第19回　日本薬物動態学会年会
学会賞講演

演題

「CYP遺伝多型の臨床的意義に関する研究」

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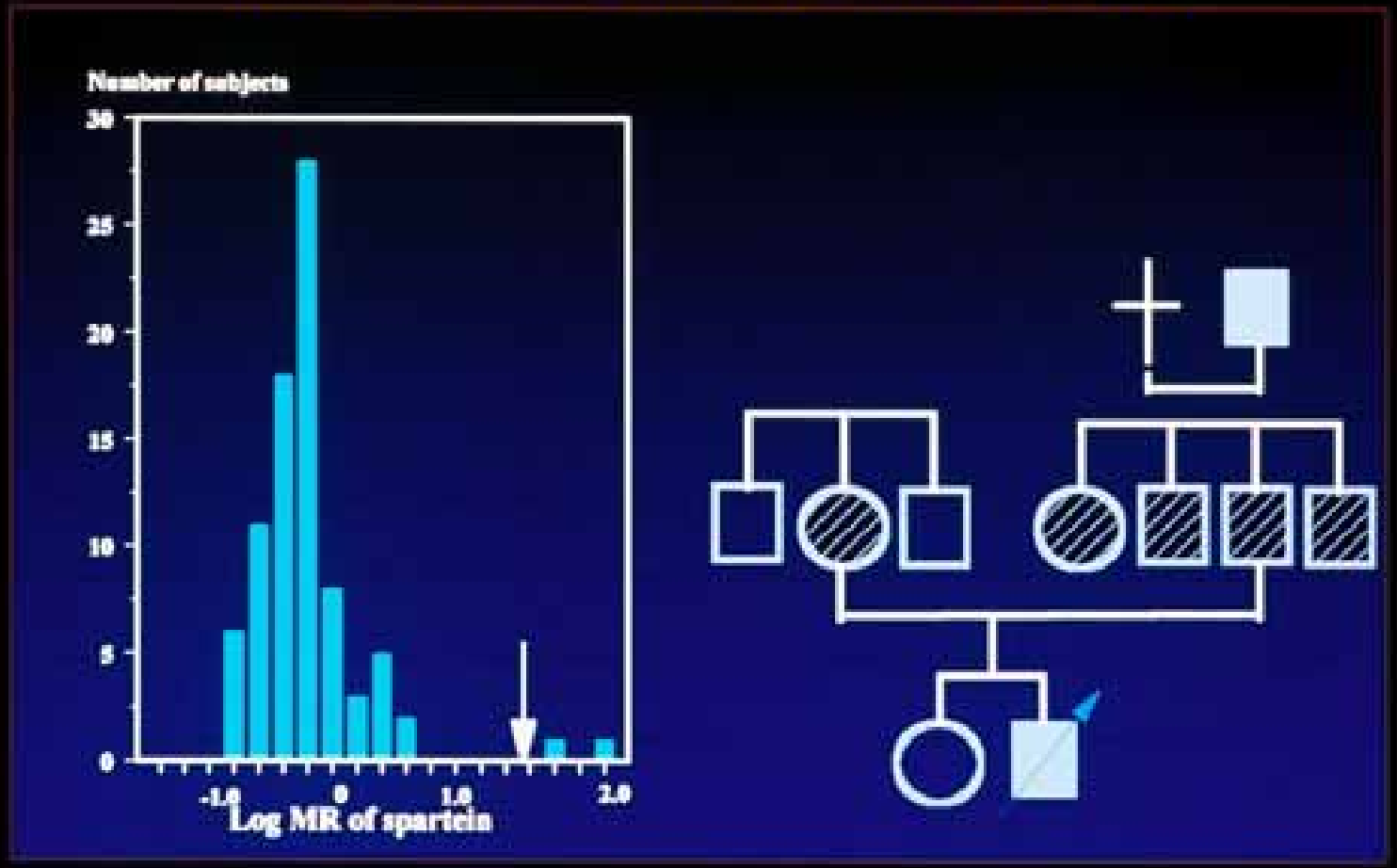
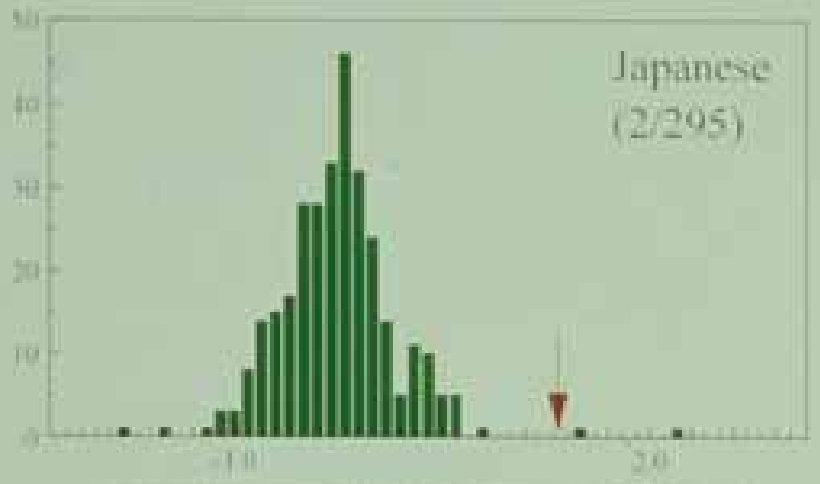
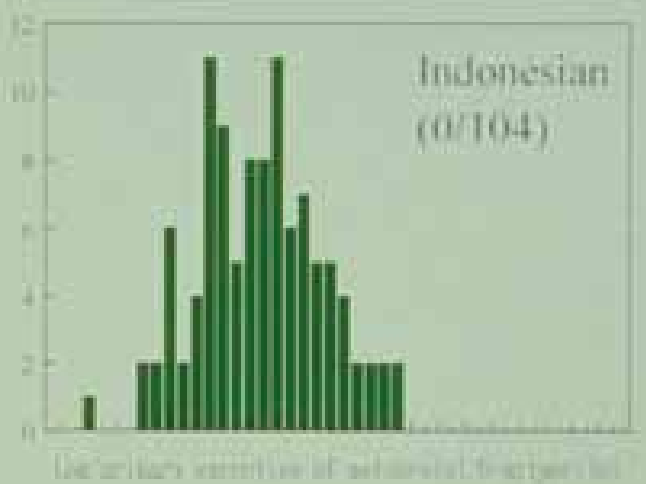
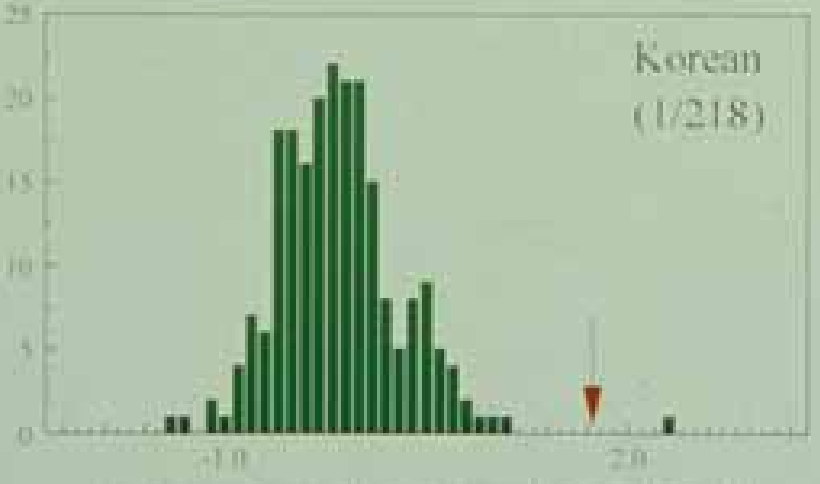
平成16年11月18日　金沢市

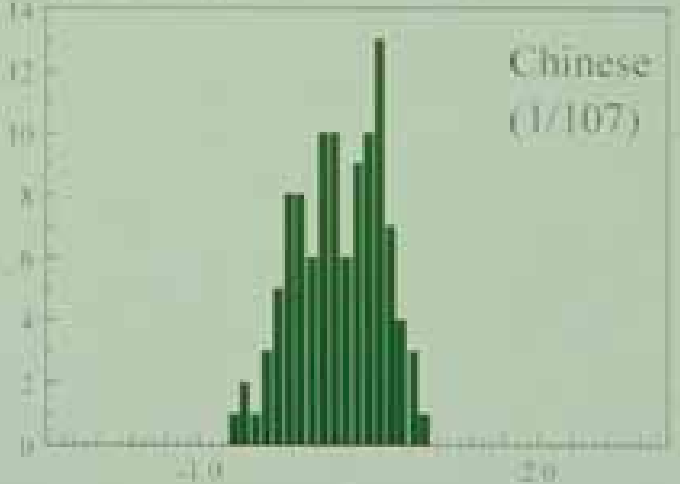
Frequency destribution histogram of log MR of spartein in 84 Japanese subjects (left) and pedigree of the family study (right)



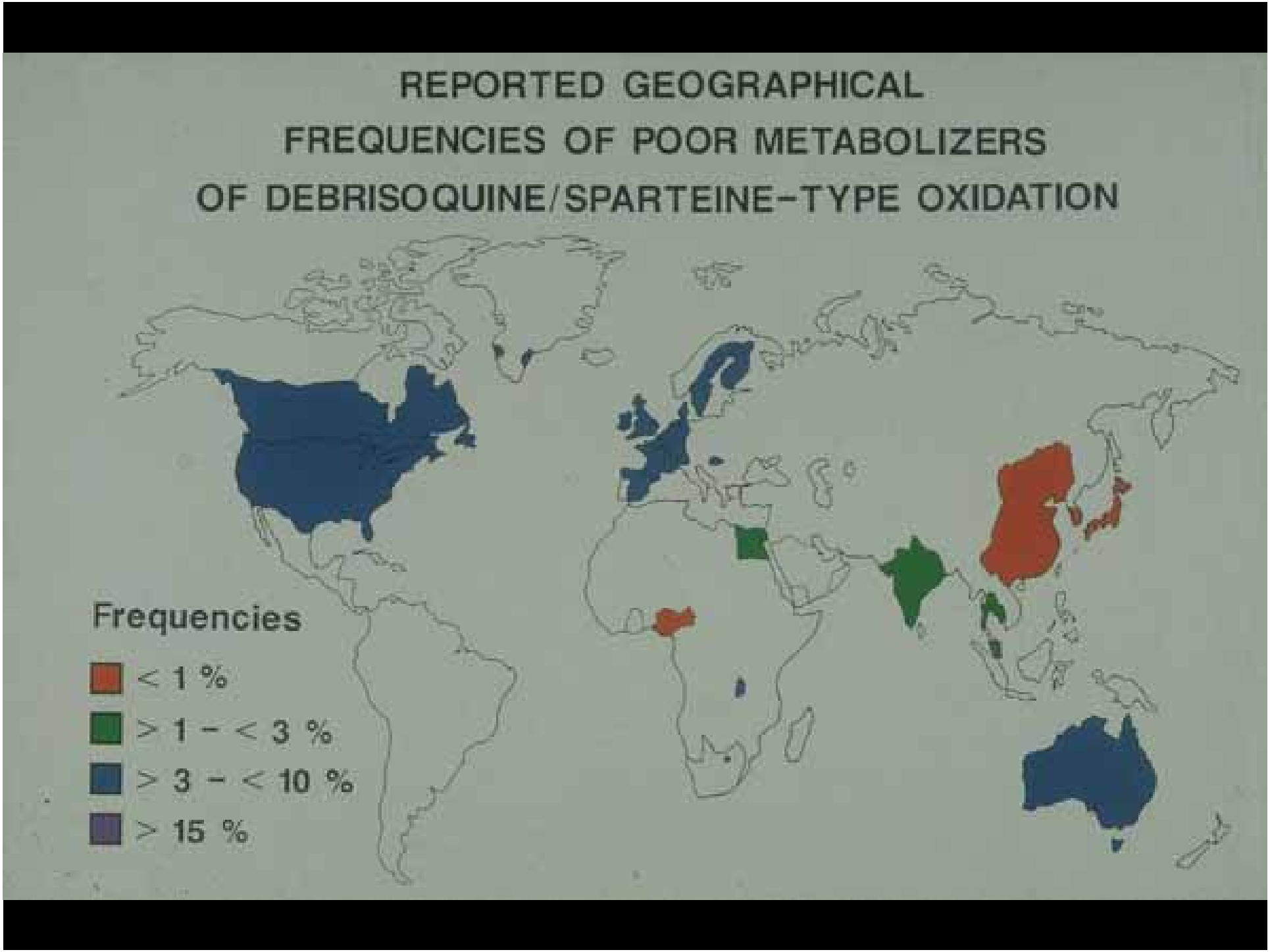

Japanese
(2/295)

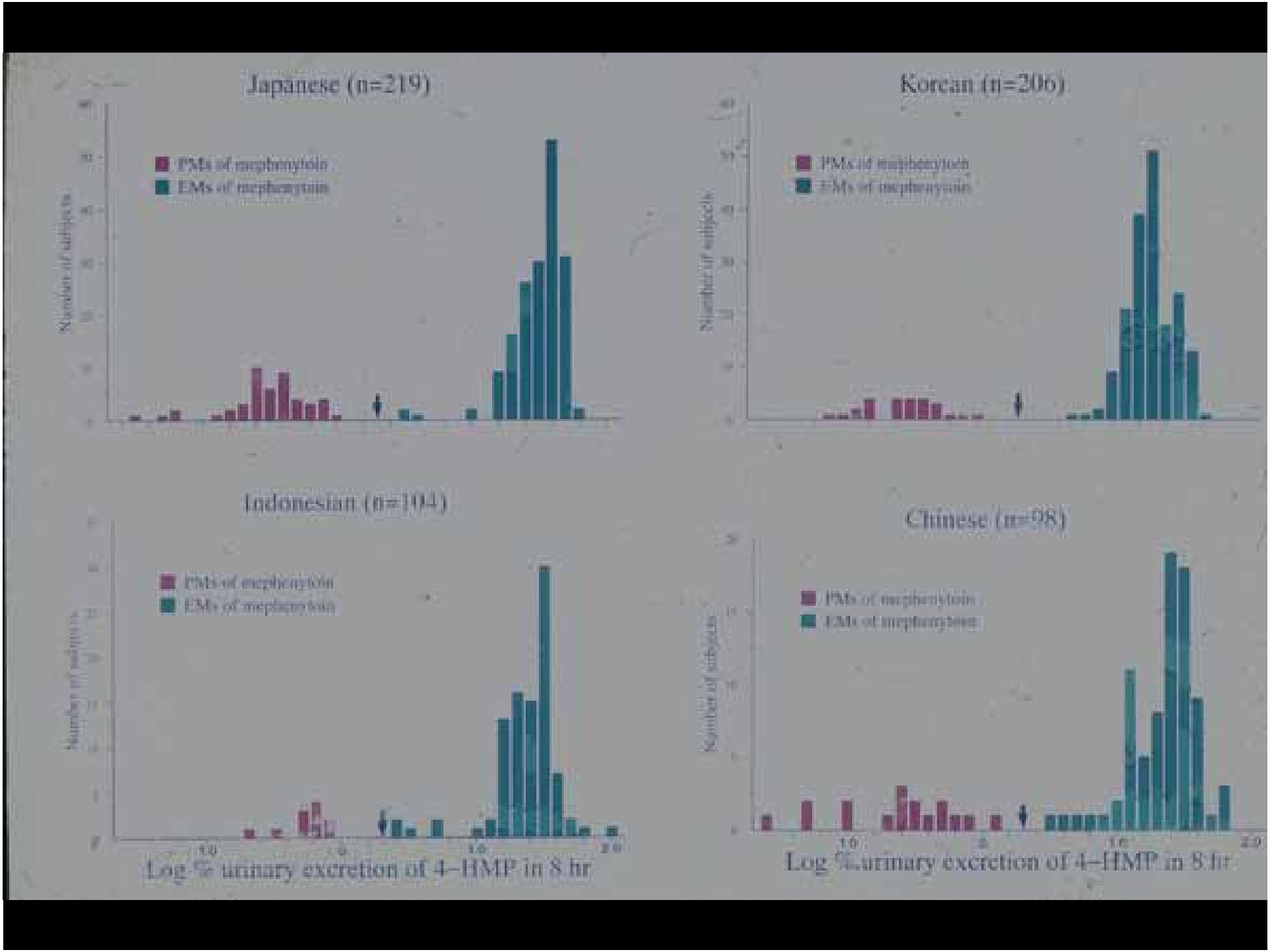

Indonesian
(0/104)


Korean
(1/218)

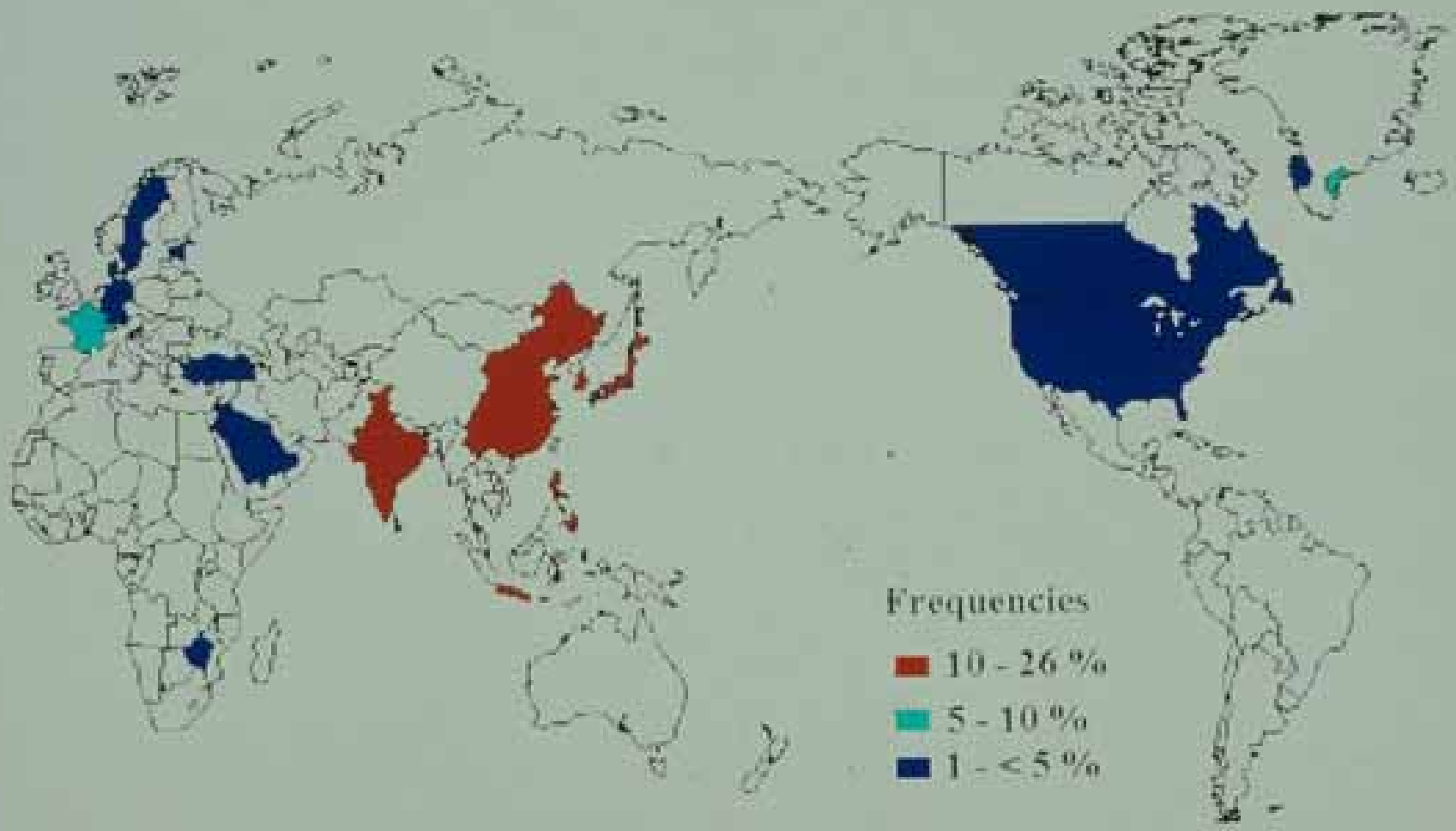

Chinese
(1/107)

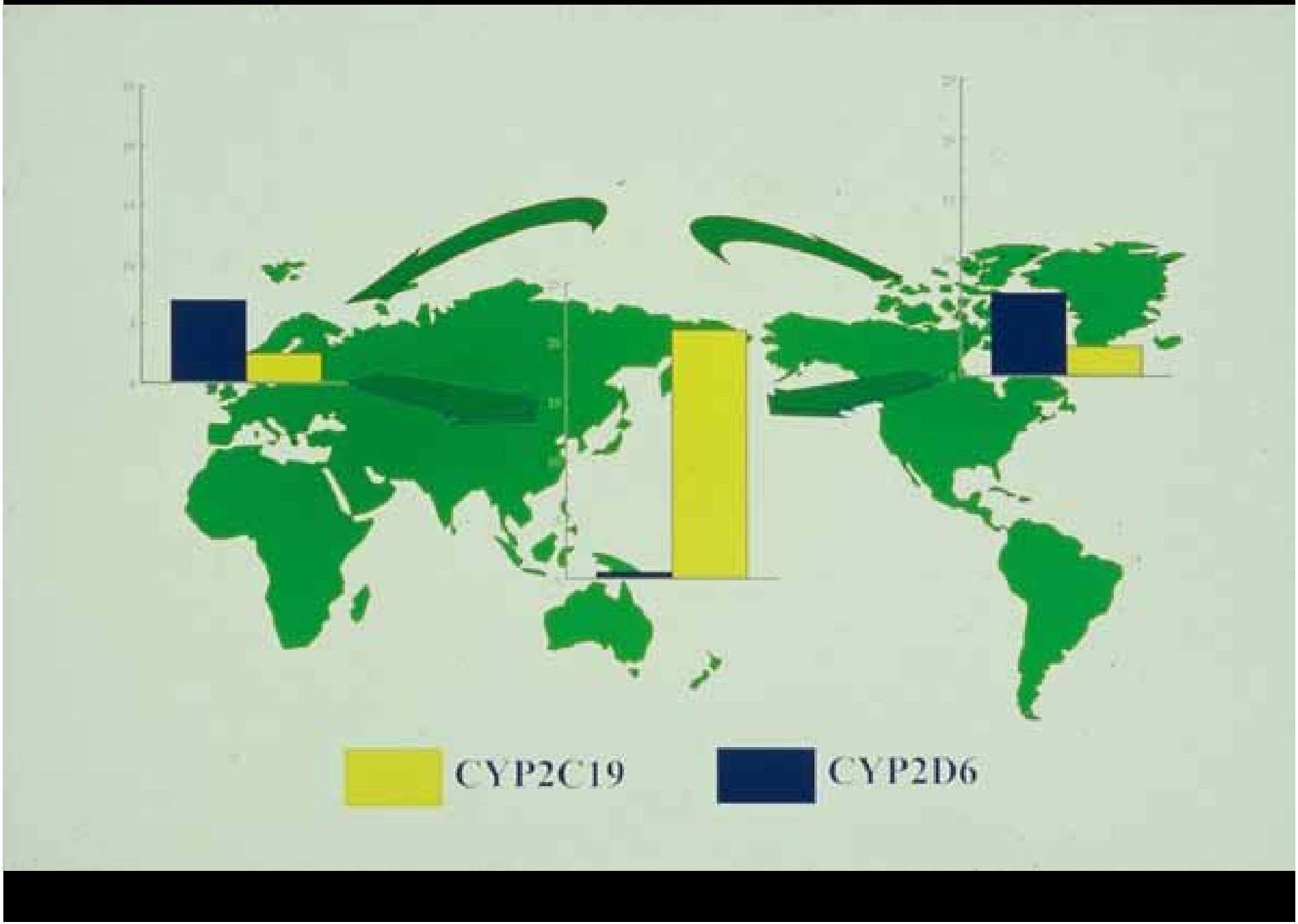
REPORTED GEOGRAPHICAL FREQUENCIES OF POOR METABOLIZERS OF DEBRISOQUINE/SPARTEINE-TYPE OXIDATION

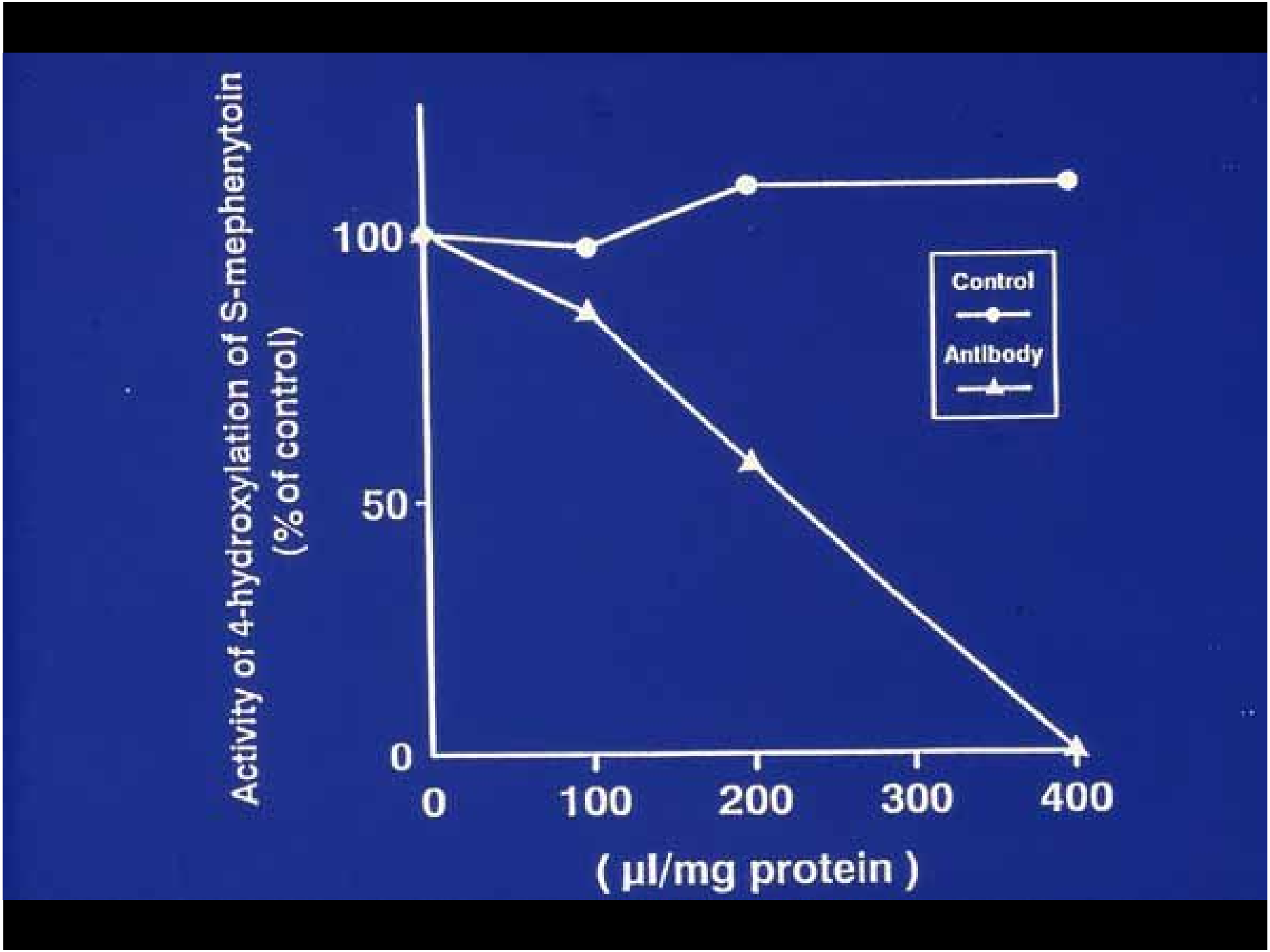


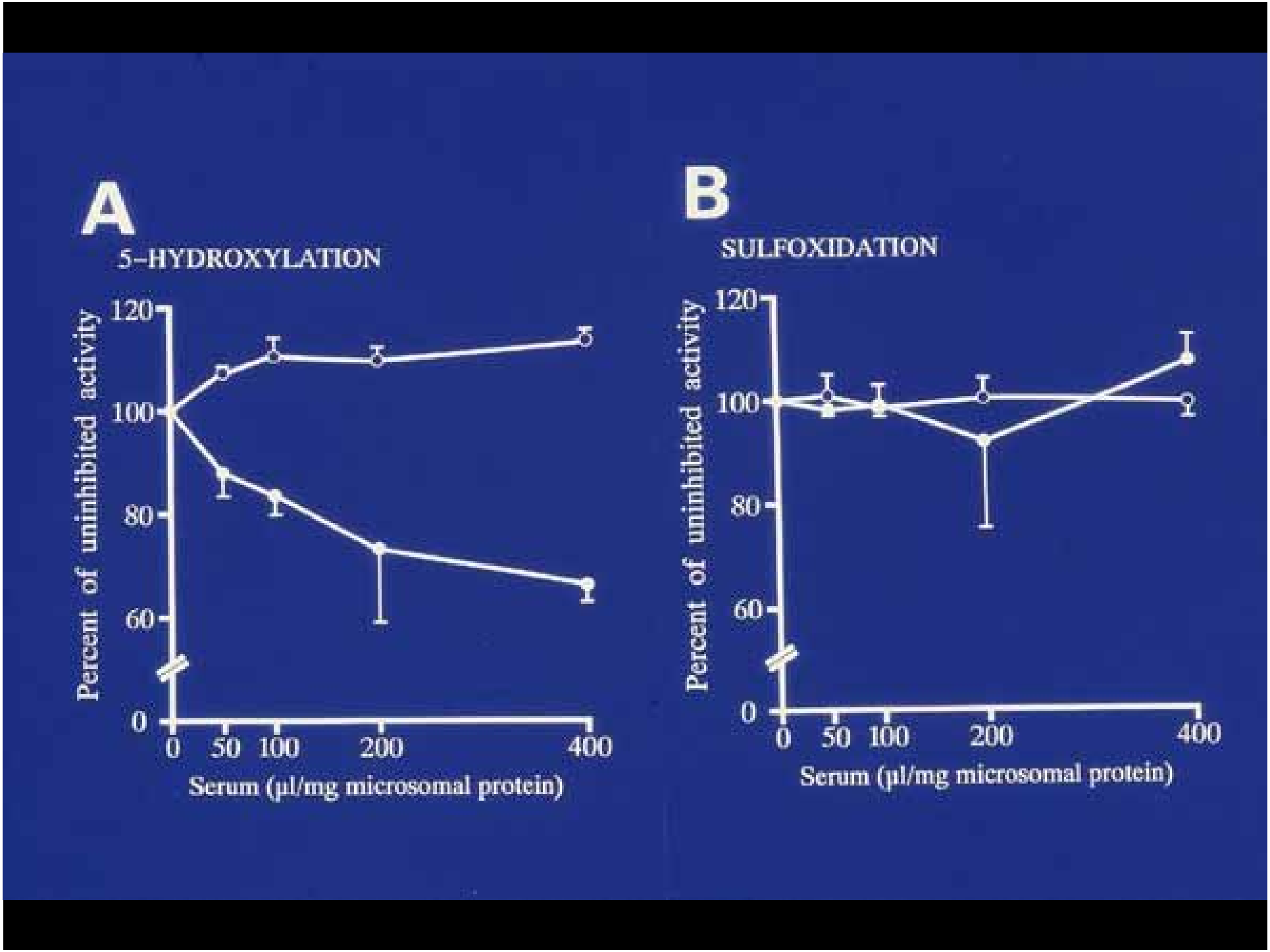

Japanese (n=219)
PMs of mephenytoin
EMs of mephenytoin
Korean (n=206)
Indonesian (n=104)
Chinese (n=98)
Log % urinary excretion of 4-HMP in 8 hr

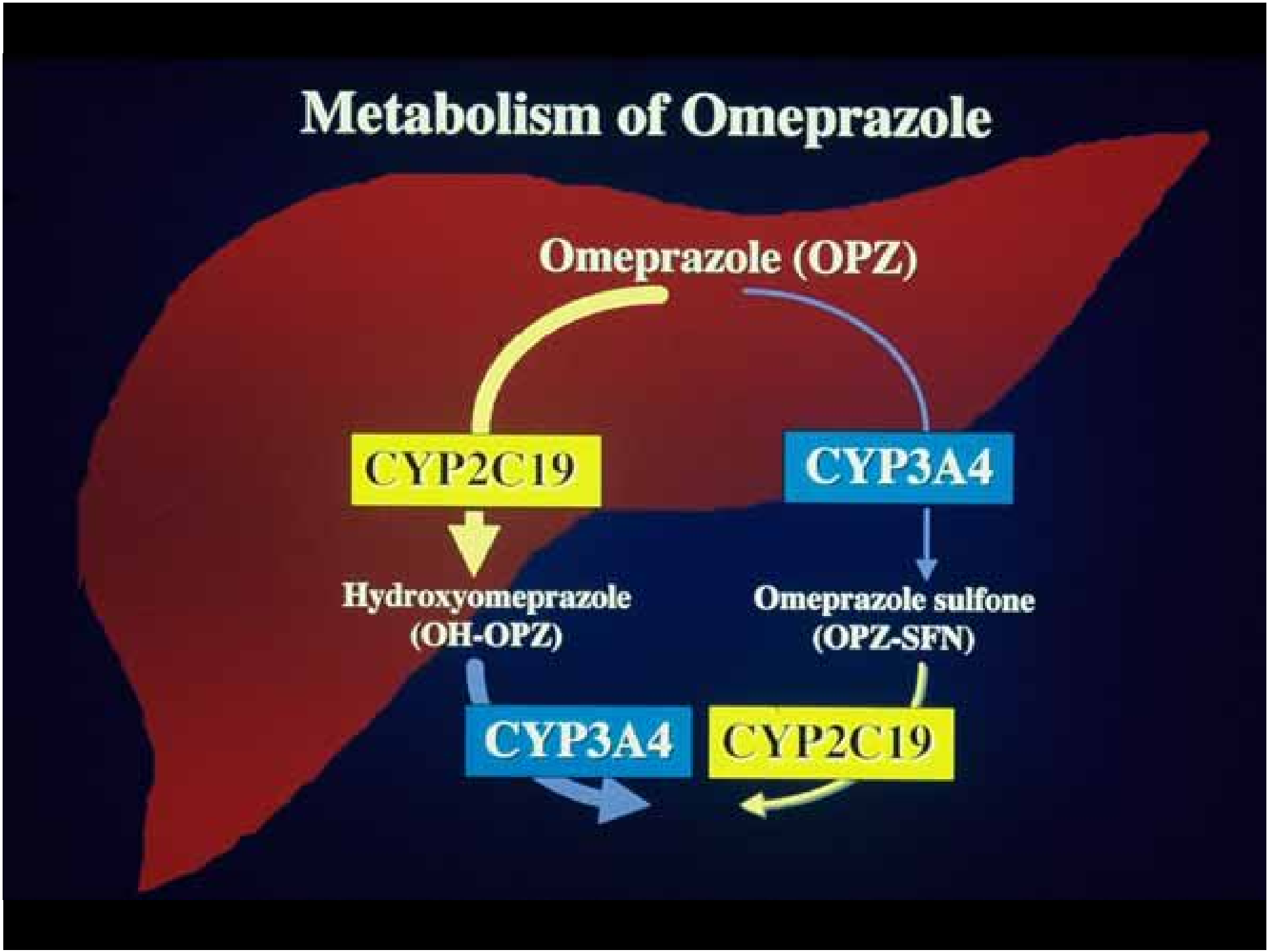
Reported Geographical Distribution of the Frequency (%) of Poor Hydroxylators of Mephenytoin

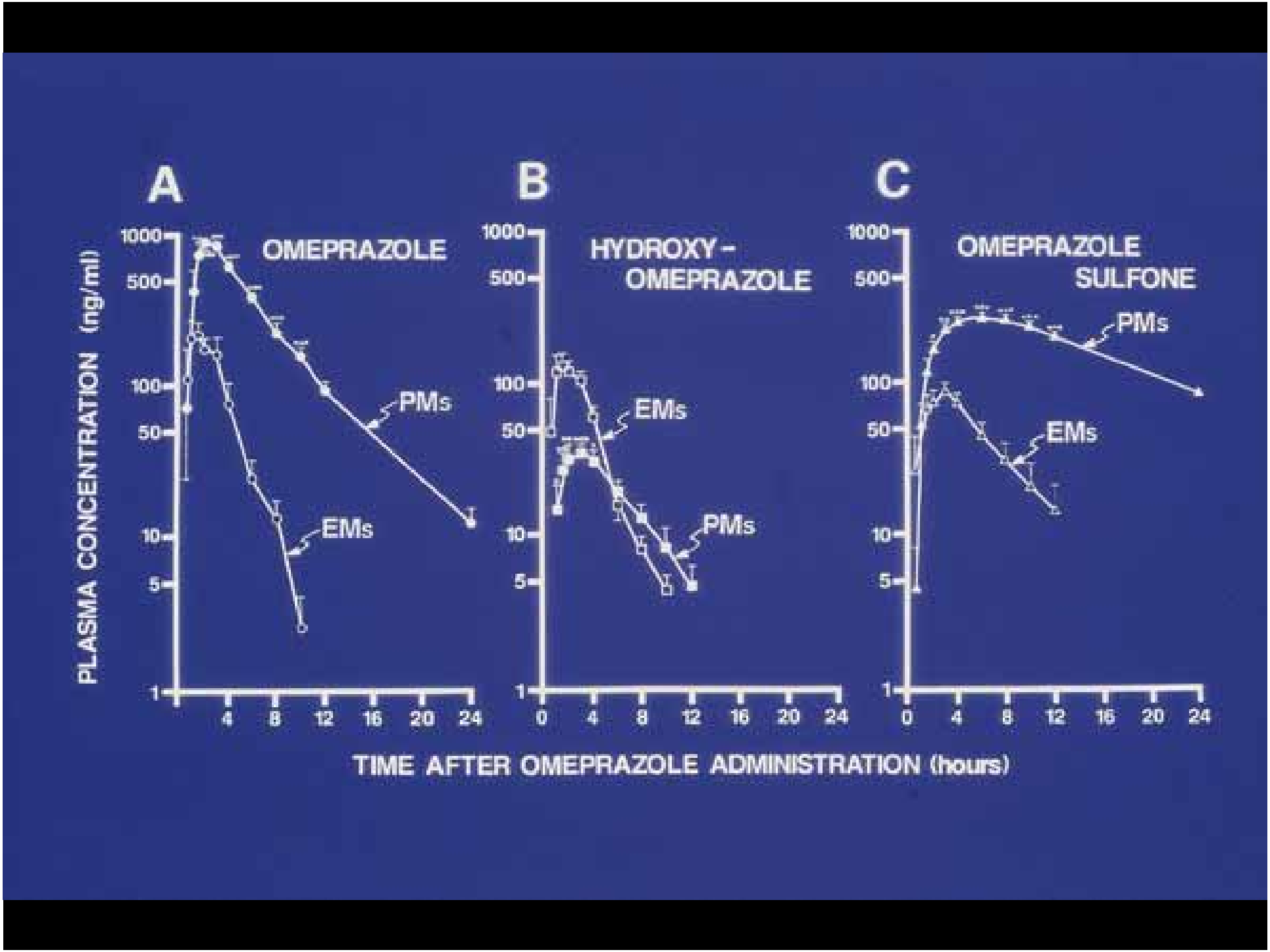



CYP2C19
CYP2D6


Activity of 4-hydroxylation of S-mephenytoin
(% of control)
100
50
0
0
100
200
300
400
(µl/mg protein)
Control
Antibody

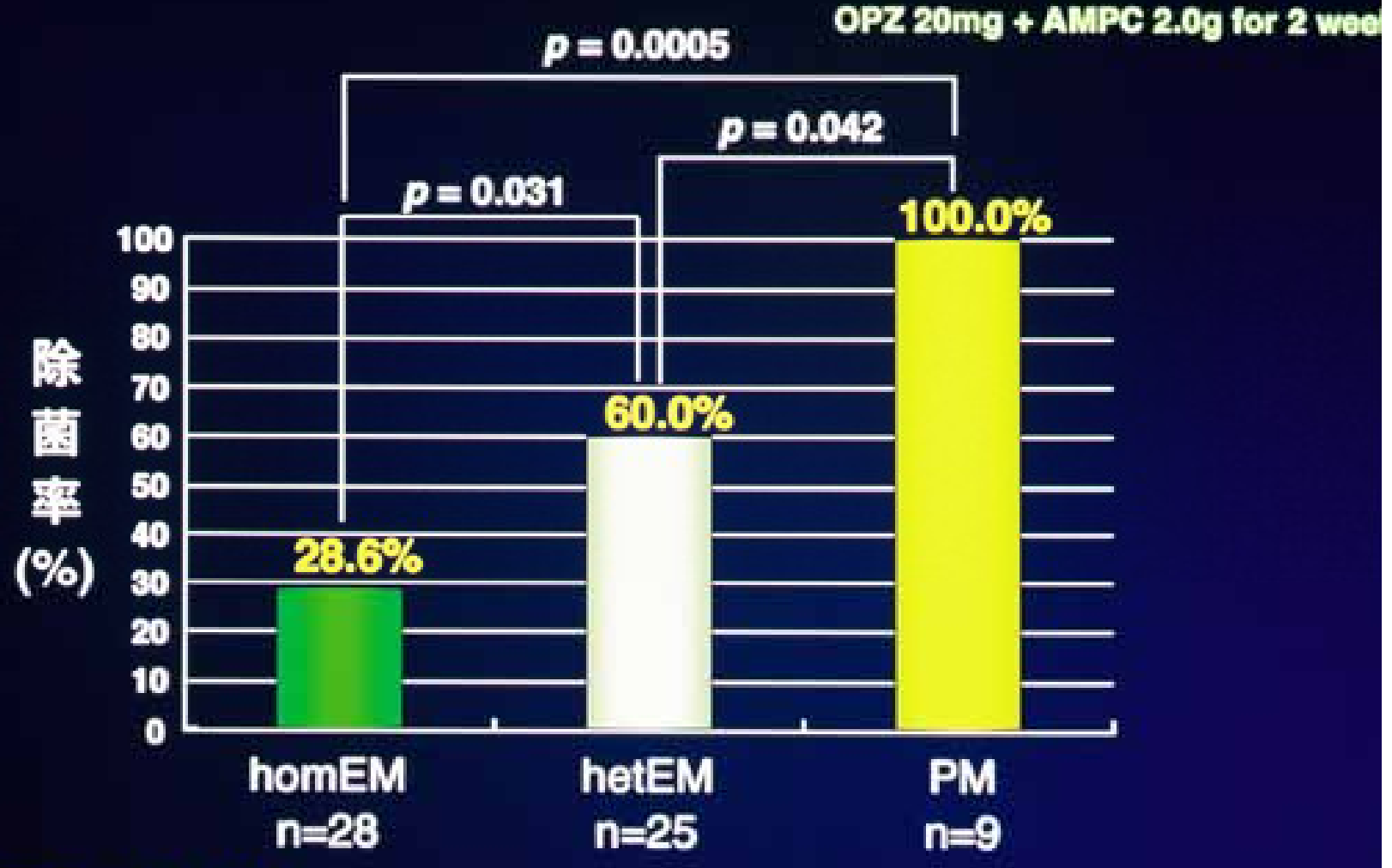

A
5-HYDROXYLATION
Percent of uninhibited activity
120
100
80
60
0
0
50
100
200
400
Serum (µl/mg microsomal protein)
B
SULFOXIDATION
Percent of uninhibited activity
120
100
80
60
0
0
50
100
200
400
Serum (µl/mg microsomal protein)


Metabolism of Omeprazole
Omeprazole (OPZ)
CYP2C19
CYP3A4
Hydroxyomeprazole
(OH-OPZ)
Omeprazole sulfone
(OPZ-SFN)
CYP3A4
CYP2C19


A
B
C
OMEPRAZOLE
HYDROXY-
OMEPRAZOLE
OMEPRAZOLE
SULFONE
PMs
EMs
PMs
EMs
PMs
EMs
PLASMA CONCENTRATION (ng/ml)
1000
500
100
50
10
5
1
0
4
8
12
16
20
24
TIME AFTER OMEPRAZOLE ADMINISTRATION (hours)

A
HALF-LIFE OF OMEPRAZOLE
(hours)
5
4
3
2
1
0
EM
PM
B
CLEARANCE OF OMEPRAZOLE
(ml/hr/kg)
1000
800
600
400
200
0
EM
PM
C
HALF-LIFE OF HYDROXYOMEPRAZOLE
(hours)
5
4
3
2
1
0
EM
PM
D
HALF-LIFE OF OMEPRAZOLE SULFONE
(hours)
15
12
9
6
3
0
EM
PM

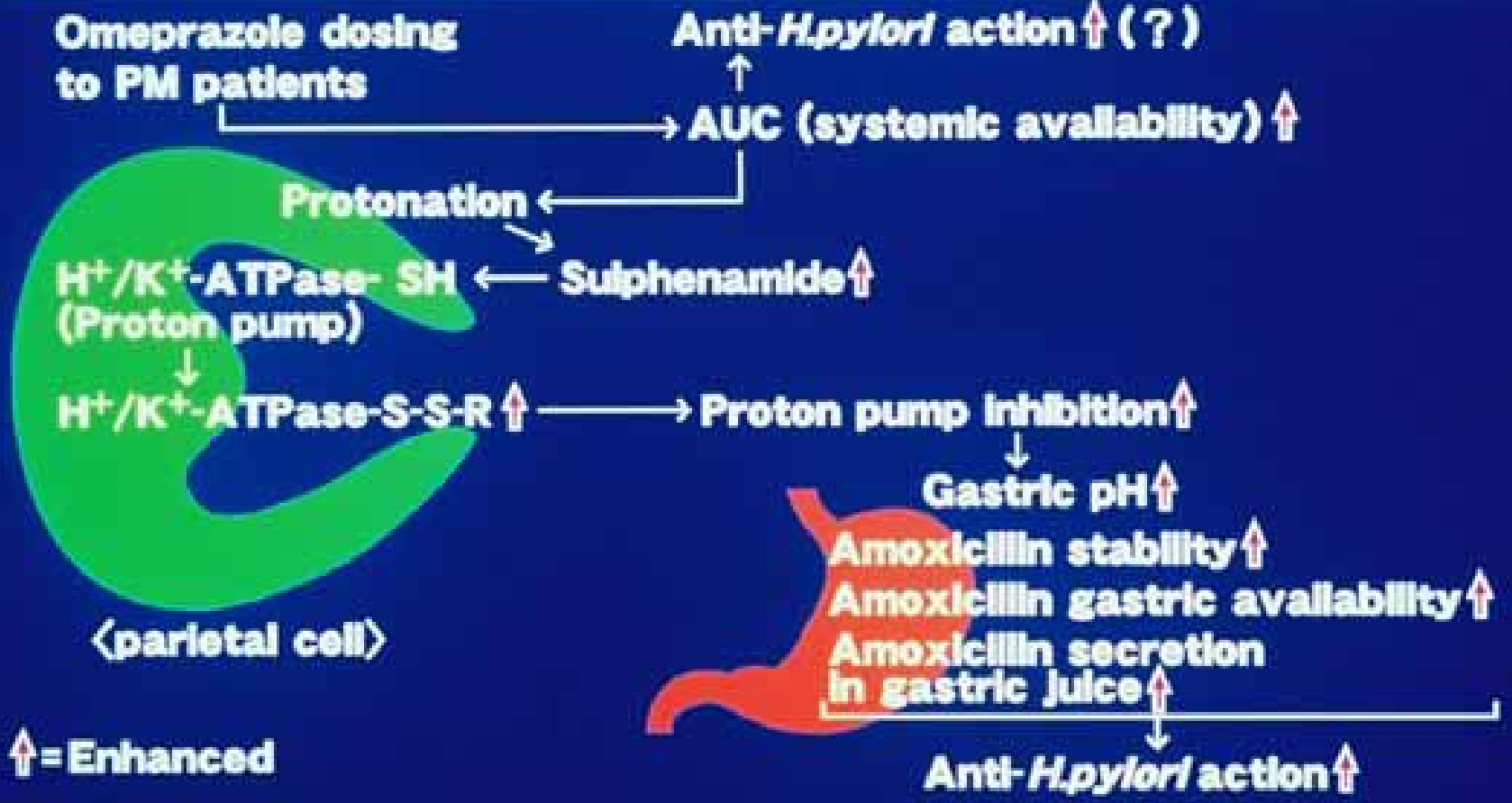
2剤OPZ/AMPC療法による除菌率はCYP2C19の多型で異なる



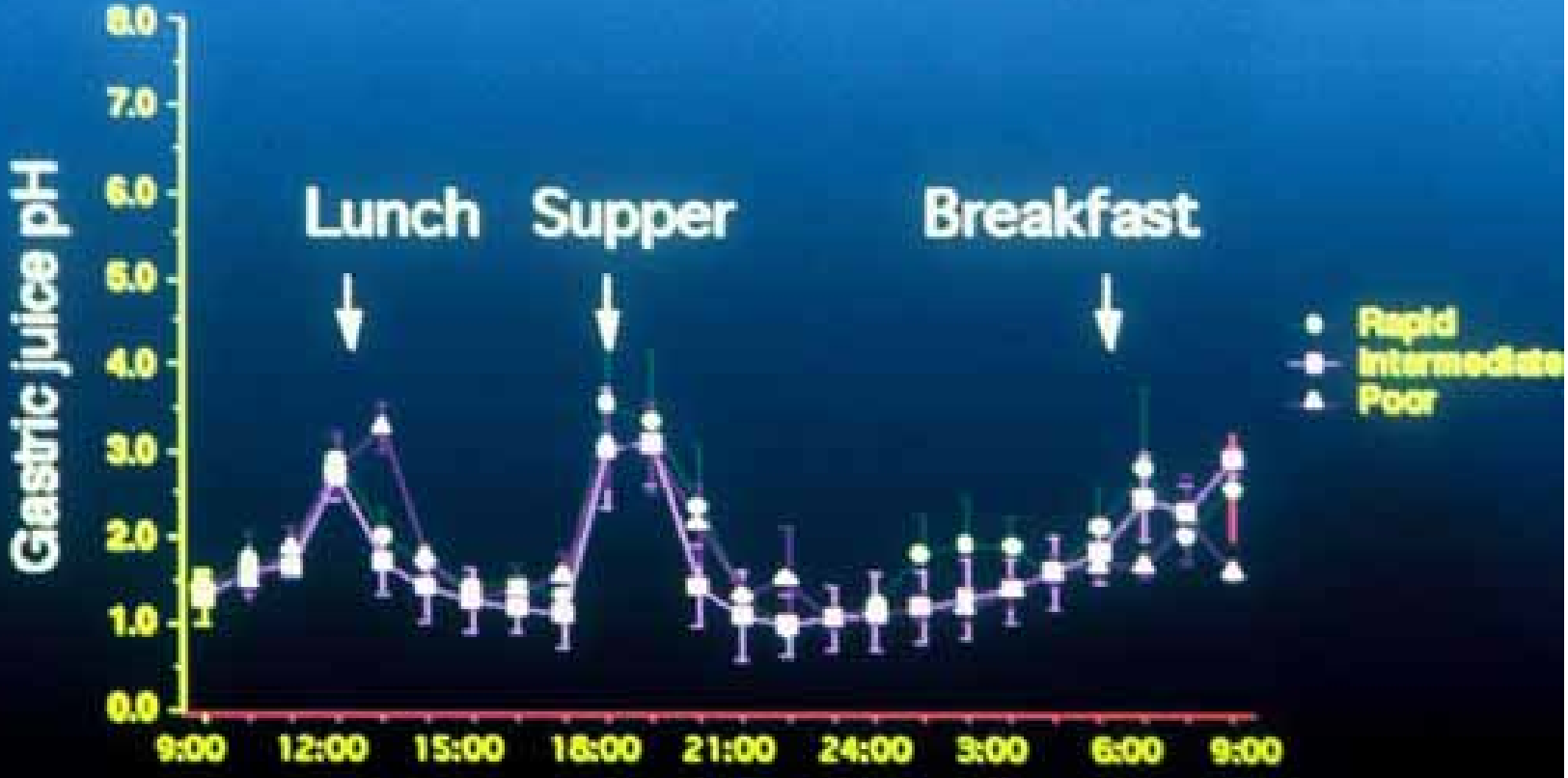
全体の除菌率 ：51.6 %

Furuta T, et al. Ann Intern Med 1998; 129:1027

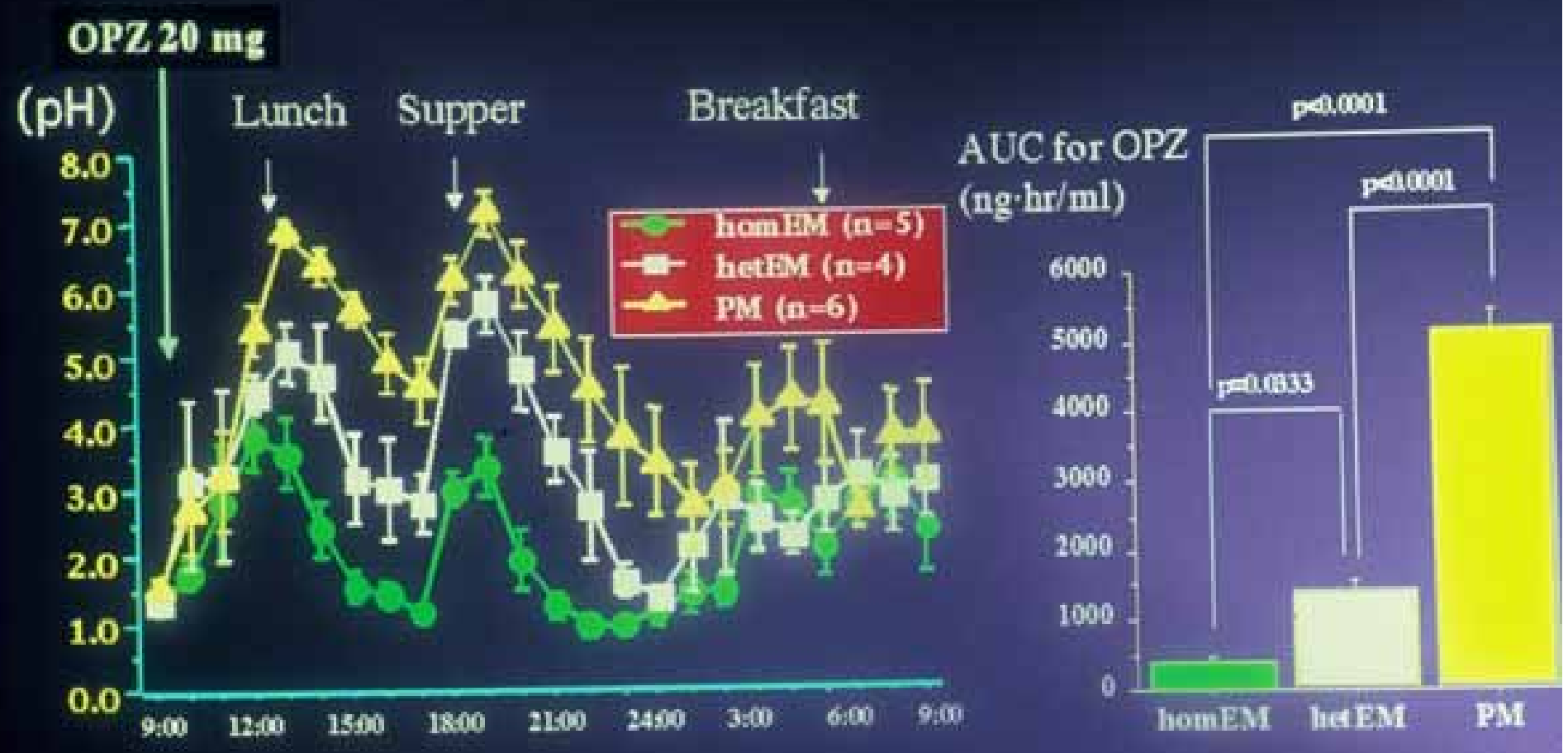
Hypothetical Explanation for an Enhanced Efficacy of Dual (Omeprazole+Amoxicillin) Therapy in Poor Metabolizer (PM) Patients with Peptic Ulcer



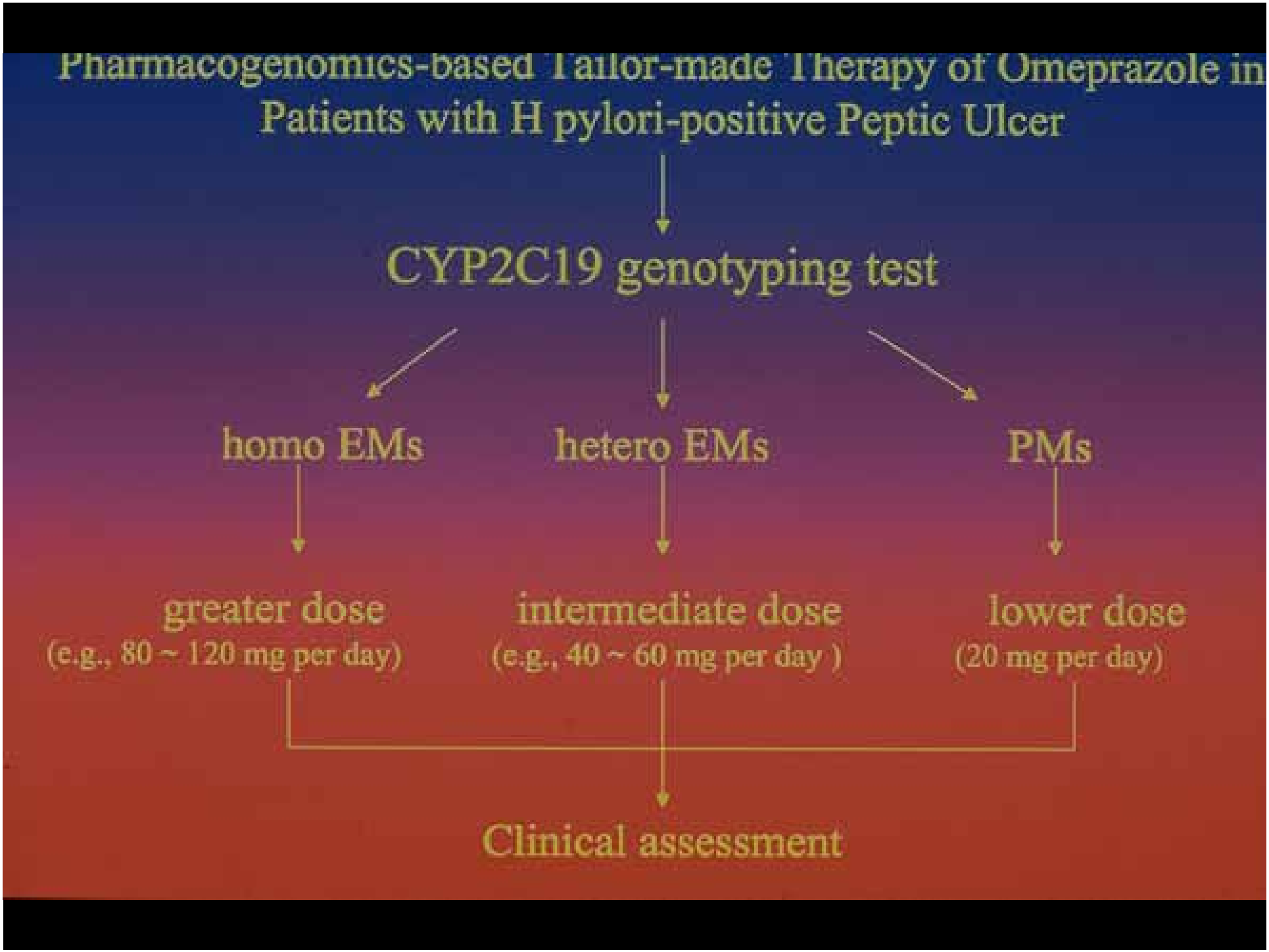
Placebo投与時の24H胃内pH モニターリング



Plasma OPZ concentration and intragastric pH as a function of CYP2C19 status

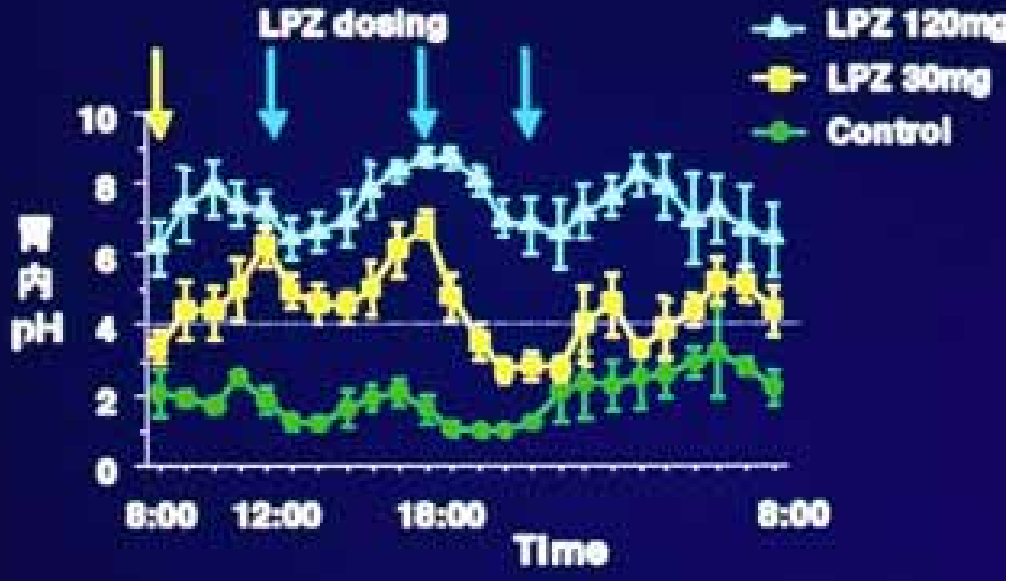


Gastroenterology 1998; 114: A127

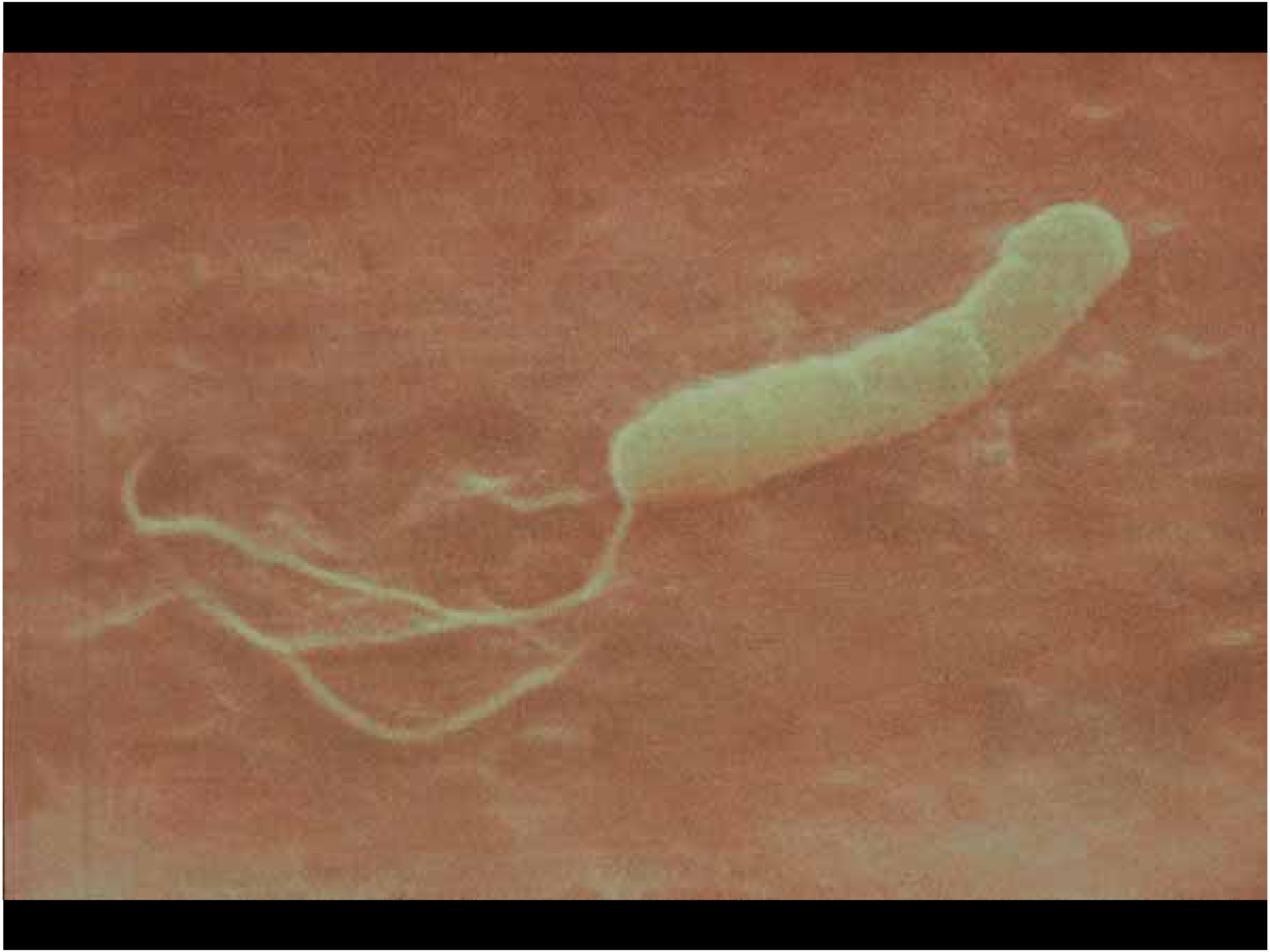

Pharmacogenomics-based Tailor-made Therapy of Omeprazole in Patients with H pylori-positive Peptic Ulcer
CYP2C19 genotyping test
homo EMs
hetero EMs
PMs
greater dose
(e.g., 80 ~ 120 mg per day)
intermediate dose
(e.g., 40 ~ 60 mg per day)
lower dose
(20 mg per day)
Clinical assessment

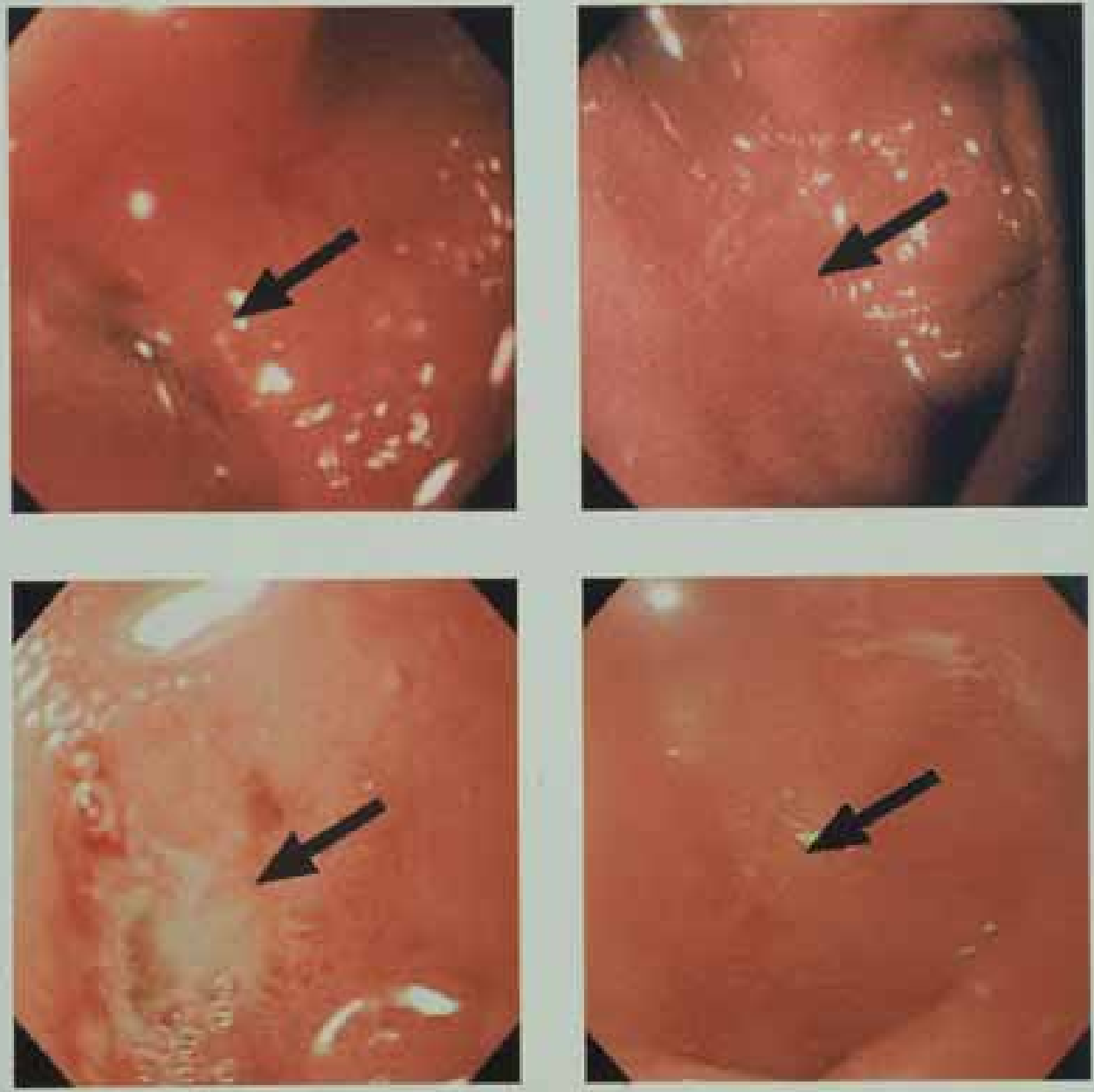
CYP2C19のhomEMでもPPIの高用量を頻回分割投与すると完全に胃酸を抑制することができる。

対象：CYP2C19 homEM 5名
プロトコール：LPZ 30mg/dayを8:00に8日間連続内服(↓)または，LPZ 120mg/dayを8:00, 12:00, 18:00, 22:00の4回に分け，8日間連続内服(↓ ↓ ↓ ↓)し，8日目に24時間胃内pH測定を行った。



Furuta T, *et al* Clin Pharmacol Ther. 2





A, Endoscopic finding at admission. Active bleeding from the ulcer lesion *(arrow)* in the duodenal bulb was observed. **B,** Endoscopic findings 2 months after the first triple therapy with lansoprazole, amoxicillin, and clarithromycin. The ulcer in the duodenal bulb has been cured and scarring of the ulcer was observed, as indicated by the *arrow*. However, results of histologic examination and rapid urease test performed during endoscopy showed that the *H pylori* infection had not been cured. **C,** Endoscopic findings 2 months after the third triple therapy with lansoprazole, cefaclor, and minocycline. The ulcer in the duodenal bulb had relapsed. The *arrow* indicates the ulcer bed. The results of histologic examination, rapid urease test, and culture test performed during endoscopy showed that *H pyroli* infection has not been cured. The strain was clarithromycin-resistant but amoxicillin-sensitive. **D,** Endoscopic findings 2 months after the high-dose dual therapy with omeprazole and amoxicillin. The ulcer in duodenal bulb had been cured, as indicated by the *arrow*. The results of histologic examination, rapid urease test, culture test, and ^{13}C-urea breath test showed that a cure of *H pylori* infection had been achieved.

A	B
C	D

Response Rates of Patients to Major Drugs for a Selected Group of Therapeutic Areas[1]

Therapeutic Area	Response Rate (%)
Alzheimer's disease	30
COX-2 inhibitors (analgesics)	80
Asthma	60
Cardiac arrhythmias	60
Depression (SSRIs)	62
Diabetes	57
HCV	47
Migraine	50
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

Pharmacogenetic Tests (practical items)

- To determine drug selection
- To determine or adjust drug dosage
- To enhance therapeutic efficiency with maximizing drug effectiveness and minimizing side-effects
- To be cost-effective
- To be useful for new drug development

Pharmacogenetic Tests for Drug Selection

Examples in poor metabolizers who cannot gain therapeutic effectiveness are:

Codeine	CYP2D6 →	Morphine
Tramadol	CYP2D6 →	Hydroxytramadol
Losartan	CYP2C9 →	Active metabolite
Amodiaquine	CYP2C8 →	Desethylamodiaquine
Proguanil	CYP2C19 →	Cycloquanil(?)

Pharmacogenetic Tests for Preventing Serious Side-effects or Adjusting Dosage in Poor Metabolizers

CYP2C9

- Warfarin — Oral sulfonylureas (e.g., tolbutamide)
- Phenytoin

CYP2D6

- Nortriptyline — Antipsychotics(?)

Thiopurine methyltransferase

- 6-Mercaptopurine — Azathioprine

N-Acetyltransferase

- Isoniazid — Procainamide(?)

UDP-Glucuronosyltransferase

- Irinotecan

Pharmacogenomic Test for Evaluating Cost-effectiveness in Clinical Practice

Cost / Effectiveness of Pharmacogenomic-based (CYP2C9-genotyped) Warfarin Therapy

- Cost of treating a major bleeding episode by warfarin

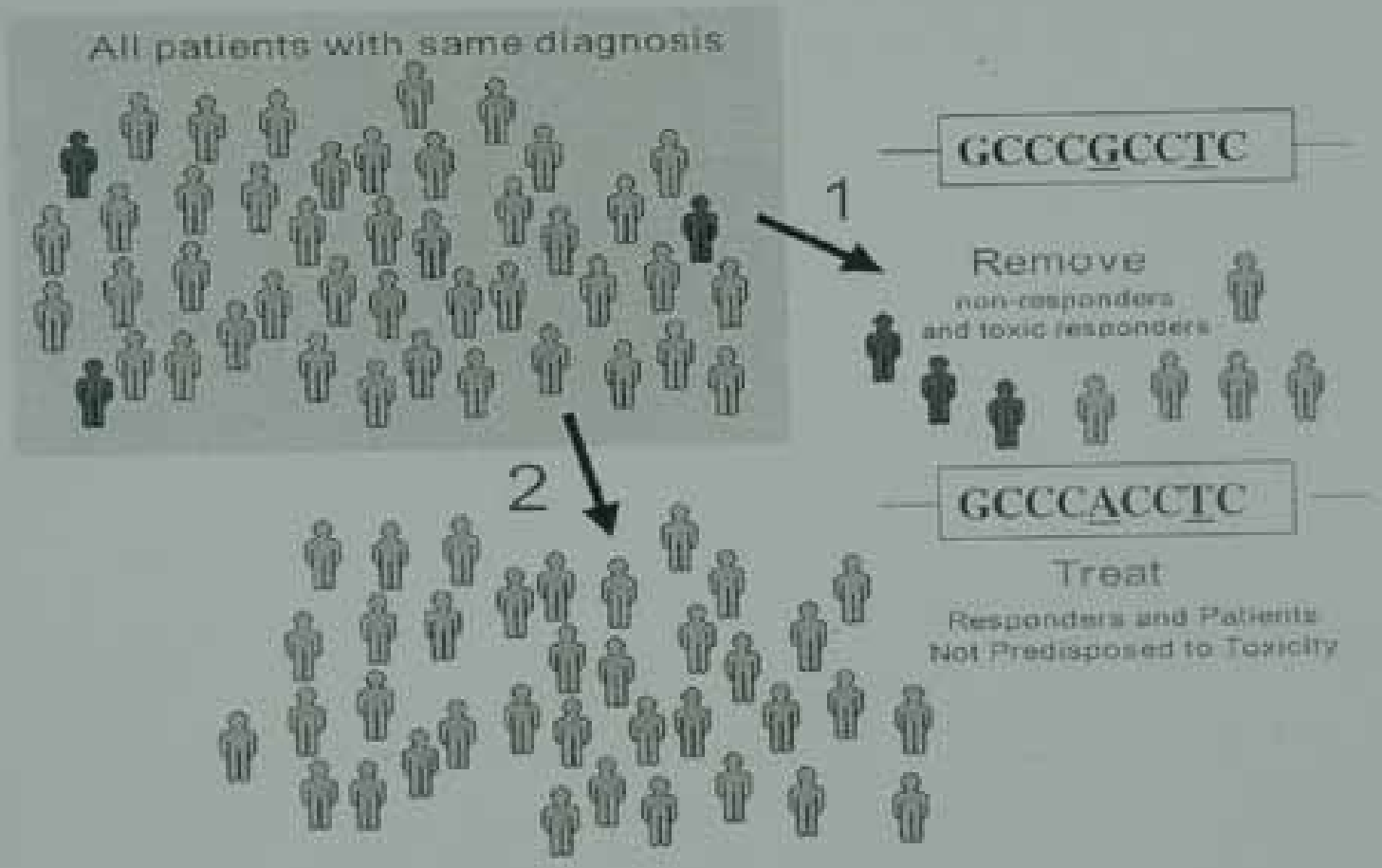
  $ 1245 for a hospitalized patient

  $ 4149 for an outpatient

- < $ 100 for genotyping test

(Redman AR. Pharmacother 2001 ; 21 : 235 – 42)

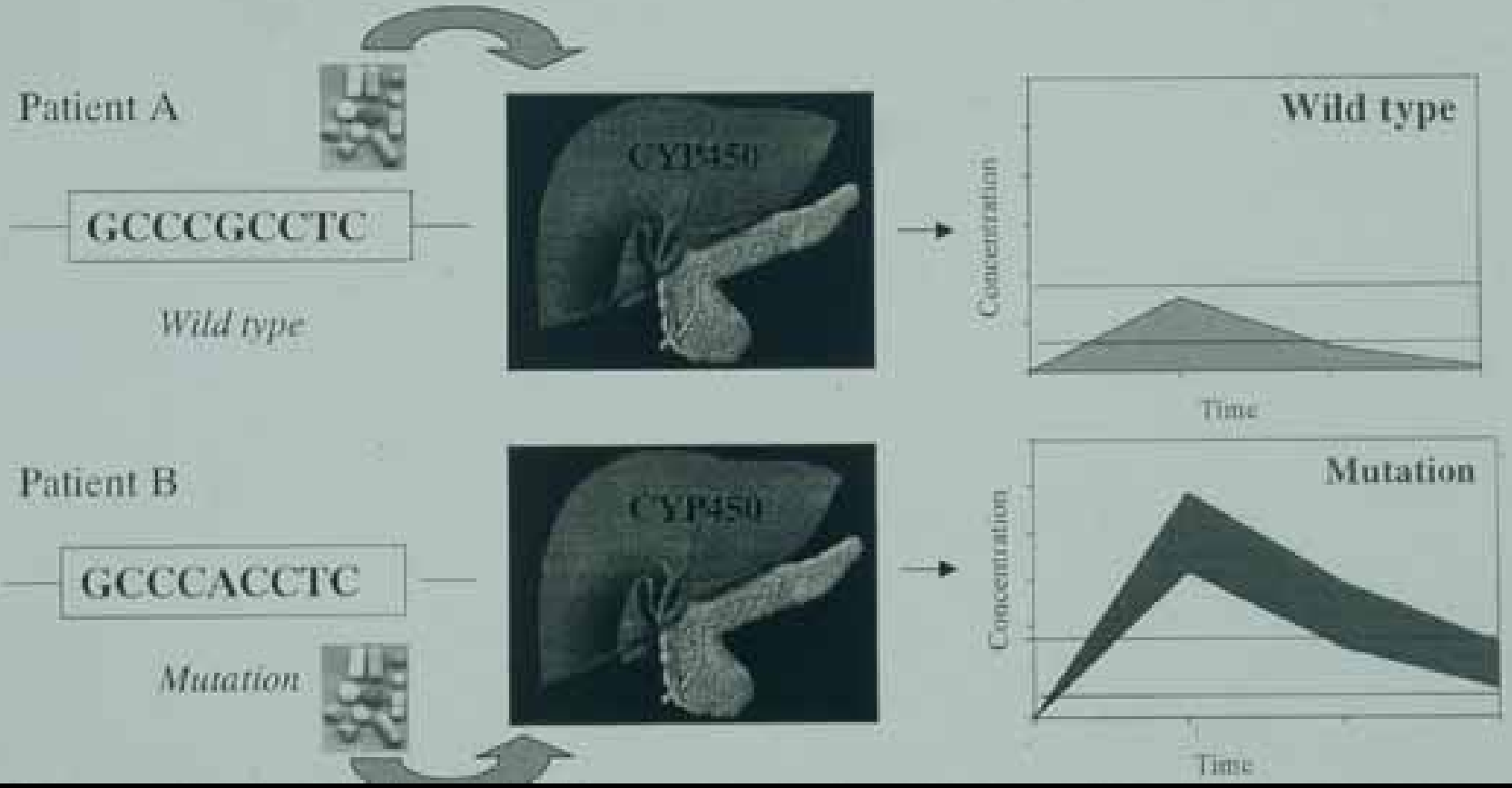
Translation of PGx to Bedside Medicine: Predict Drug Response in Advance



Ann Rev of Pharmacol and Toxicol, 2001: 41,101-121

Pharmacogenetics (PGt): Variation in Genes Encoding for CYP Enzyme Activity

Same dose but different plasma concentrations



Which is Better?

- Genotyping → Clinical Trial
- Clinical Trial → Genotyping

Pharmacogenomics-based Clinical Trials Require a Langer Number of Patients

- **Example-Angiotensin System Genes**

Angiotensinogen (AGT) (G → A at position– 6)	Increased production of AGT
Angiotensin – converting enzyme (ACE) [Insertion (I) → Deletion (D)]	Greater angiotensin II activity
Type 1 angiotensin II receptor (A →C at position 1166)	Greater sensitivity to angiotensin II

- **Genotypes are subgrouped into G/G, GA, AA, I/I, I/D, DD, AA, A/C and CC**

- **Angiotensin system genes alone require : $3^3 = 27$ subgroup comparisons !**

Applying Pharmacogenetics in Clinical Research

To precisely prescribe or design

- the right drug
- at the right dose
- for the right patient

(Shi MM et al. Drug Metab Dispos 2001 ; 29 : 591-5)

Pharmacogenetics Research Collaborators in Asia

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