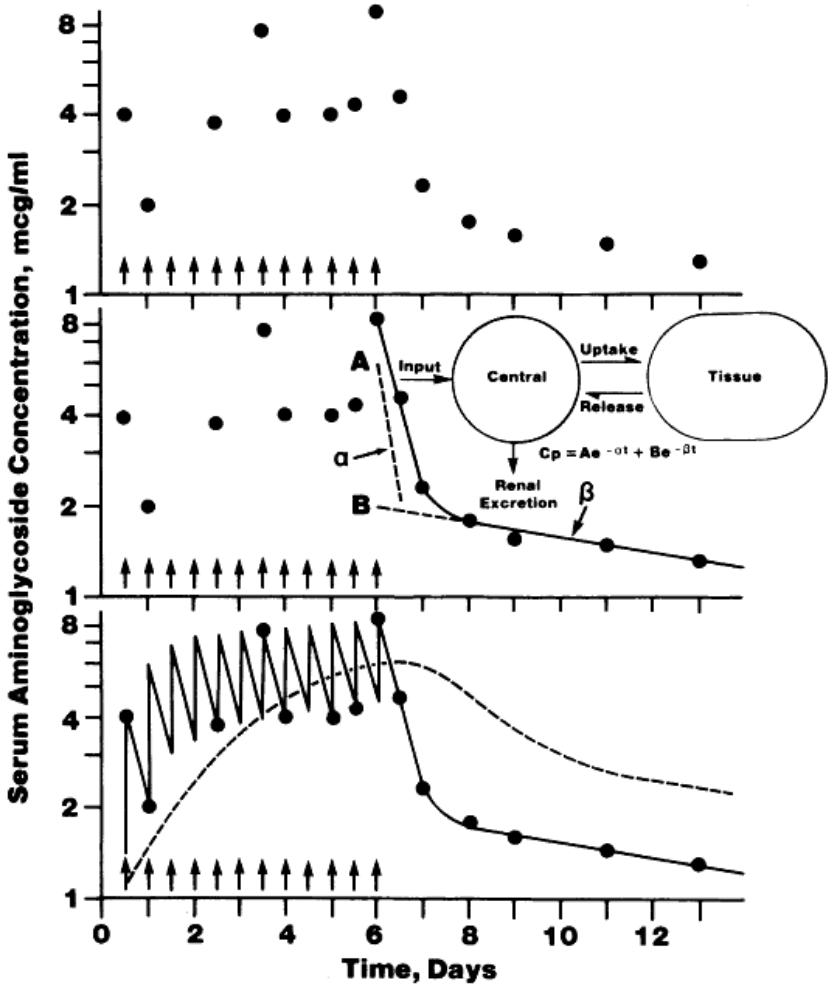


FIG. 1. *Protocol for patient studies and data analysis, including peak and trough serum concentrations during multiple-dose therapy, the two-compartment open model used to fit the washout data in the center frame, and the fitted serum concentrations as a solid line in the bottom frame. Also shown is the simulated peripheral compartment uptake amount as a dashed line (scale, ×10).*

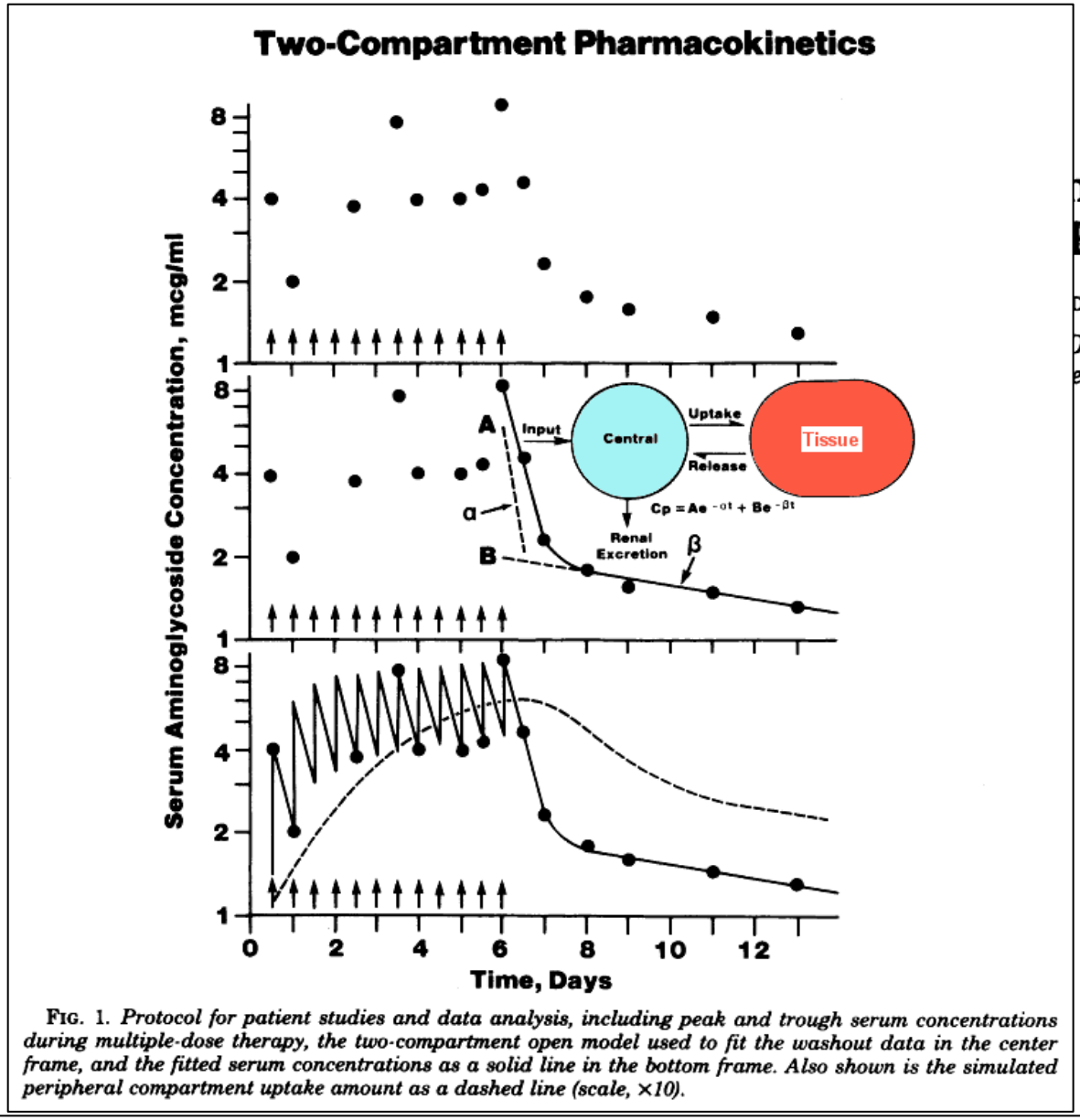
Vol. 19, No. 1

harmacokinetics
Patients

o JEROME J. SCHENTAG[1]*
Departments of Medicine[3] and
ew York 14209

JJ Schentag, PharmD

But toxicity is linked to renal accumulation ! …



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Vol. 19, No. 1

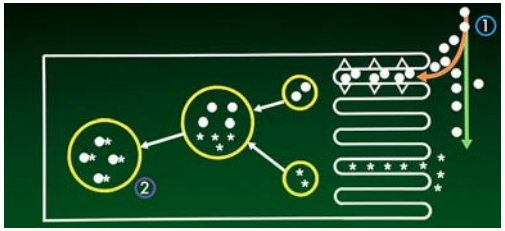
harmacokinetics
Patients

JEROME J. SCHENTAG[1]*

Departments of Medicine[3] and
ew York 14209

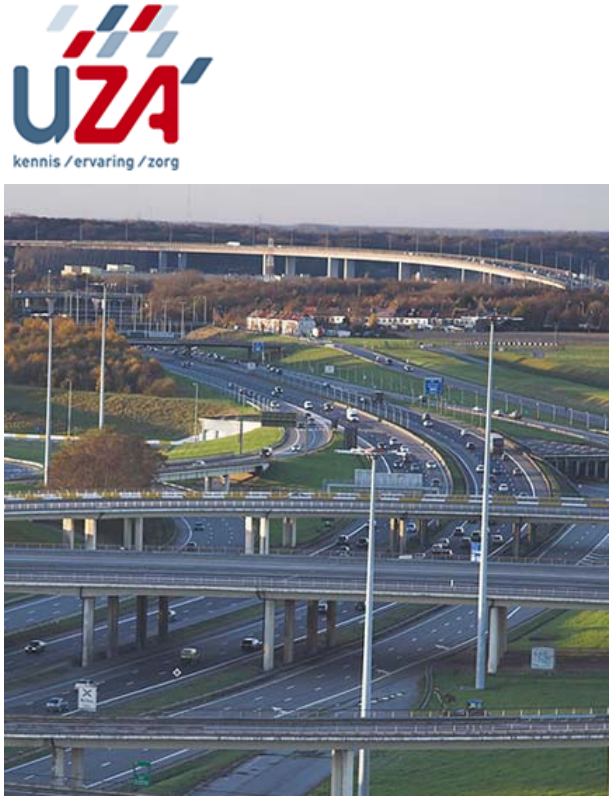
JJ Schentag, PharmD

Would this be the "deep tissue" compartment

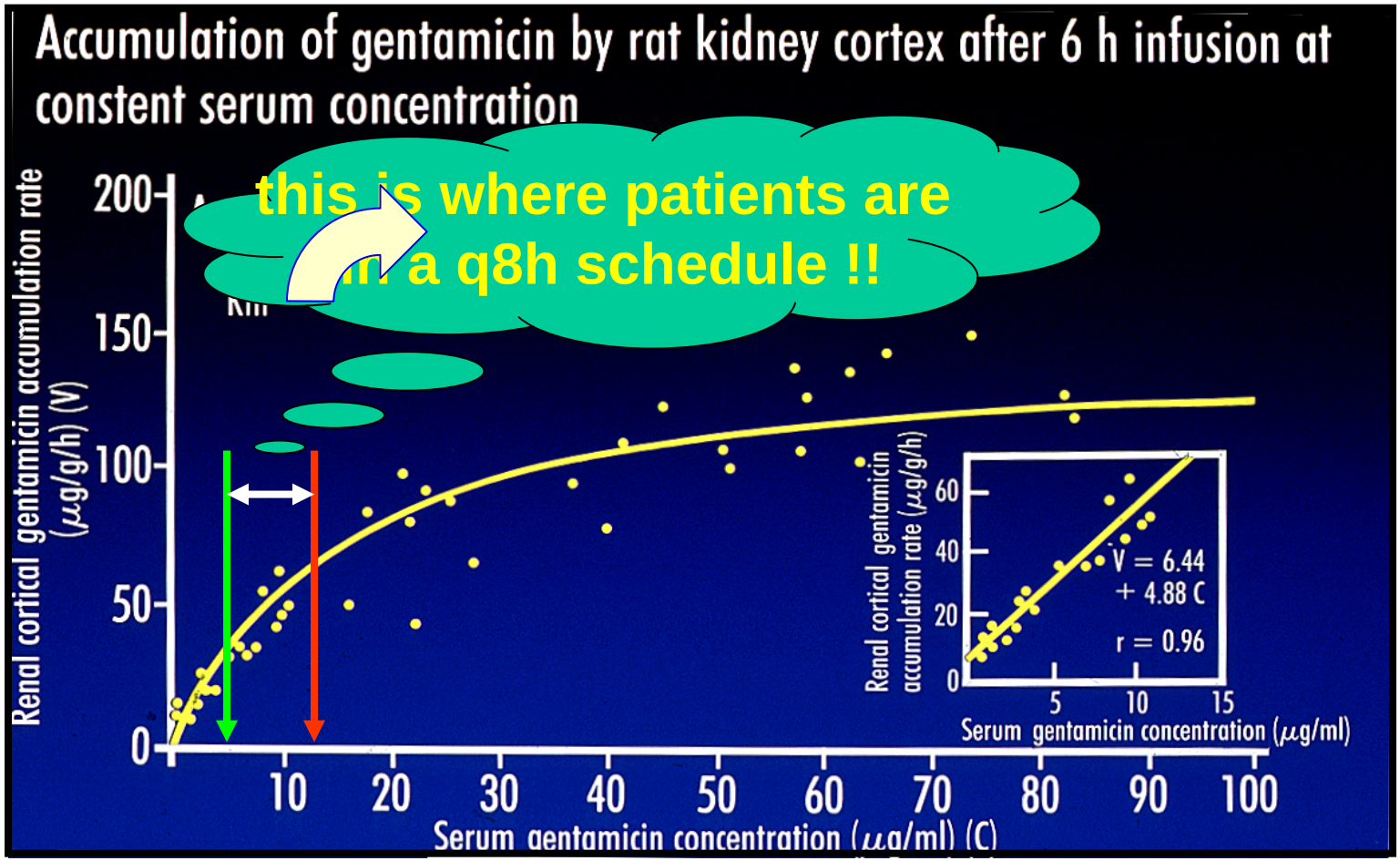


or where PharmD and MD meet …

And could this accumulation be saturable ? ...

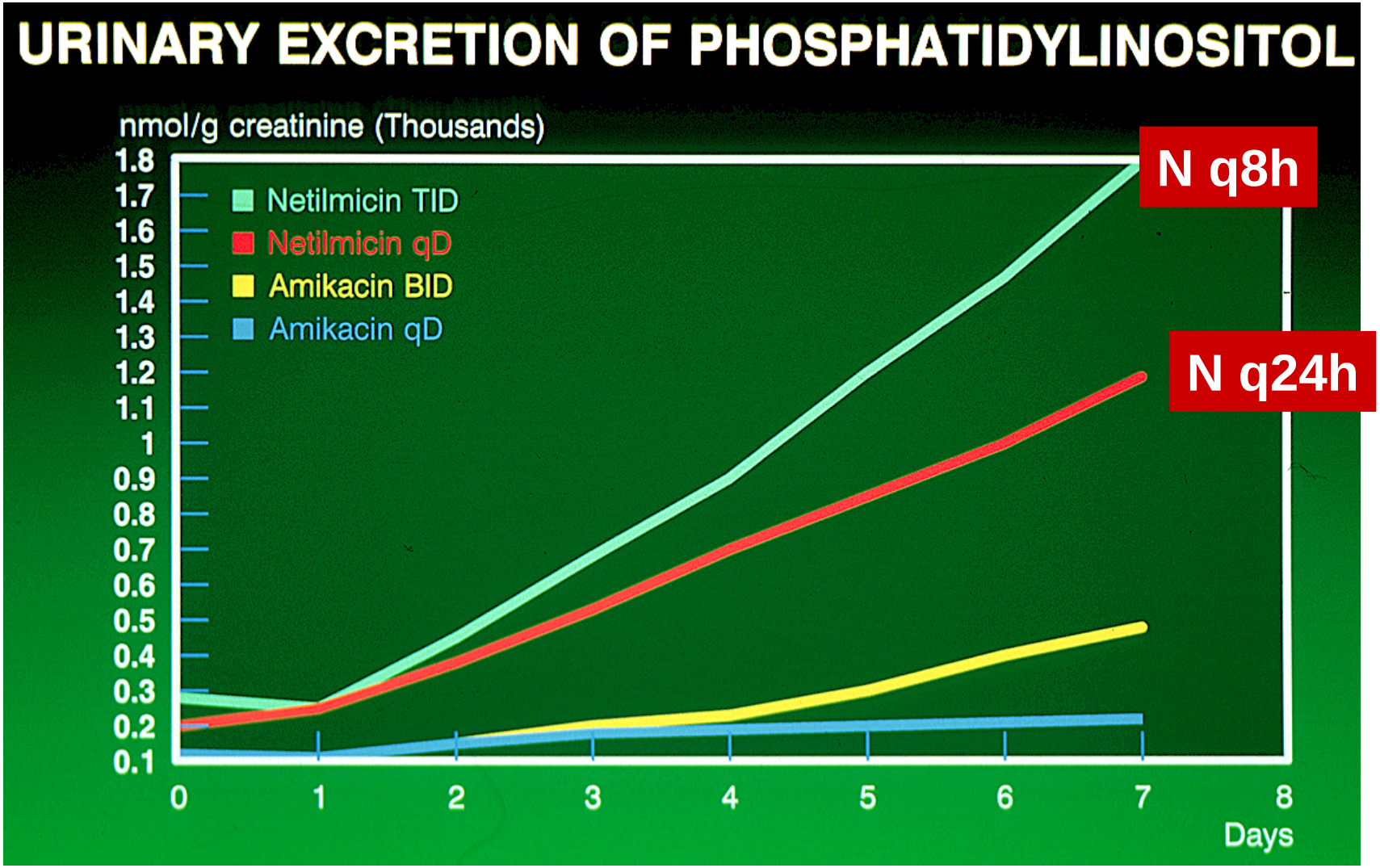


Aminoglycoside accumulation is kidney is saturable at clinically meaningful concentrations ...



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

And if you have less accumulation, you also have less phospholipid accumulation …



adapted from Tulkens *et al.*, J Drug Devel (1988) 1:71-82. 1989

But can you show this with "real patients" ?

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1991, p. 640–647 Vol. 35, No. 4
0066-4804/91/040640-08$02.00/0

Pharmacodynamic Parameters and Toxicity of Netilmicin (6 Milligrams/Kilogram/Day) Given Once Daily or in Three Divided Doses to Cancer Patients with Urinary Tract Infection

P. VAN DER AUWERA,[1]* F. MEUNIER,[1] S. IBRAHIM,[2] L. KAUFMAN,[3] M. P. DERDE,[3] AND P. M. TULKENS[2]

Service de Médecine et Laboratoire d'Investigation Clinique H.J. Tagnon, Clinique des Maladies Infectieuses et Laboratoire de Microbiologie, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, Rue Héger-Bordet 1, 1000 Brussels,[1] and Laboratoire de Chimie Physiologique, International Institute of Cellular and Molecular Pathology, Université Catholique de Louvain,[2] and Farmaceutische Instituut, Vrije Universiteit Brussel,[3] Brussels, Belgium

Received 14 March 1990/Accepted 21 January 1991

Institut Jules Bordet

Vrije Universiteit Brussel

But can you show this with "real patients" ?

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1991, p. 640–647
0066-4804/91/040640-08$02.00/0

Vol. 35, No. 4

Pharmacodynamic Parameters and Toxicity of Netilmicin (6 Milligrams/Kilogram/Day) Given Once Daily or in Three Divided Doses to Cancer Patients with Urinary Tract Infection

)ERDE,[3] AND P. M. TULKENS[2]
e des Maladies Infectieuses et
niversité Libre de Bruxelles,
ogique, International
ue de Louvain,[2]
els, Belgium

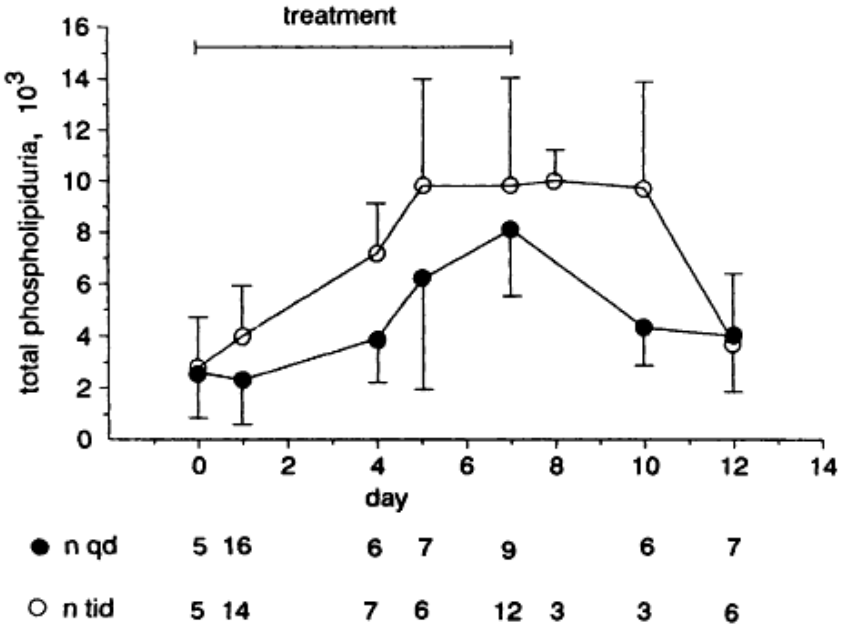
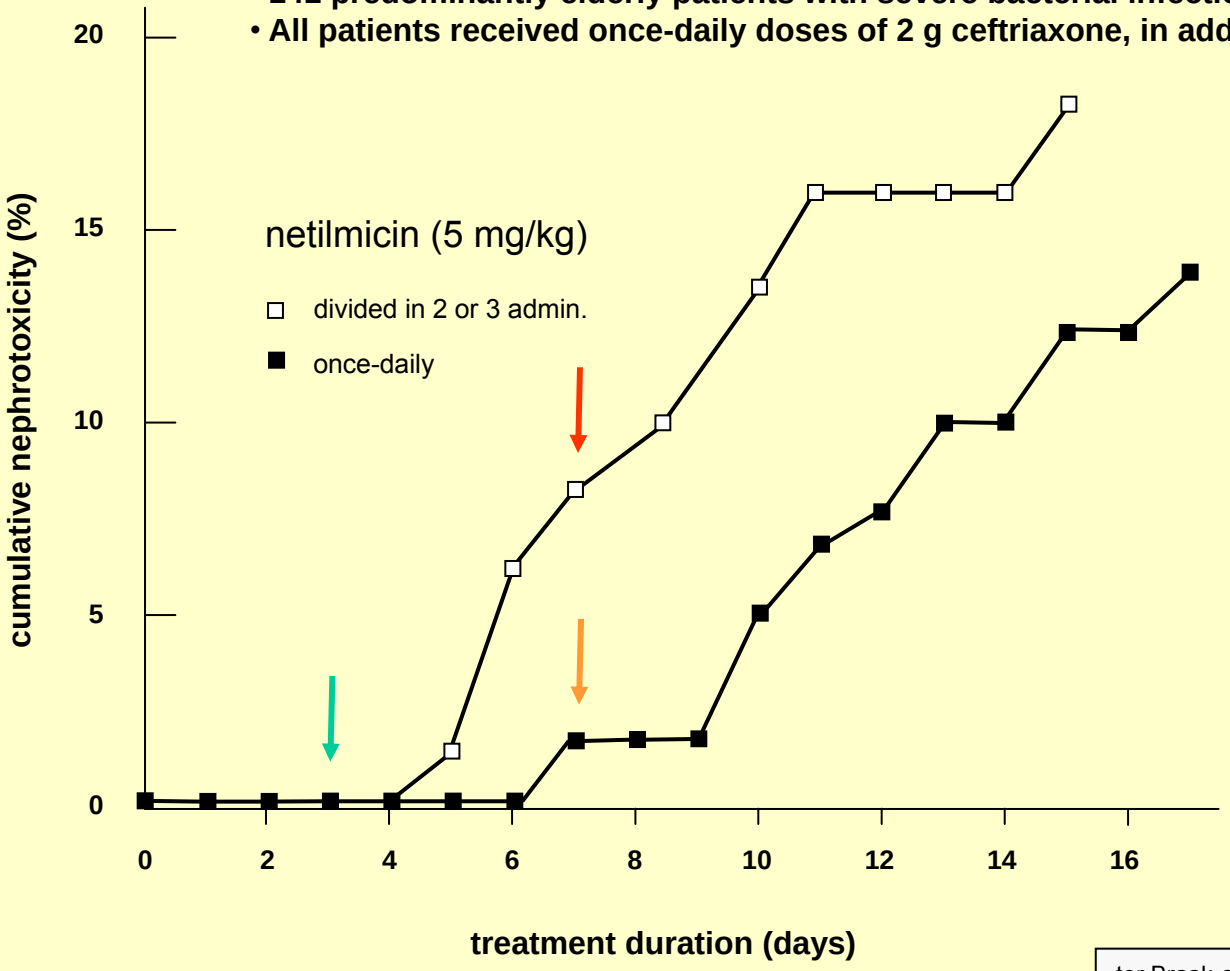


FIG. 1. Total phospholipid urinary excretion in patients receiving netilmicin (n) qd and tid during treatment and posttreatment periods. Results are means ± standard deviation; the numbers indicate the numbers of patients examined for each point. The rate of increase of phospholipiduria between day 0 or 1 and day 4 or 5 is greater in the tid group than in the qd group ($P = 0.09$).

Van der Auwere *et al.*, Antimicrob. Agents Chemother. (19891) 35:640-647

Néphrotoxicité et schéma d'administration en clinique : l'exemple de la nétilmicine …

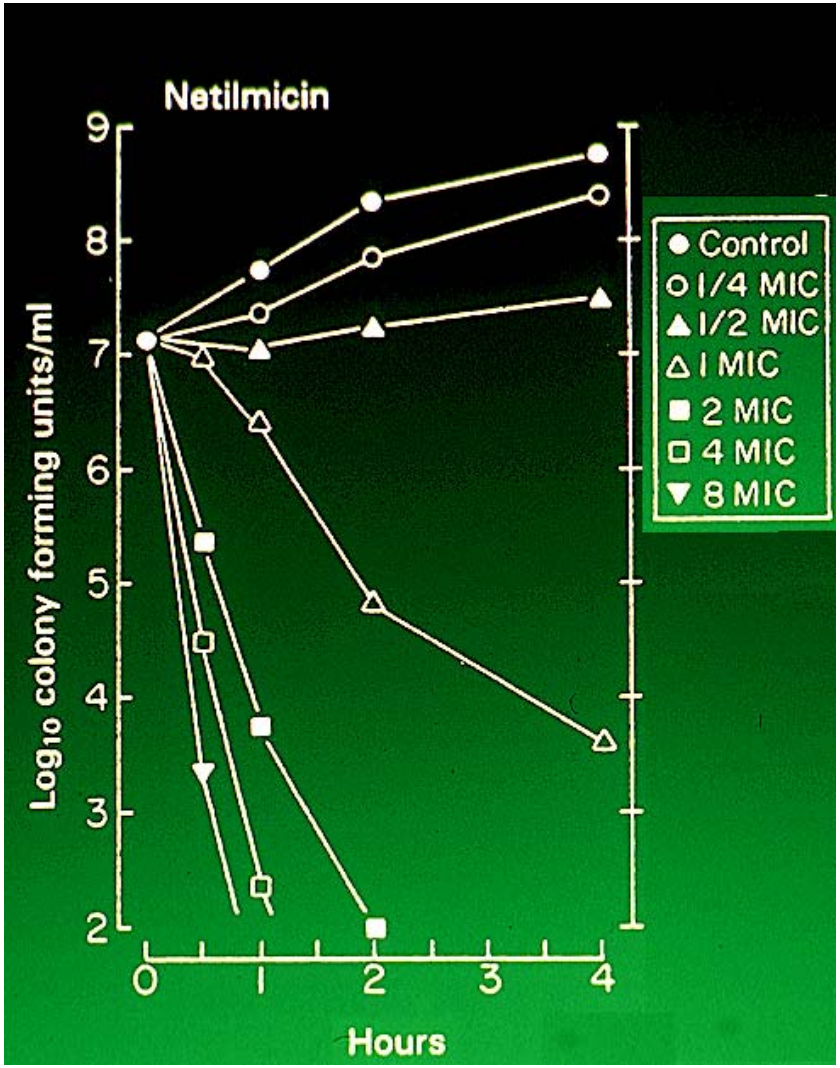
- **141 predominantly elderly patients with severe bacterial infections.**
- **All patients received once-daily doses of 2 g ceftriaxone, in addition to netilmicin.**



"Netilmicin-induced toxicity may be reduced by using once-daily dosing regimens and limiting the duration of treatment."

ter Braak *et al.*, Am J Med. 1990 Jul;89(1):58-66.

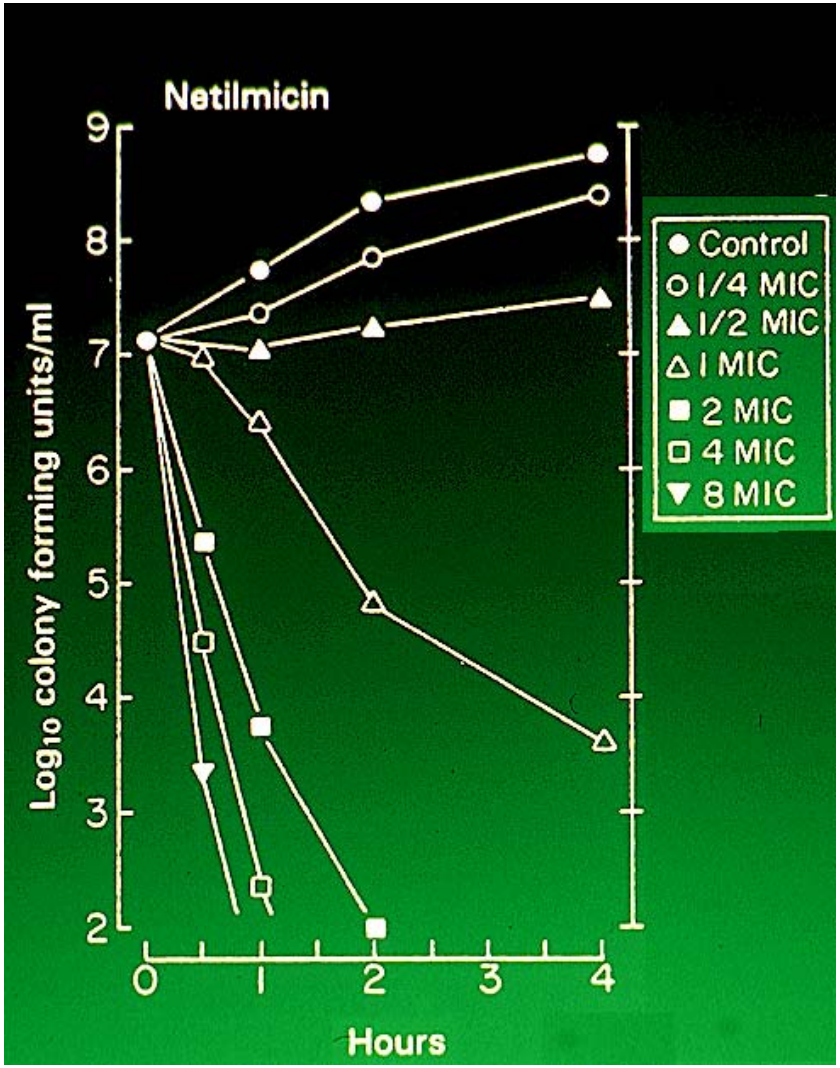
But would a high peak be efficacious ?



W.A. Craig, MD
VA Hospital,
Madison, WI

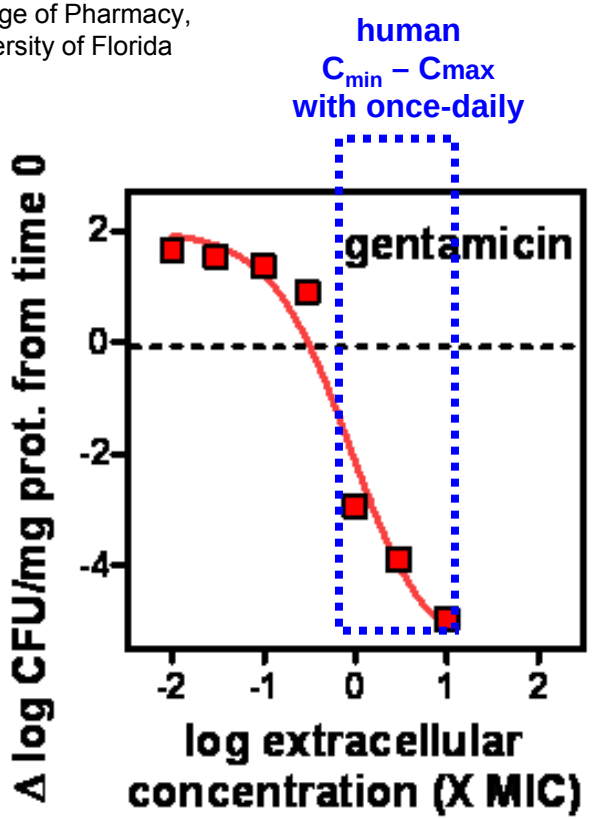
Paul,
Think about
pharmacodynamics
…

But would a high peak be efficacious ?



And now, add pharmacokinetics …

H. Derendorf, PhD
College of Pharmacy,
University of Florida



Attention: ceci n'est pas vrai pour tous les antibiotiques...

demandez à votre pharmacien

LOUVAIN MED. 118: 43-63, 1999.

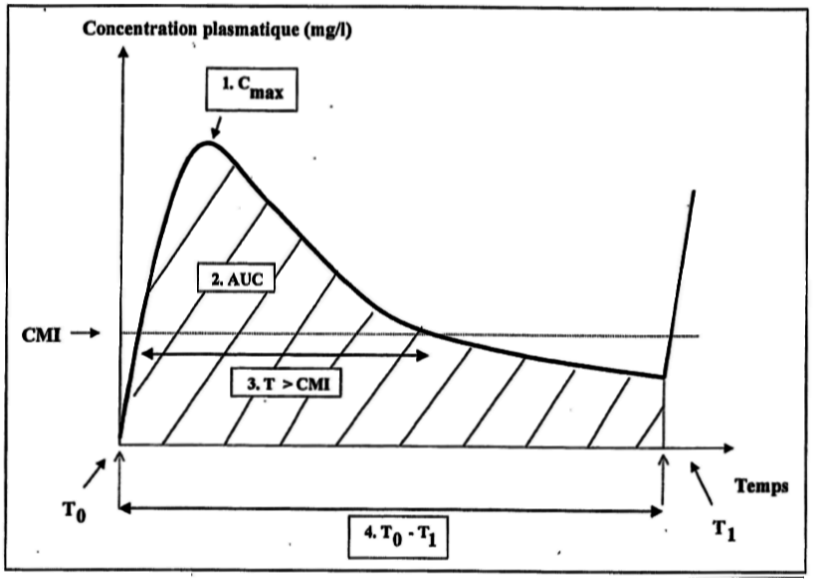


Fig. 2

Paramètres pharmacocinétiques d'un antibiotique à considérer dans l'étude de ses propriétés pharmacodynamiques. Les paramètres directs d'intérêt sont la concentration maximale (C_{max}), l'aire sous la courbe (AUC de la fonction concentration x temps), le temps pendant lequel la concentration est supérieure à la CMI (T > CMI) et le temps séparant deux expositions successives (T_1 - T_0). Les paramètres dérivés les plus importants sont le rapport C_{max}/CMI et le rapport AUC/CMI (appelé AUIC qui est l'acronyme de *Area Under the curve divided by the minimum Inhibitory Concentration)* (emprunté à W.A. Craig)

LOUVAIN MED. 118: 43-63, 1999.

OPTIMISATION DES TRAITEMENTS ANTIBACTÉRIENS SUR BASE DE PROPRIÉTÉS PHARMACODYNAMIQUES DES ANTIBIOTIQUES

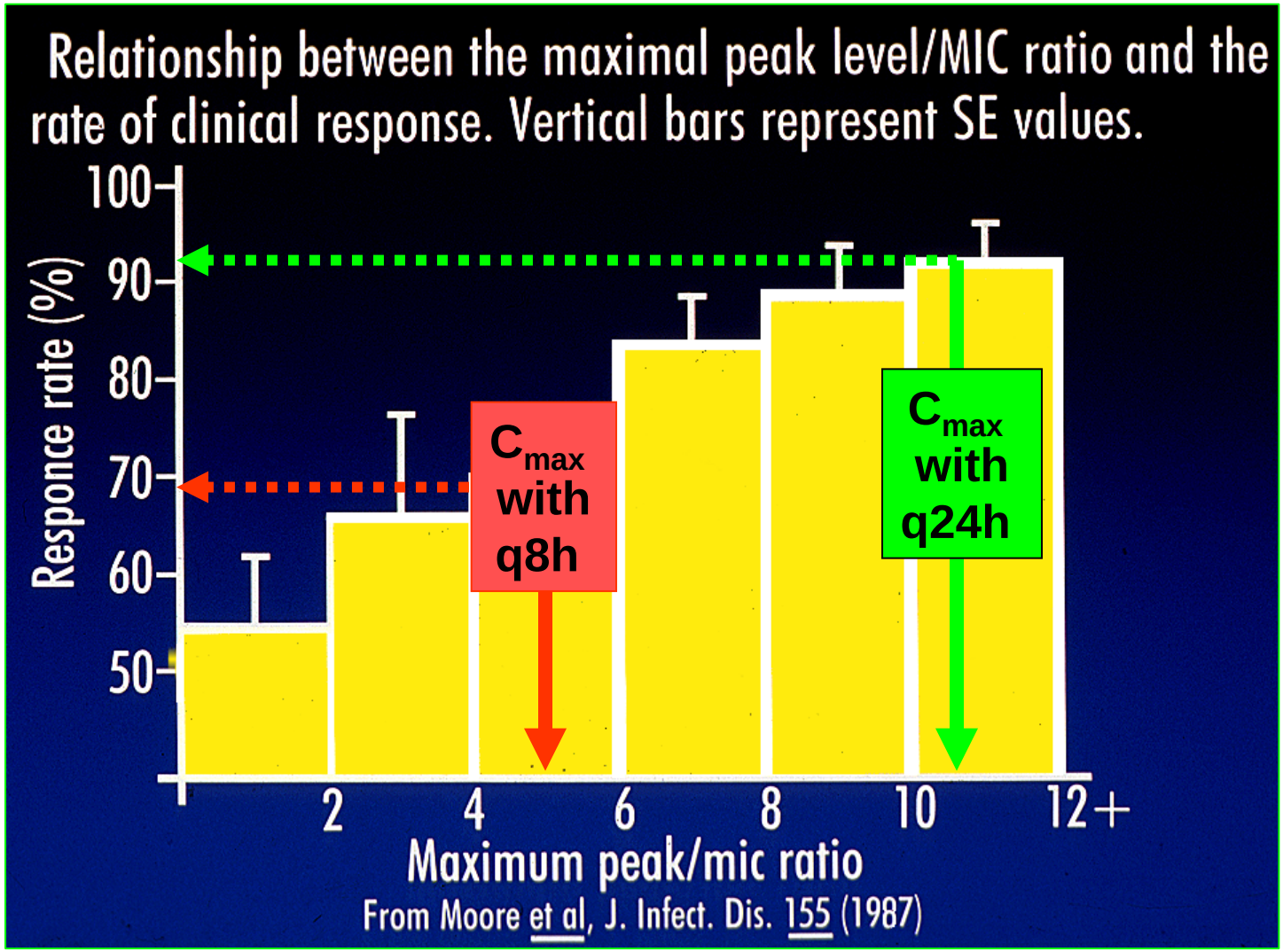
(Mise au point basée sur les exposés des Professeurs W.A. Craig, M.D.[1], J.J. Schentag, Pharm. D.[2] et Ch. Nightingale, Pharm. D.[3], ainsi que sur une analyse de la littérature)

F. VAN BAMBEKE, D. TYTECA,
Y. OUADRHIRI et P.M. TULKENS

Paramètres pharmacocinétiques prédictifs de l'efficacité des antibiotiques dans des modèles animaux et en clinique humaine

Classe d'antibiotique	*Paramètre prédictif d'efficacité chez l'animal*	*Paramètre en relation avec l'efficacité chez l'homme*
ß-lactames pénicillines céphalosporines carbapénèmes	t > CMI	t > CMI (AUIC)
Aminoglycosides	AUIC (Pic/CMI)	Pic/CMI (AUIC)
Fluoroquinolones	AUIC (Pic/CMI)	AUIC (Pic/CMI)

Is this true in the clinic ?



Aminoglycosides high: Yes !

Chemotherapy. 1990;36(1):1-7.

One shot of high-dose amikacin: a working hypothesis.

Yourassowsky E, Van der Linden MP, Crokaert F.

Department of Microbiology, Brugmann University Hospital Brussels, Belgium.

Abstract

Recent information suggests that single, large daily dosages of amikacin are less nephrotoxic. The killing rate of amikacin for Escherichia coli and Pseudomonas aeruginosa also suggests to put emphasis on a high peak value. A decrease of 3 log10 CFU/ml was observed for E. coli and P. aeruginosa at 64 and 128 micrograms/ml in 20 min. In comparison, the killing rate of piperacillin was dose-independent and about 6 h were required for a reduction of 10(3) CFU/ml of P. aeruginosa. In theory, the way to proceed in the future would possibly be the one-shot administration of amikacin, followed by a long course of a beta-lactam antibiotic.

L'Histoire va maintenant aller très vite…

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1991, p. 399–405 Vol. 35, No. 3
0066-4804/91/030399-07$02.00/0

MINIREVIEW

Once-Daily Aminoglycoside Therapy

DAVID N. GILBERT

Medical Education and Chiles Research Institute, Providence Medical Center, and Oregon Health Sciences University, 4805 NE Glisan, Portland, Oregon 97213

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1995, p. 650–655 Vol. 39, No. 3
0066-4804/95/$04.00+0

Experience with a Once-Daily Aminoglycoside Program Administered to 2,184 Adult Patients

DAVID P. NICOLAU,[1,2,3]* COLLIN D. FREEMAN,[1,3]† PAUL P. BELLIVEAU,[1,3]‡ CHARLES H. NIGHTINGALE,[3,4] JACK W. ROSS,[2] AND RICHARD QUINTILIANI[2,5]

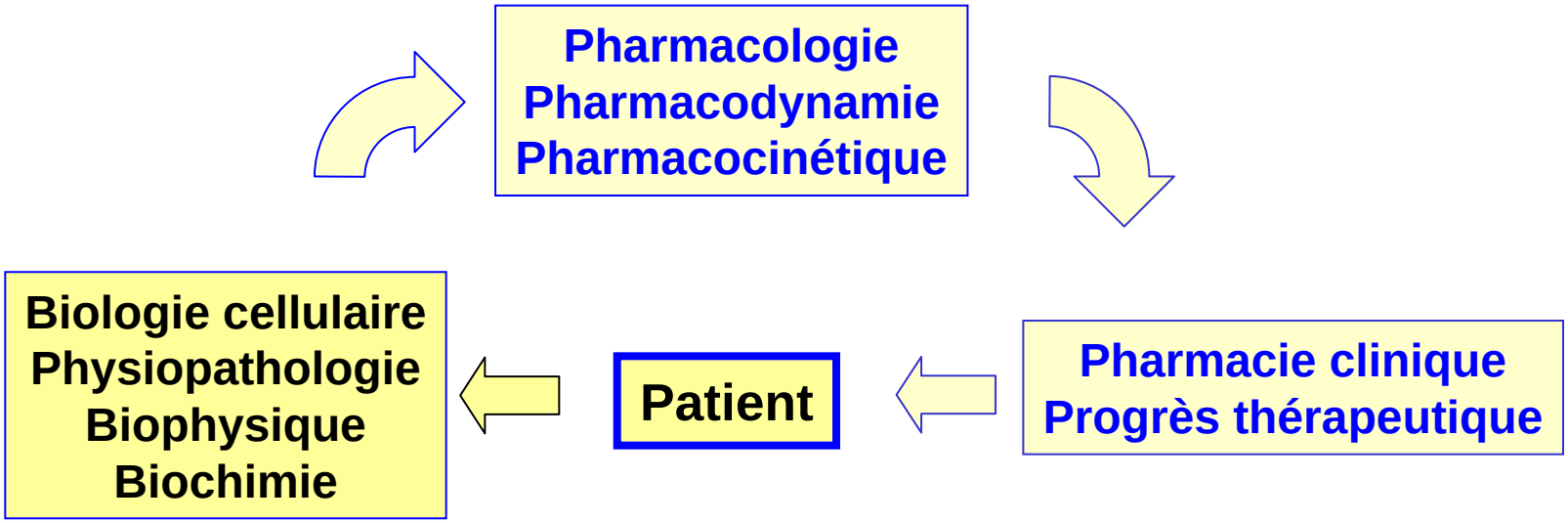
Department of Pharmacy,[1] Office for Research[4] and Department of Medicine,[2] Division of Infectious Diseases, Hartford Hospital, Hartford, Connecticut 06102; School of Pharmacy, University of Connecticut, Storrs, Connecticut 06268[3]; and School of Medicine, University of Connecticut, Farmington, Connecticut 06032[5]

PubMed search (25 April 2010) on
(aminoglycosid* OR gentamicin OR amikacin OR netilmicin) AND (once-daily OR "once daily" OR "once a day" OR qd)

Filter your results:

- All (680)
- Review (132)
- Clinical Trial (201)
- Free Full Text (155)

Progression dans le modèle ...



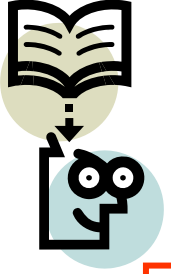
Is the once-a-day schedule used ?

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)**



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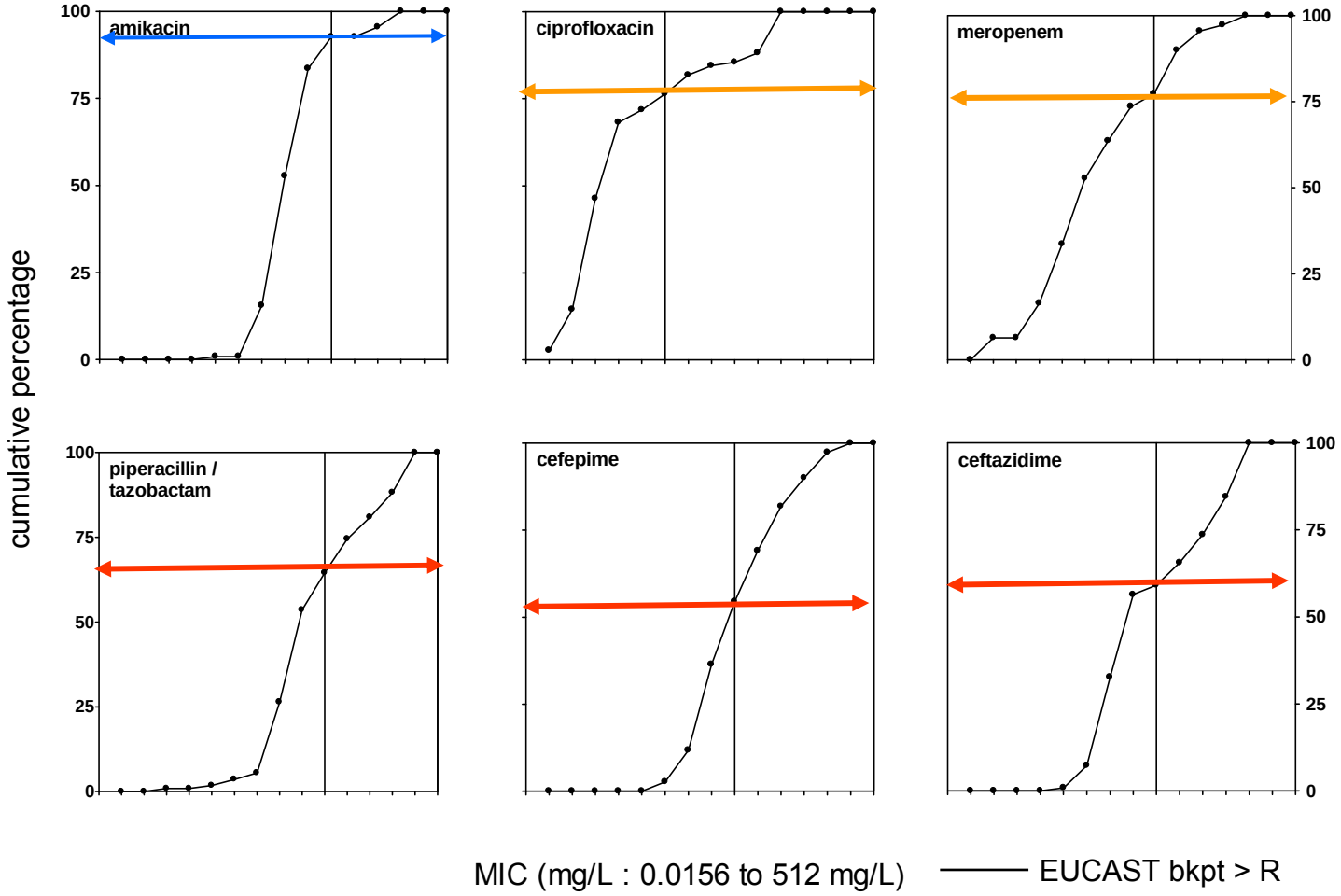
- Défense et illustration des sciences de base:
  Comment acquérir les connaissances nécessaires

- Le rôle de la pharmacologie
  Des modèles à la réalité biologique et thérapeutique
- De la pharmacologie vers la clinique
  Comment améliorer les traitements ?
- Le médicament optimisé pour le patient
  Intégration par le pharmacien clinicien

Mais que se passe-t-il en 2010 ?

- La résistance des bactéries Gram (-) devient alarmante…
  L'exemple de *P. aeruginosa* en Soins Intensifs dans 5 hôpitaux bruxellois



Riou *et al.*, ECCMID 2008 and submitted for publication

Et ceci n'est pas pure théorie...

BONNE ANNEE 2010

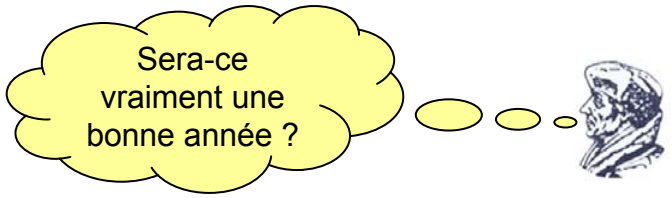
Madame, Monsieur,

Nous avons le plaisir de vous rappeler la séance du séminaire de microbiologie et maladies infectieuses de ce mercredi 6 janvier 2010 :

QUEL TRAITEMENT POUR LES INFECTIONS A *PSEUDOMONAS AERUGINOSA* PAN-RESISTANT ?

B. Layeux, F. Jacobs, H. Rodriguez, Clinique des Maladies Infectieuses et Service de Microbiologie, Hôpital Erasme

Auditoire Jaumotte - Niveau (-1) Hôpital Erasme
Heure : de 12H15 à 13H15



Que faire avec les aminoglycosides ?

G.H. Miller
PharmD

Voici ce qu'il faut faire …

AAC(6')-Ia, b, c…..ae
(28 genes in Gram(-), most are chromosomal in *Acinetobacter*; 3 in Gram(+))
all inactivate {Tm, Net, Amk, Abk, Km}, several can acetylate Isp & 1 Gm

ANT(4',4")
-Ia, {Km, Neo, Amk, Isp}
-IIa {Km, Neo, Amk, Isp}

AAC(6')-IIa, b {Gm, Tm, Net, Km}
(*Pseudomonas* only)

AAC(3)
-Ia, b, c, d, e {For, Gm}
-IIa, b {Gm, Tm, Net}
-IIIa {Gm, Tm}
-IVa {Gm, Tm, Net, Apr}
-VIa {Gm, Tm, Net}

APH(3')
-Ia, b, c {Km, Neo}
-IIa, b {Km, Neo}
-IIIa {Km, Neo, Amk, Isp}
-VIa {Km, Neo, Amk, Isp}
-VIIa {Km, Neo, Amk, Isp}

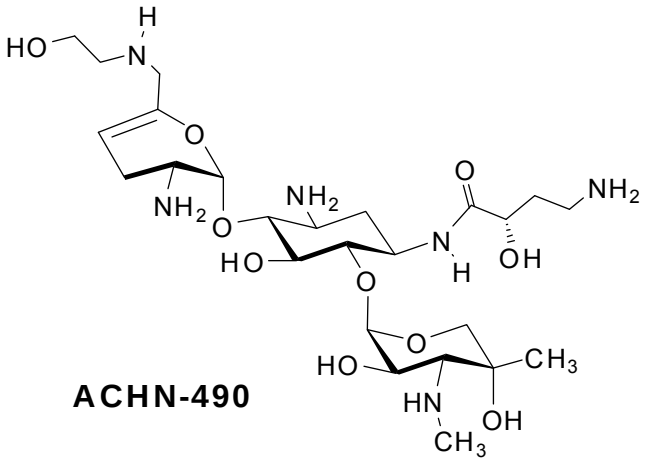
AAC(2')
-I a, b, c {Gm, Tm, Net, Km}
Chromosomal in *Providencia* and some *Mycobacterium*, not found elsewhere

ANT(2")
-Ia, b {Gm, Tm, Km}

APH(2")
-Ia, b, c, d {Gm, Tm, Km, Neo}

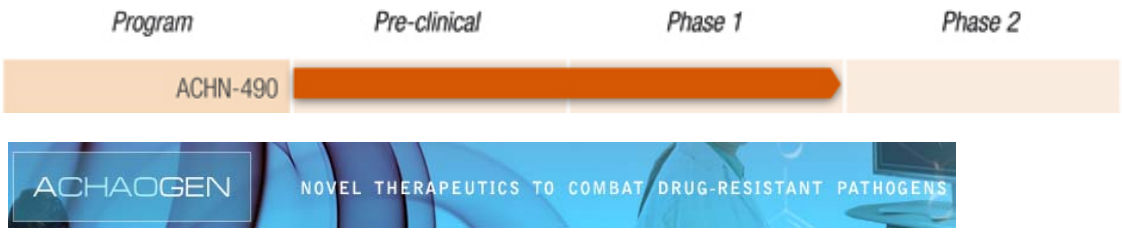
Y-a-til quelque chose dans le tuyau ?

- New aminoglycosides are being made that can cope with resistance …



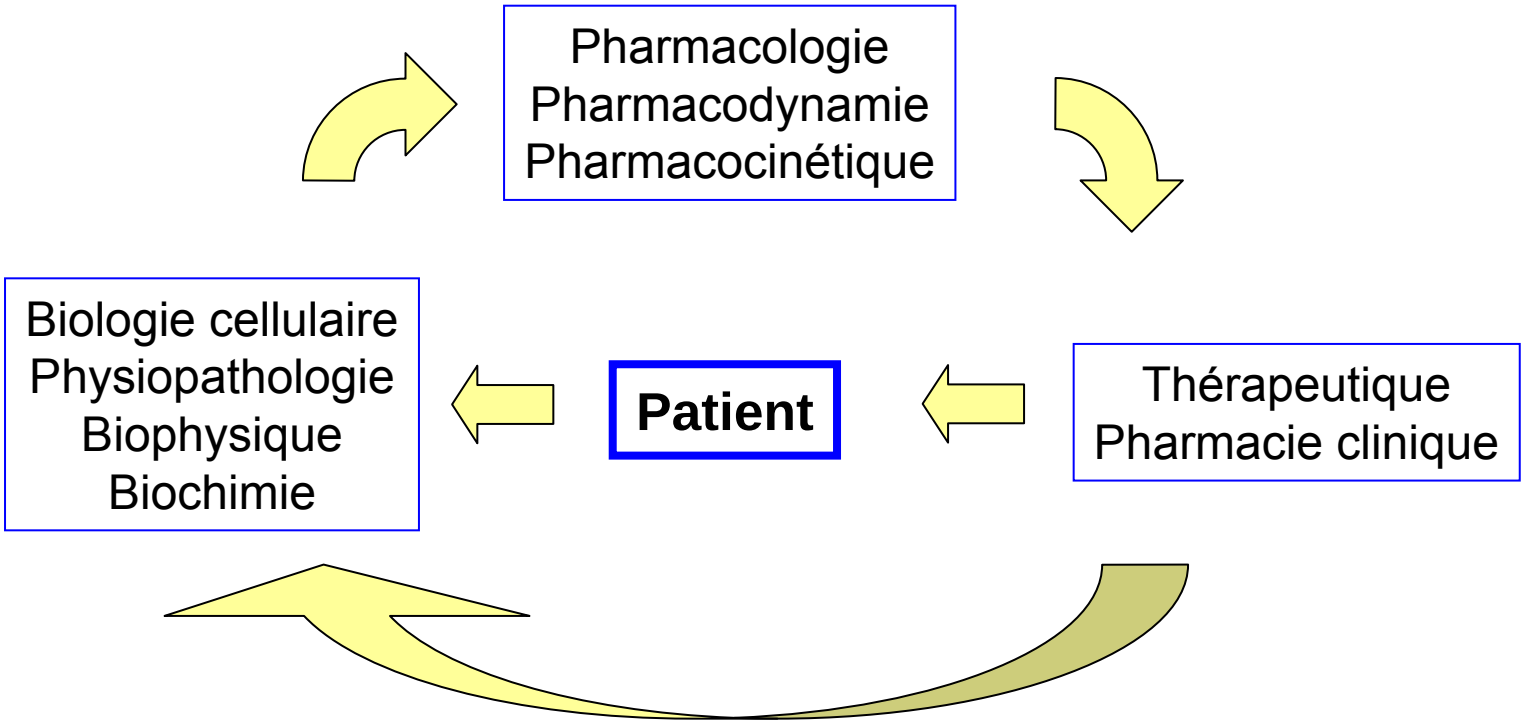
ACHN-490

- These will be developed with a "high initial dosage" approach
  - to optimize efficacy *
  - to minimize toxicity
  - to reduce the risk of emergence of resistance



* ACHN-490 is ill-active against *P. aeruginosa* due to efflux ...

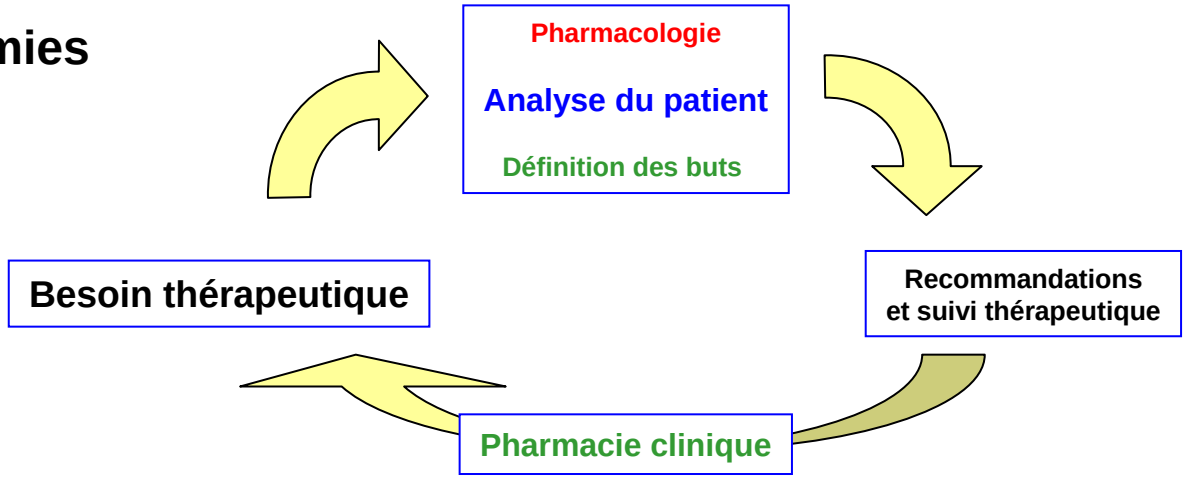
"Un" modèle pour aller de la pharmacologie spéciale à la pharmacothérapie et la pharmacie clinique



Nous verrons d'autres modèles (e.a. au départ direct du besoin thérapeutique) dans les prochaines leçons

Par exemple, …

Dyslipidémies



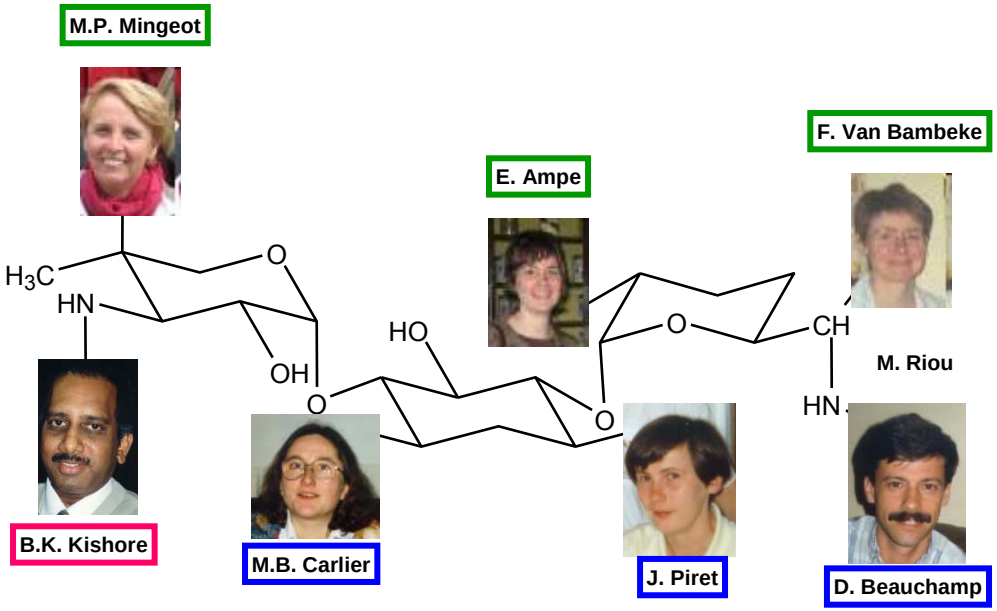
Et d'autres établies au départ de l'épidémiologie (pneumonie), de la tolérance (asthme), des effets indésirables (SIDA)…

Mais voici le chemin pour "ce" modèle…

Un bon mélange de médecins, pharmaciens, biologistes, chimistes…

sans craindre les controverses

une solide équipe locale multidisciplinaire



Il n'y pas assez de fonctions dans cette molécule...

En étant à l'écoute de la clinique, même dans le fond de son laboratoire