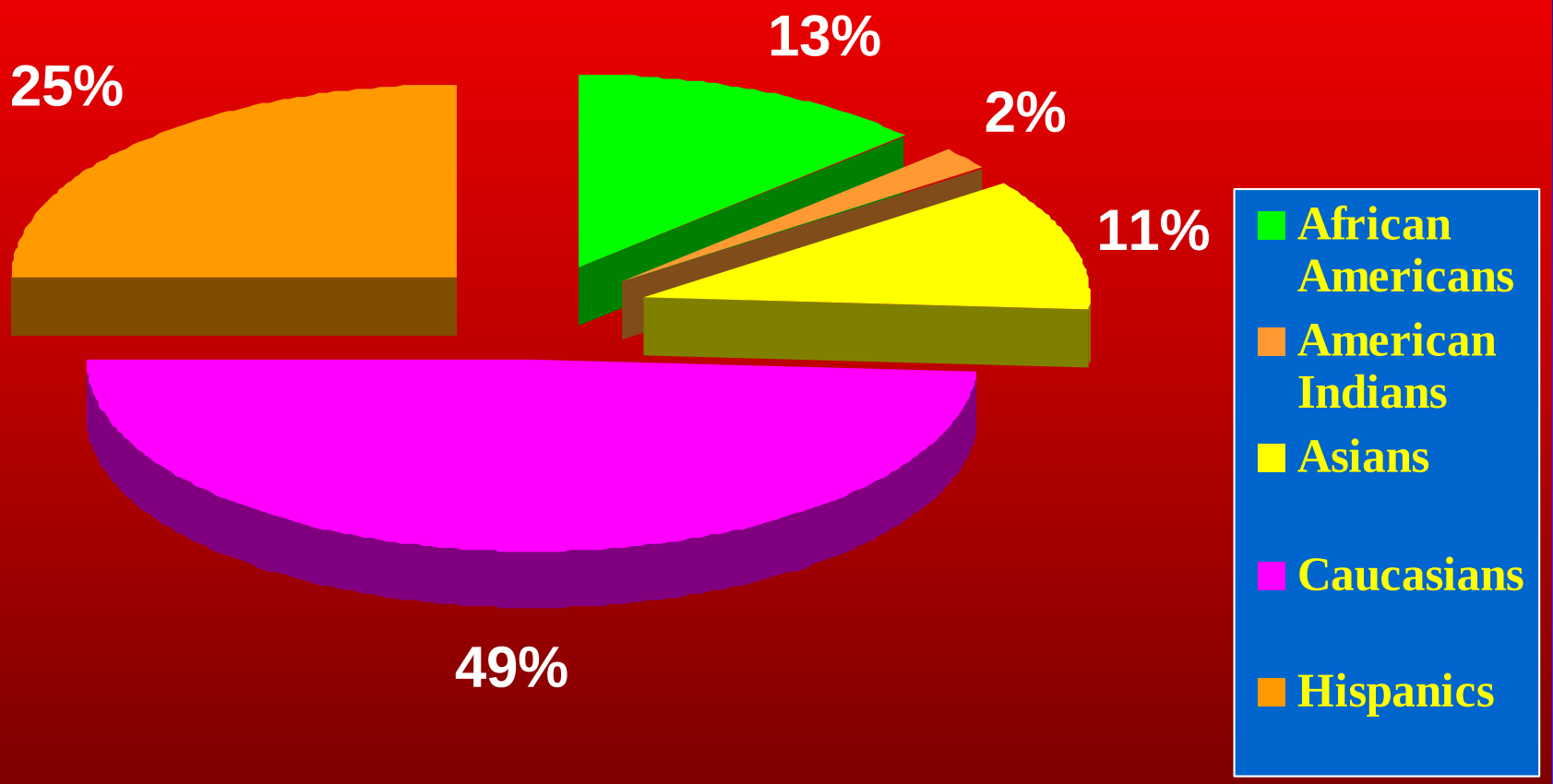
ETHNICITY, CULTURE AND PHARMACOGENETICS

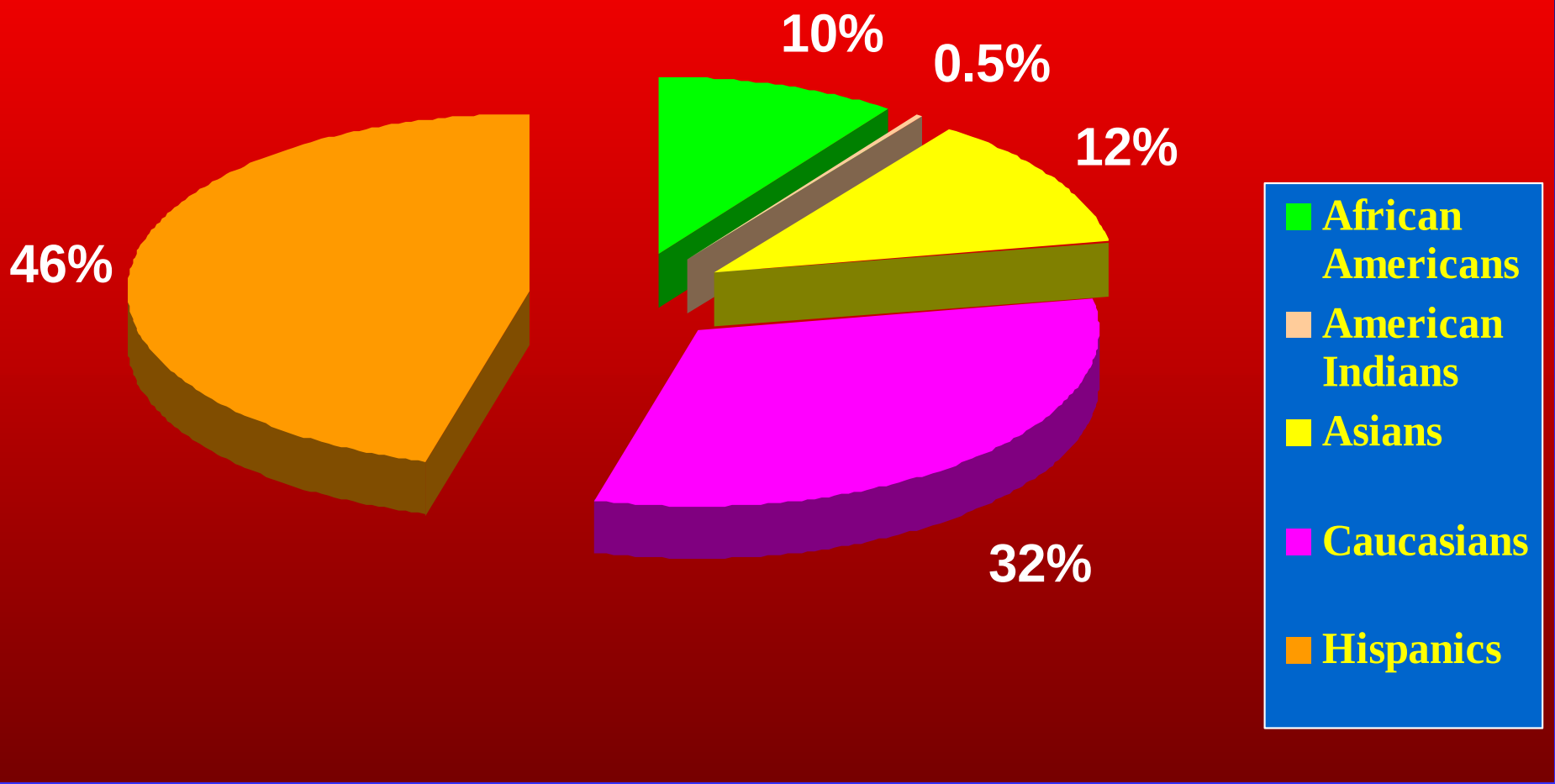
Bridging Cultures & Enhancing Minority Healthcare in the New Millennium
January 25, 2003

Keh-Ming Lin, M.D., M.P.H.
Harbor-UCLA Medical Center
Torrance CA

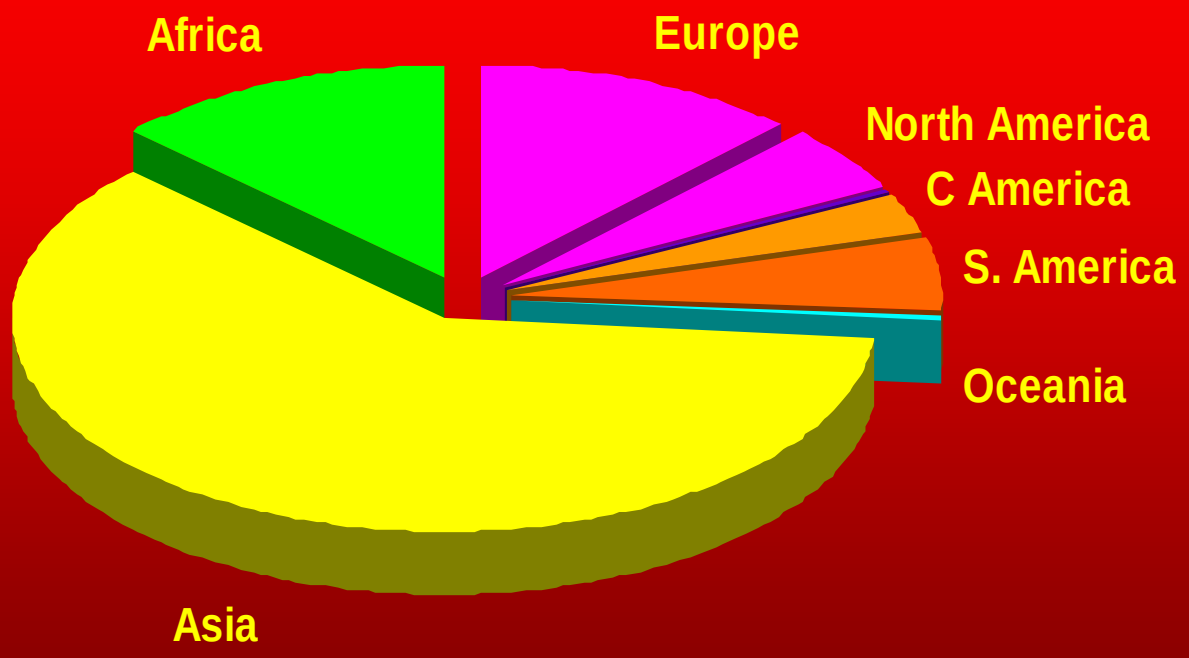
POPULATION DISTRIBUTION USA (2050)



POPULATION DISTRIBUTION
Los Angeles County (2000)

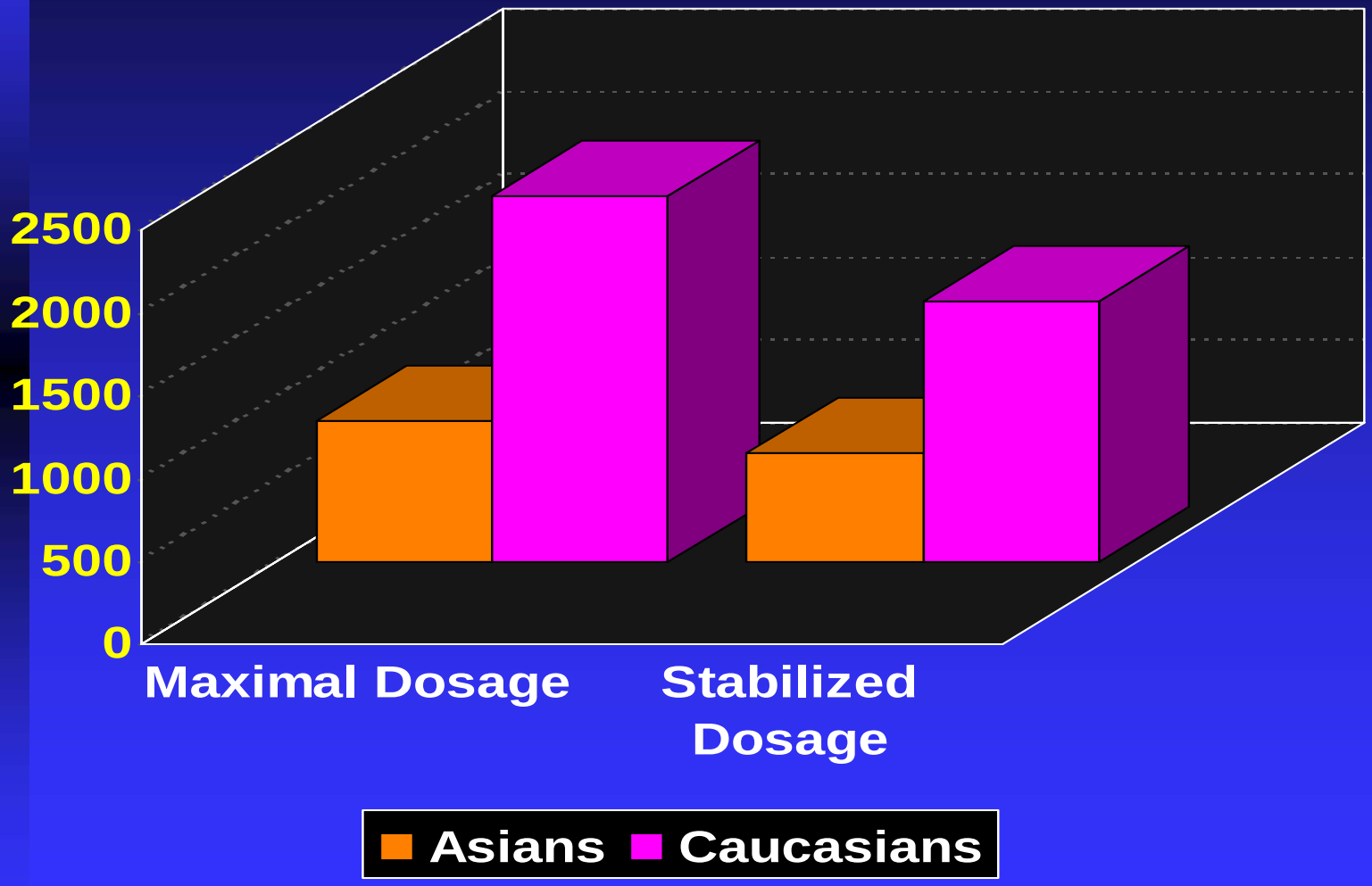


THE POPULATON OF THE WORLD

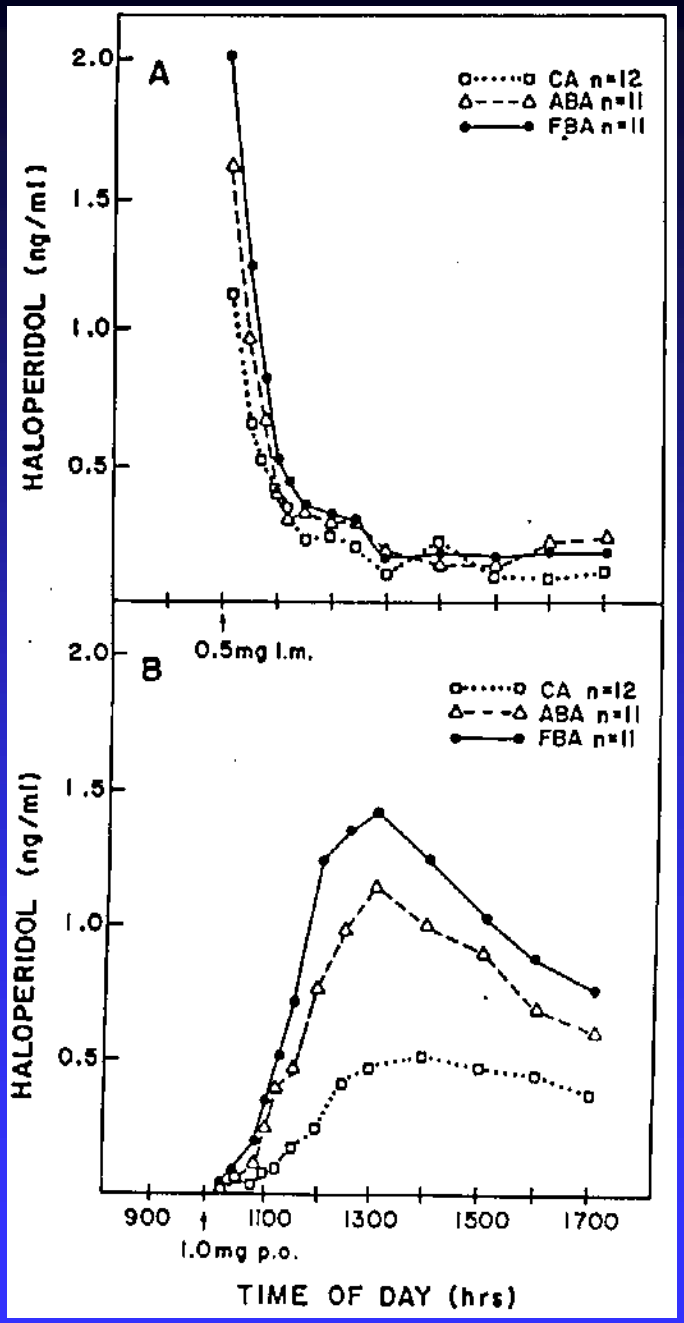


One Size Does Not Fit All

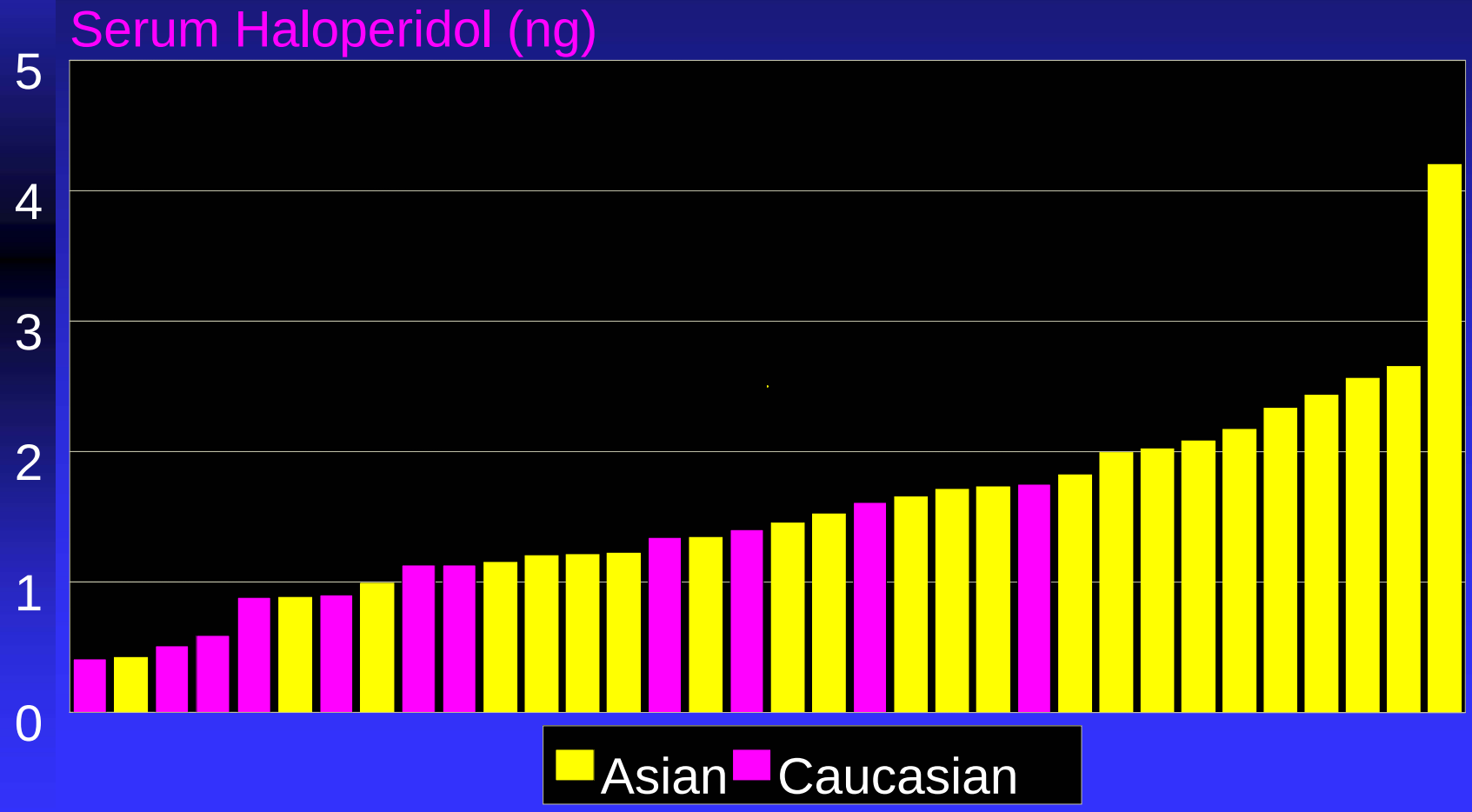
NEUROLEPTIC DOSAGE FOR HOSPITALIZED PATIENTS: ASIANS VS CAUCASIANS



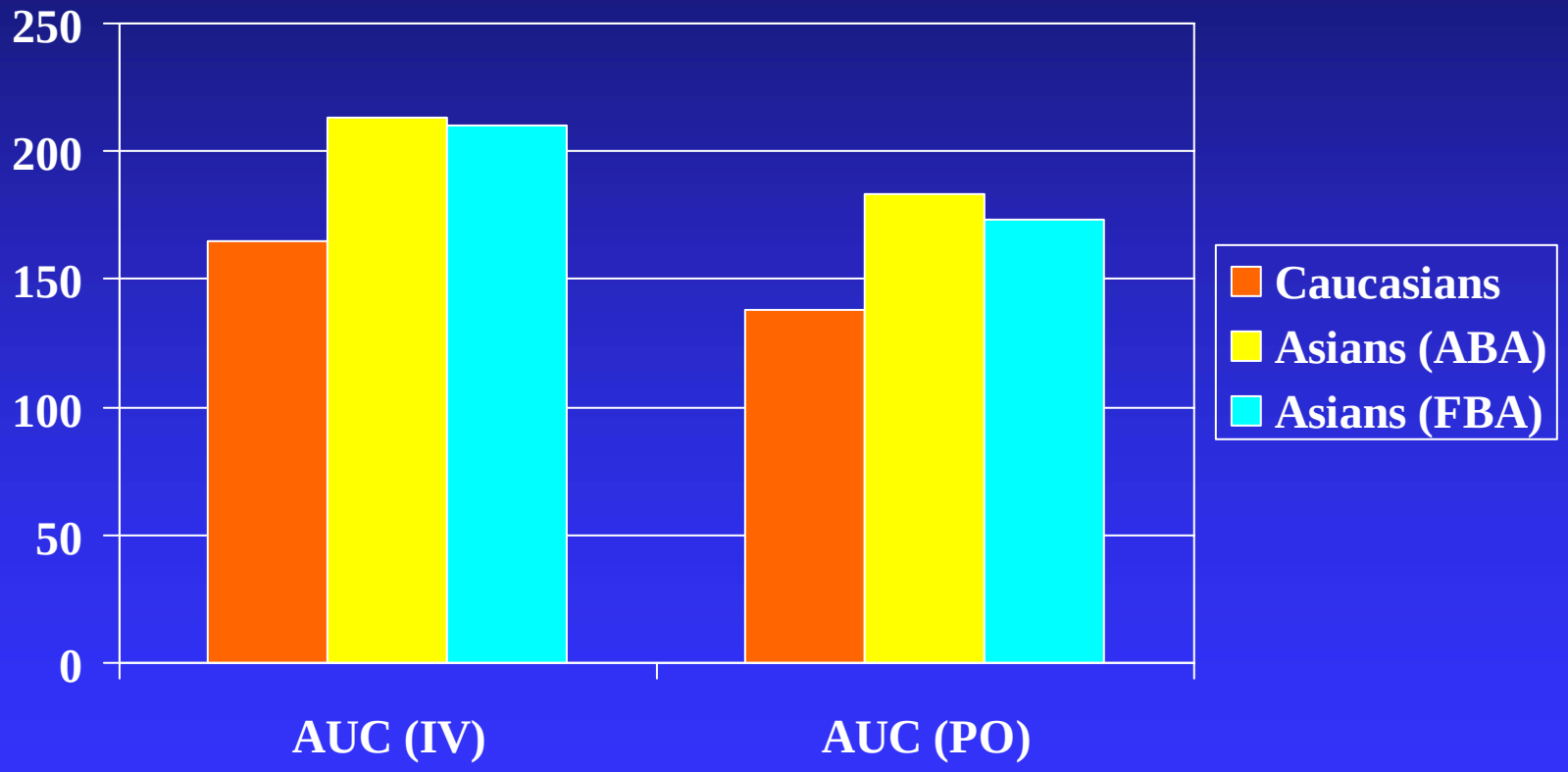
Lin & Finder, Am J Psychiatry 140:490-491, 1983


A
CA n=12
ABA n=11
FBA n=11
HALOPERIDOL (ng/ml)
2.0
1.5
1.0
0.5
0.5mg I.m.
B
CA n=12
ABA n=11
FBA n=11
HALOPERIDOL (ng/ml)
2.0
1.5
1.0
0.5
900
1100
1300
1500
1700
1.0mg p.o.
TIME OF DAY (hrs)

Maximal Haloperidol Concentration After 0.5 mg i.m. Haloperidol



Alprazolam Plasma Levels: Caucasian & Asian Volunteers



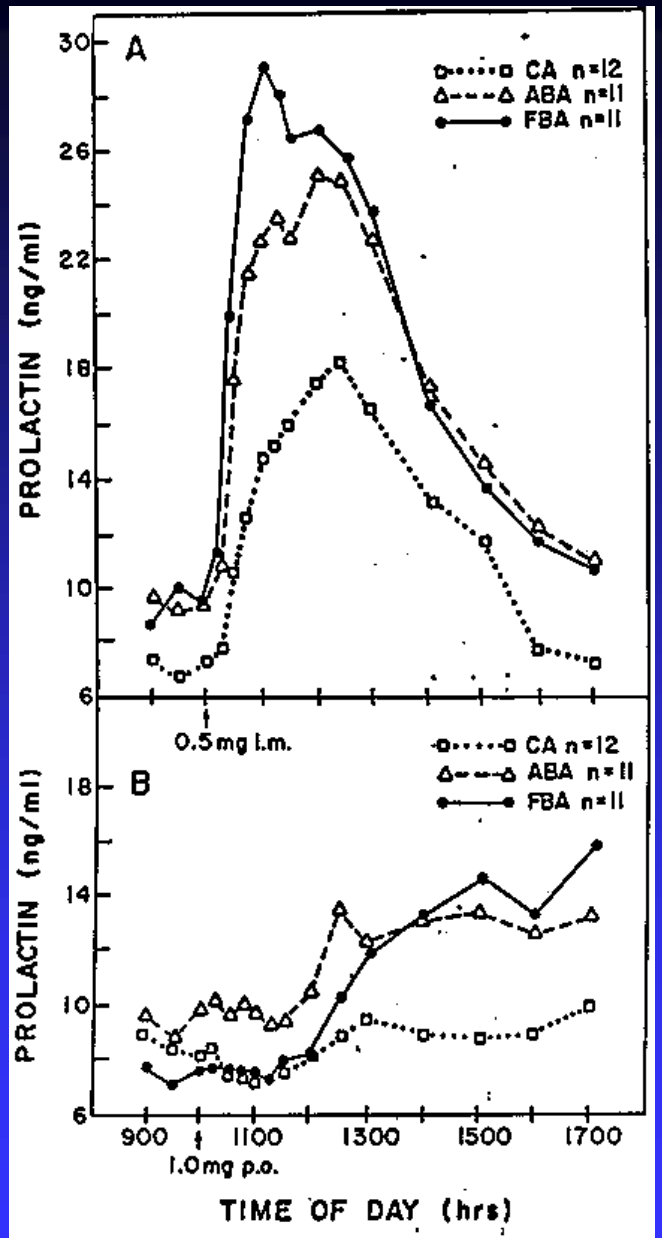
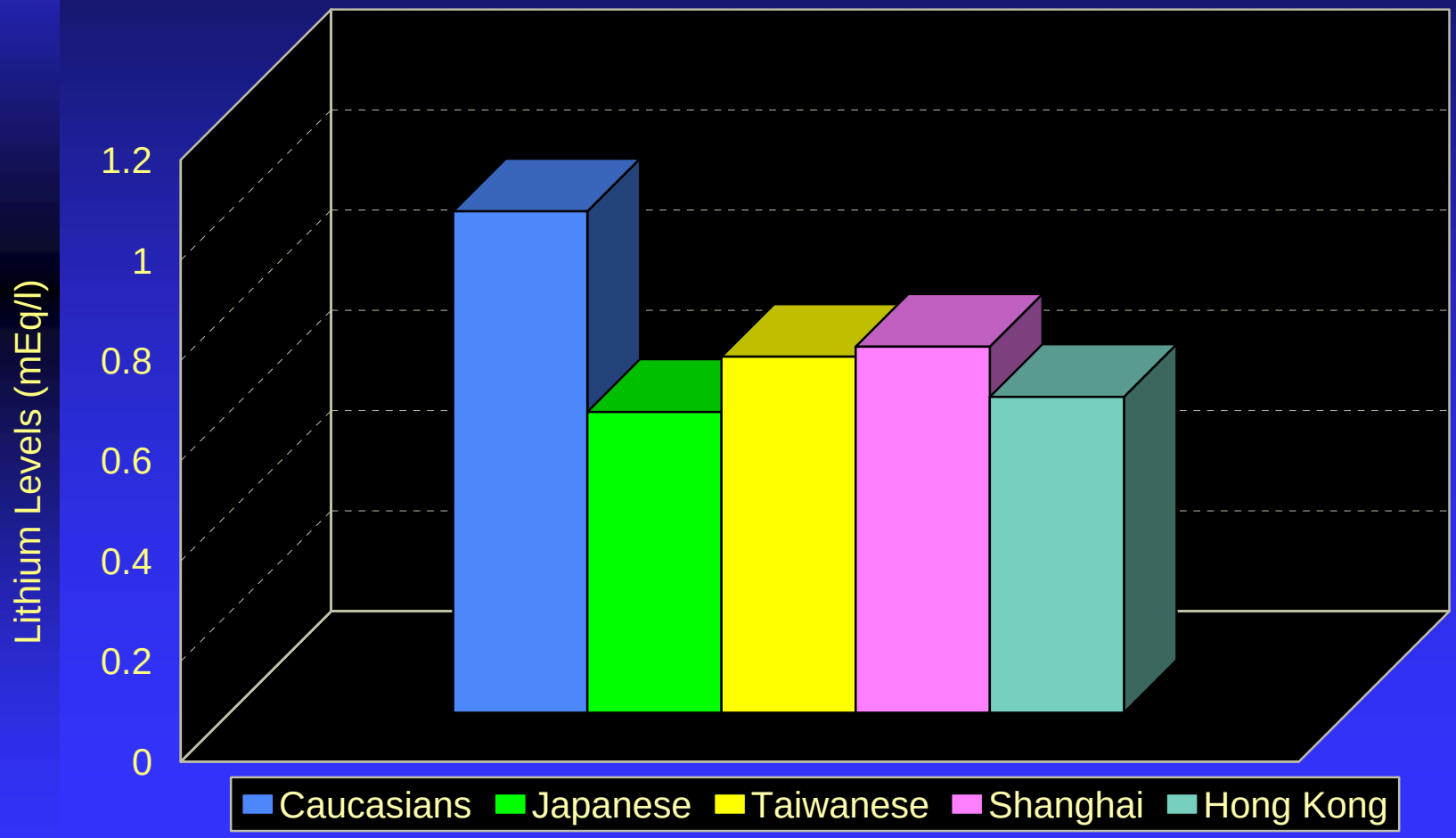
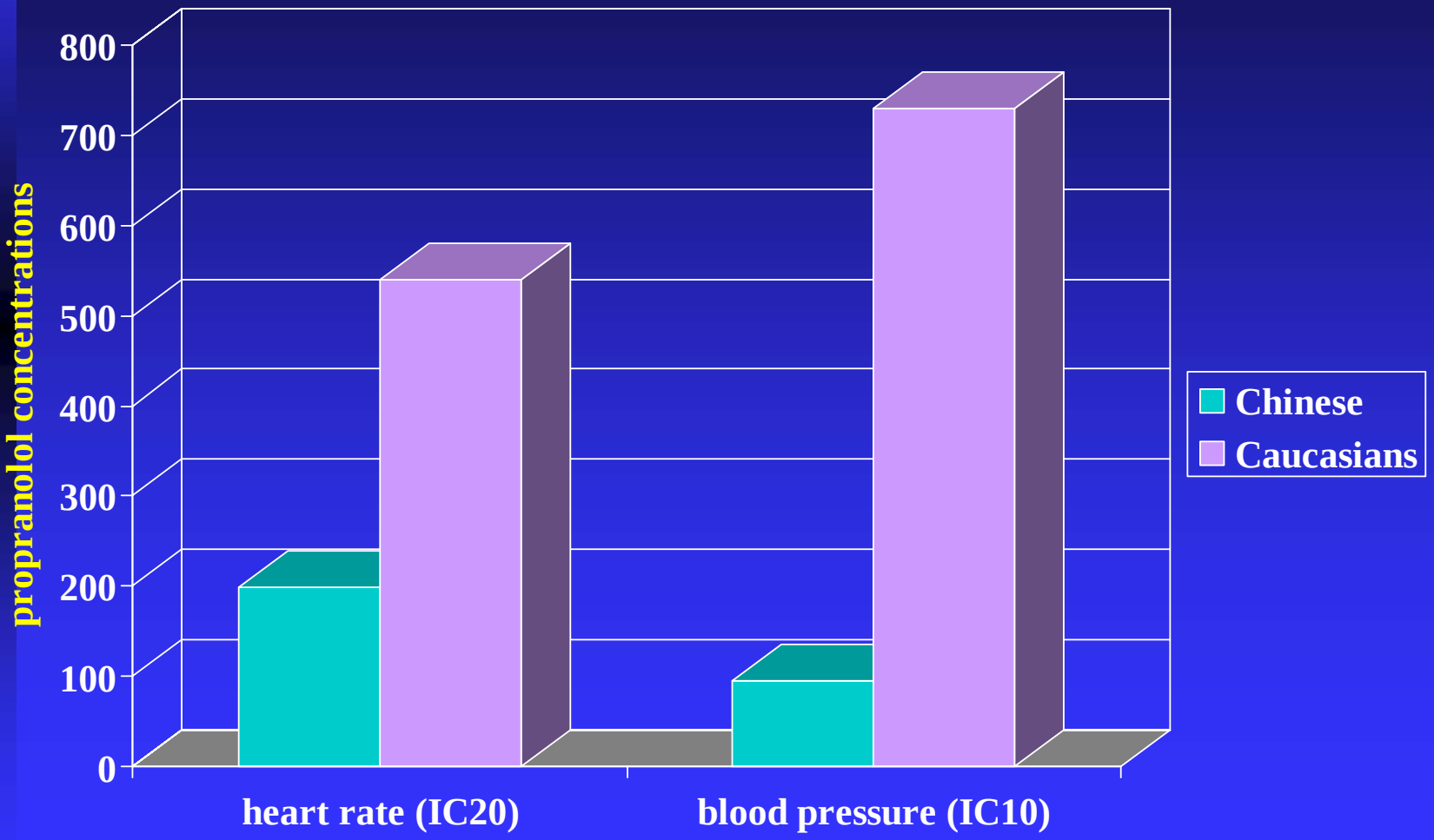


Figure 2. Mean serum prolactin concentrations the three comparison groups after (A) i.m. and (B) p.o. administration of haloperidol.

Therapeutic Lithium Concentrations

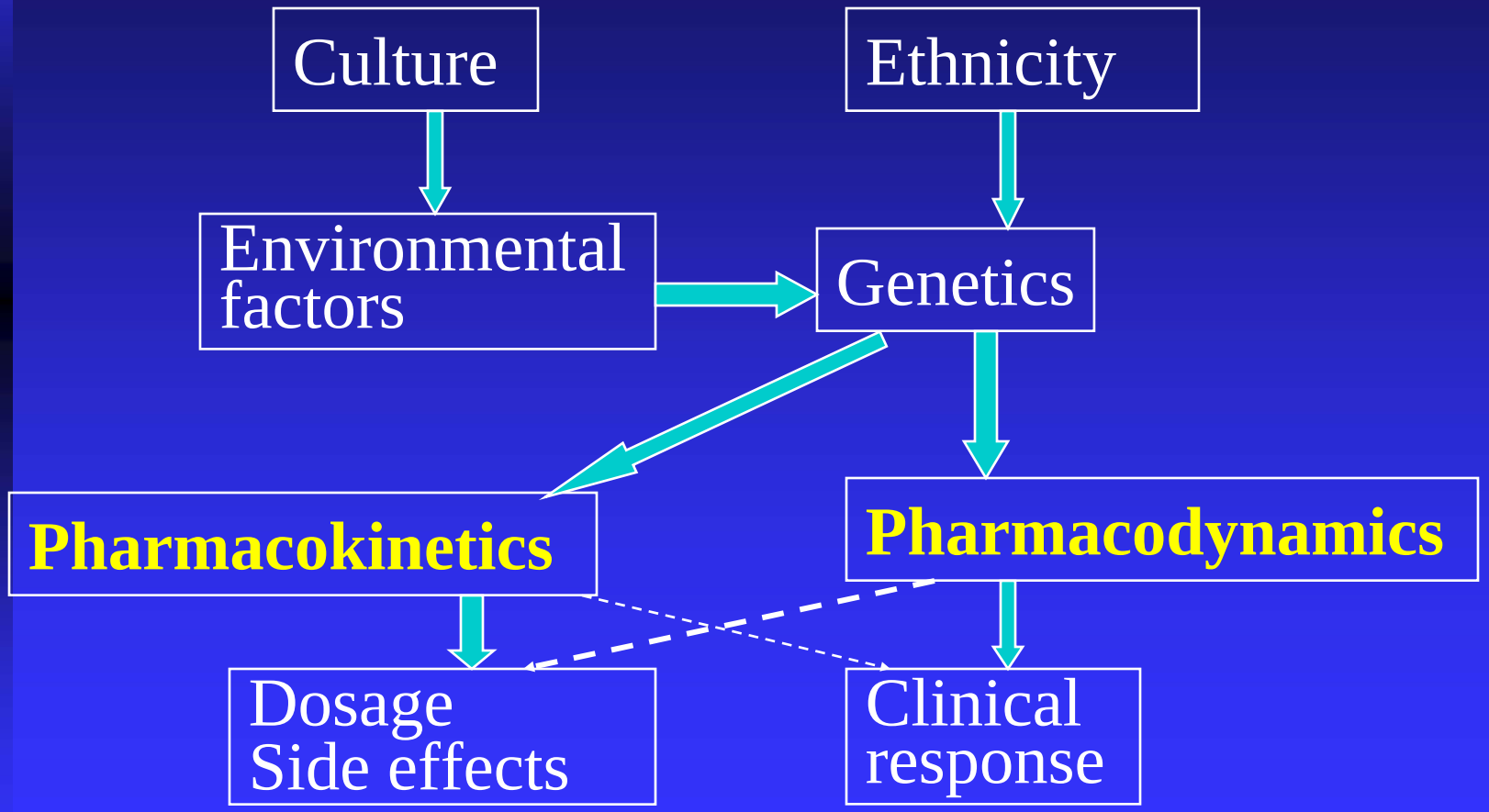


Propranolol Response: Chinese vs Caucasians

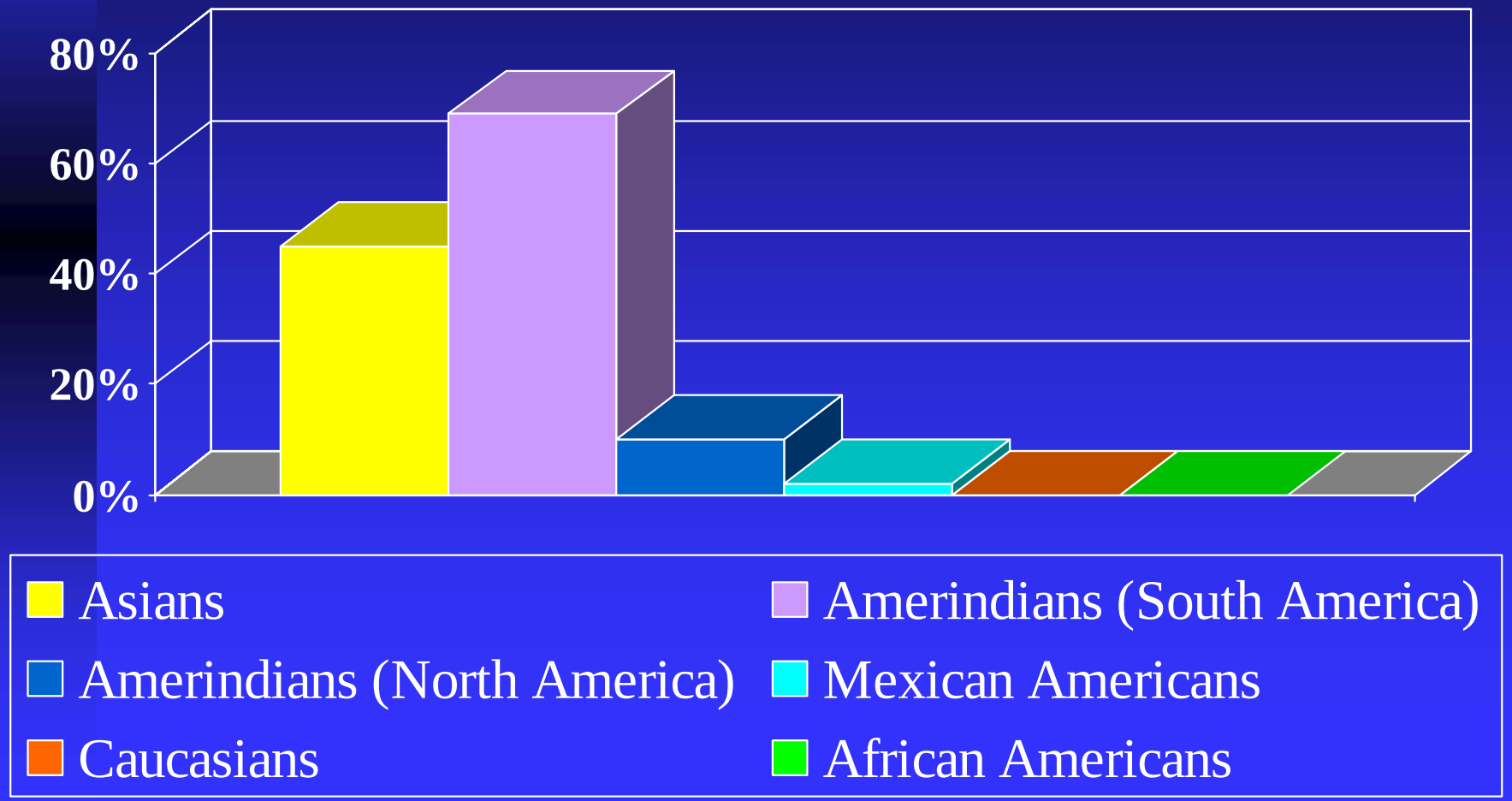


Zhou et al., NEJM 320:565-70, 1989

Factors Determining Pharmacological Response



PREVALENCE OF ACETALDEHYDE DEHYDROGENASE (ALDH) DEFICIENCY BY ETHNCIITY



CYTOCHROME P450 ENZYMES

- More than 50 expressed in humans
- The most important ones for drug metabolism are: CYP1A2, CYP**2C19, CYP2D6,** CYP2E1 and **CYP3A4**
- Variations in **CYP2D6** largely determined by genetic factors
- Variations in **CYP3A4** often influenced by environmental (dietary) factors

Cytochrome P450 Enzymes and Neuroleptics

	CYP1A2	CYP2D6	CYP3A4
Haloperidol	++	++	--
Phenothiazines	+	++	--
Clozapine	++	+	++
Olanzapine	+++	++	--
Risperidone	--	+++	+
Quetiapine	--	--	+++
ziprasidone	--	--	+++

Cytochrome P450 Enzymes and Antidepressants

	CYP1A2	CYP2C19	CYP2D6	CYP3A4
TCAs (tertiary)	++	+	++	++
Fluoxetine	+	++	+++	++
Paroxetine	+	-	+++	+
Sertraline	+	++	+	++
Mirtazapine	+	-	+	+
Nefazodone	+	-	+	+++
Venlafaxine	+	+	+	+
Bupropion	+	+	+	-
Fluvoxamine	+++	++	+	-
TCAs (secondary)	-	-	++	+

Distribution of CYP2D6 Activity in Caucasian Populations

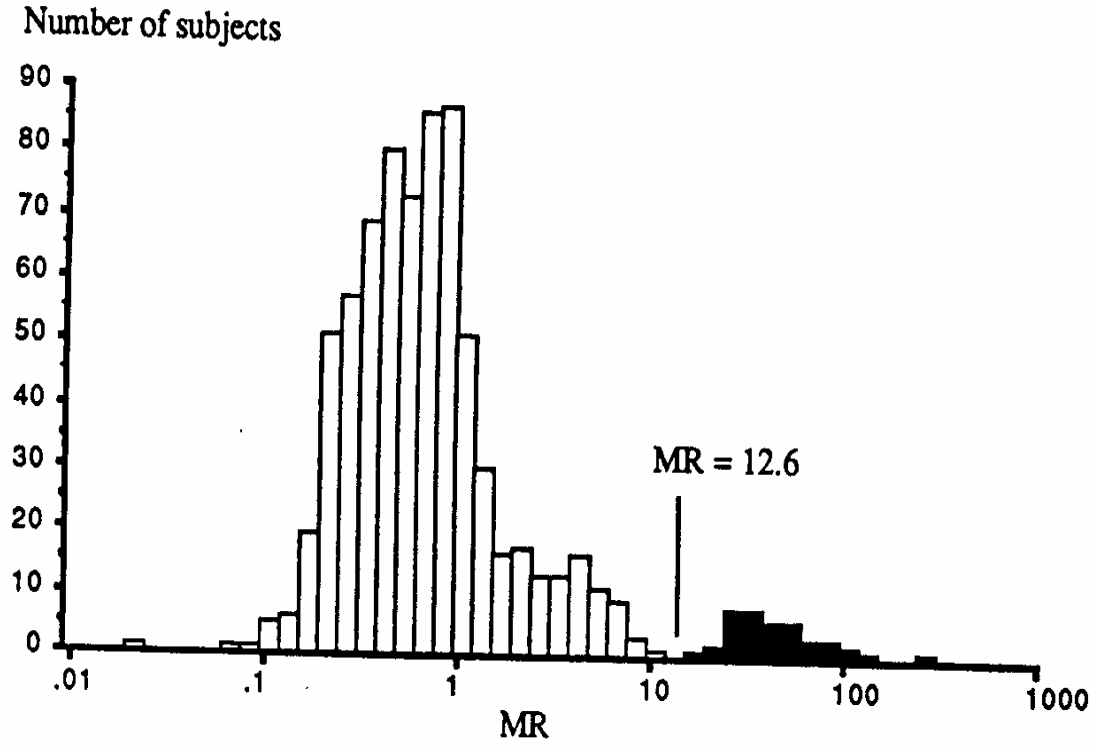


Fig. 1. Distribution of the urinary D/4-OH-D MRs among 757 white Swedish subjects. *Open bars* indicate rapid hydroxylators; *solid bars* indicate slow hydroxylators.

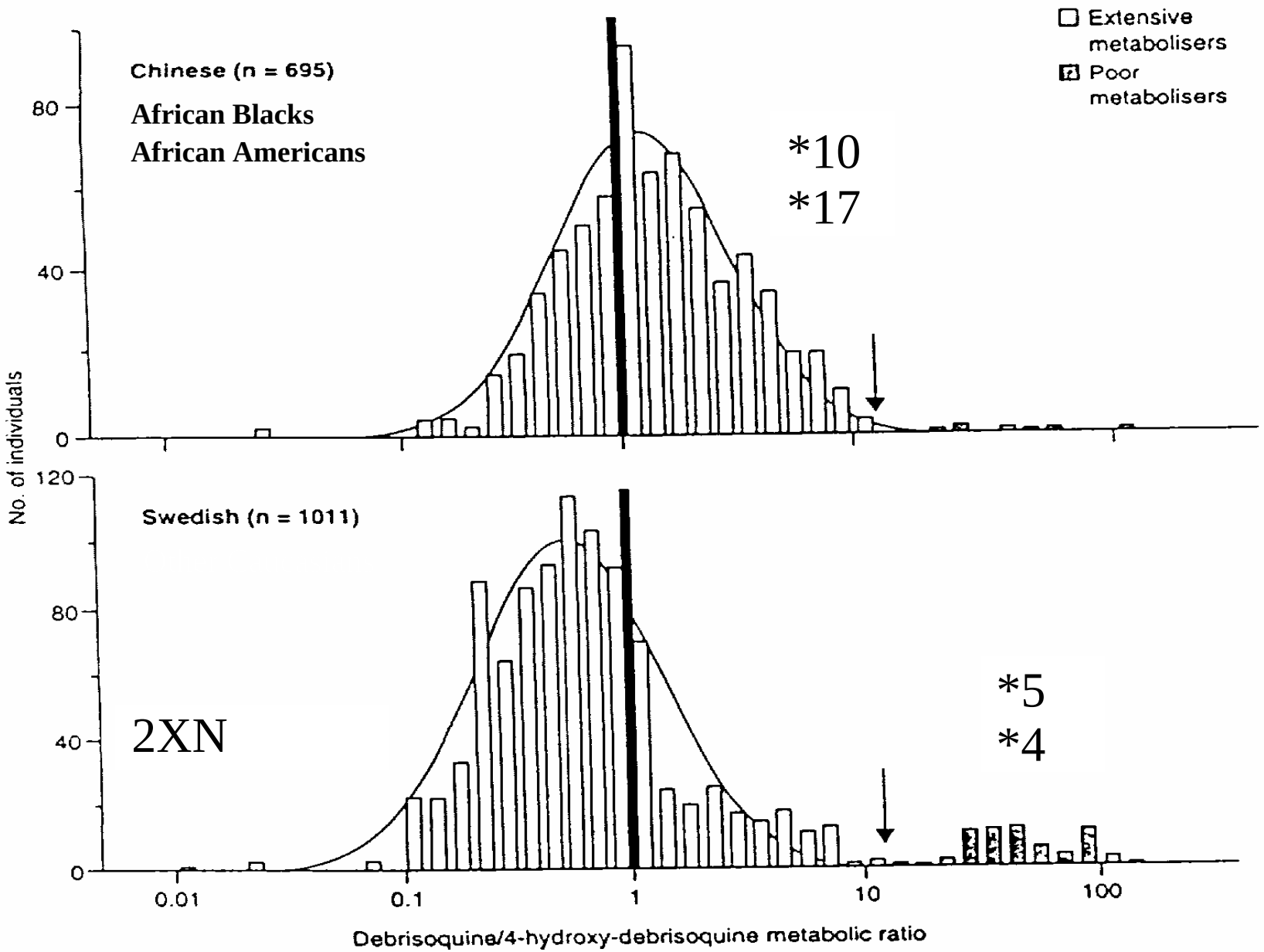
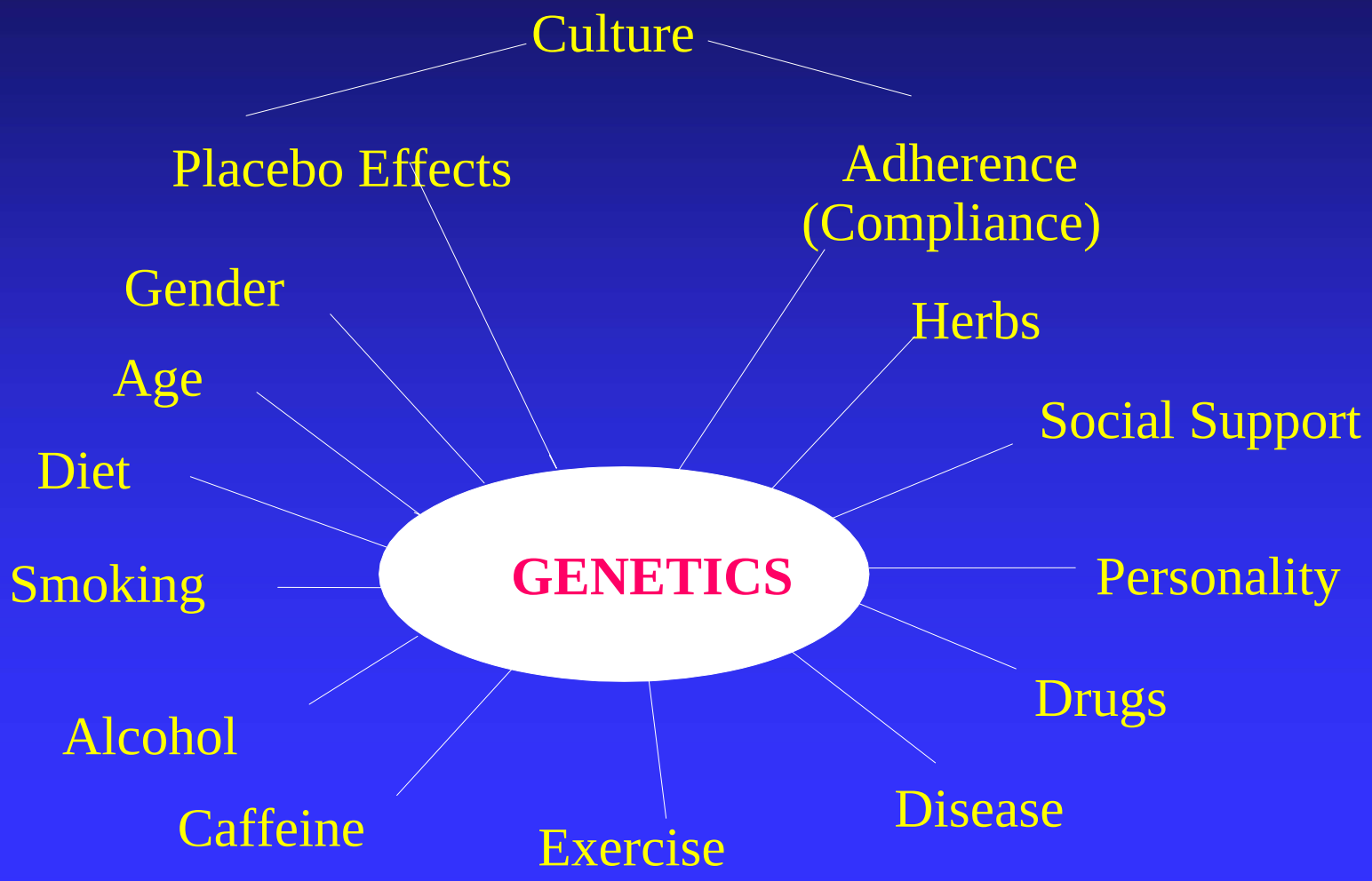


Fig. 2. Distribution of the urinary debrisoquine/4-hydroxy-debrisoquine metabolic ratio (MR) in 695 Chinese and 1011 Swedis Caucasian healthy individuals. The arrows indicate a MR of 12.6, the antimode between extensive metabolisers and poor metab olisers as established in Caucasian populations. A line is drawn at a MR of 1.0. Most Chinese extensive metabolisers have a MI >1, while most Swedish extensive metabolisers have a MR <1 (reproduced from Bertilsson et al.,[14] with permission).

FACTORS AFFECTING DRUG RESPONSE



NIFEDIPINE METABOLISM IN ASIAN INDIANS AND BRITISH WHITES

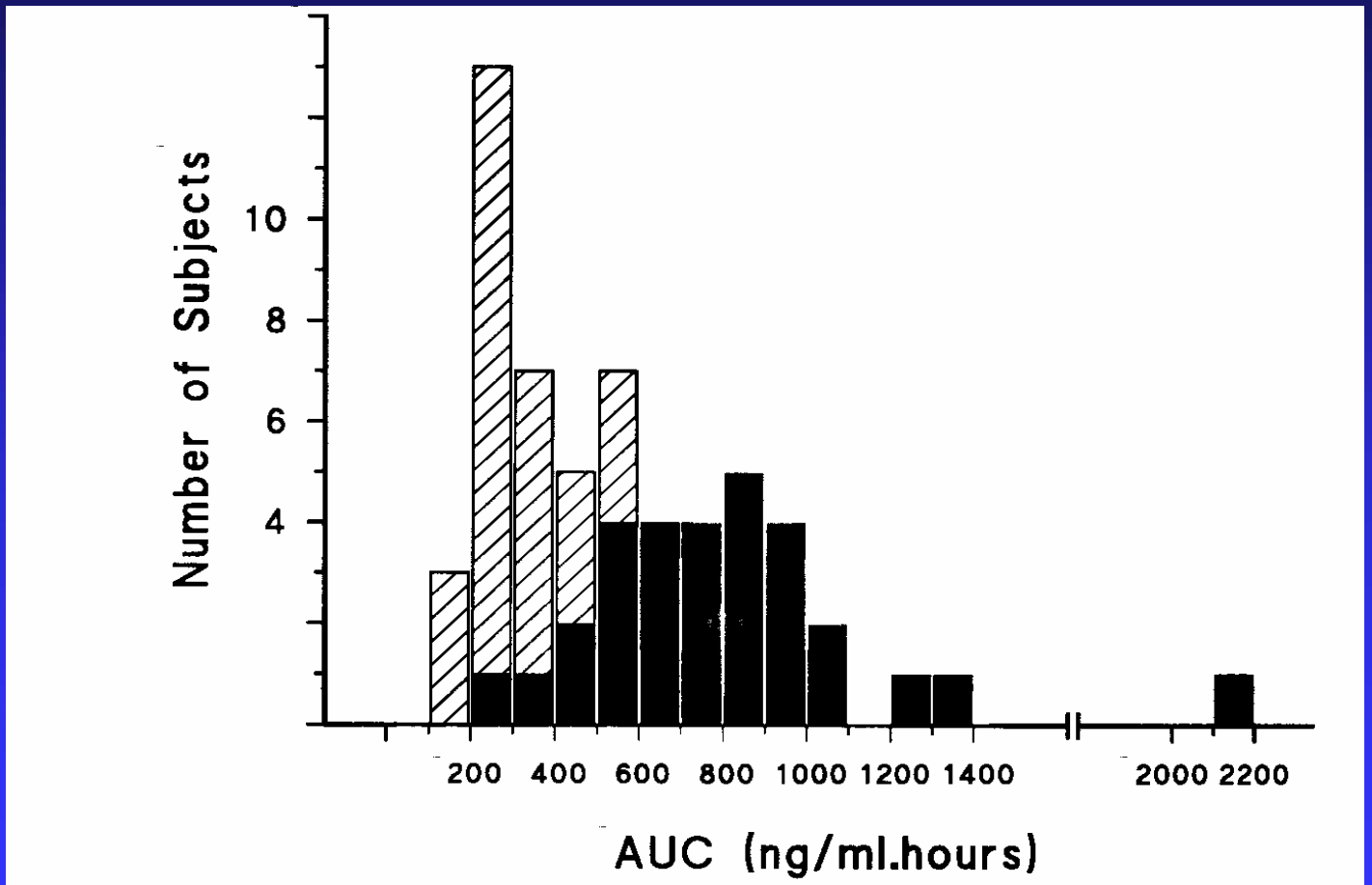
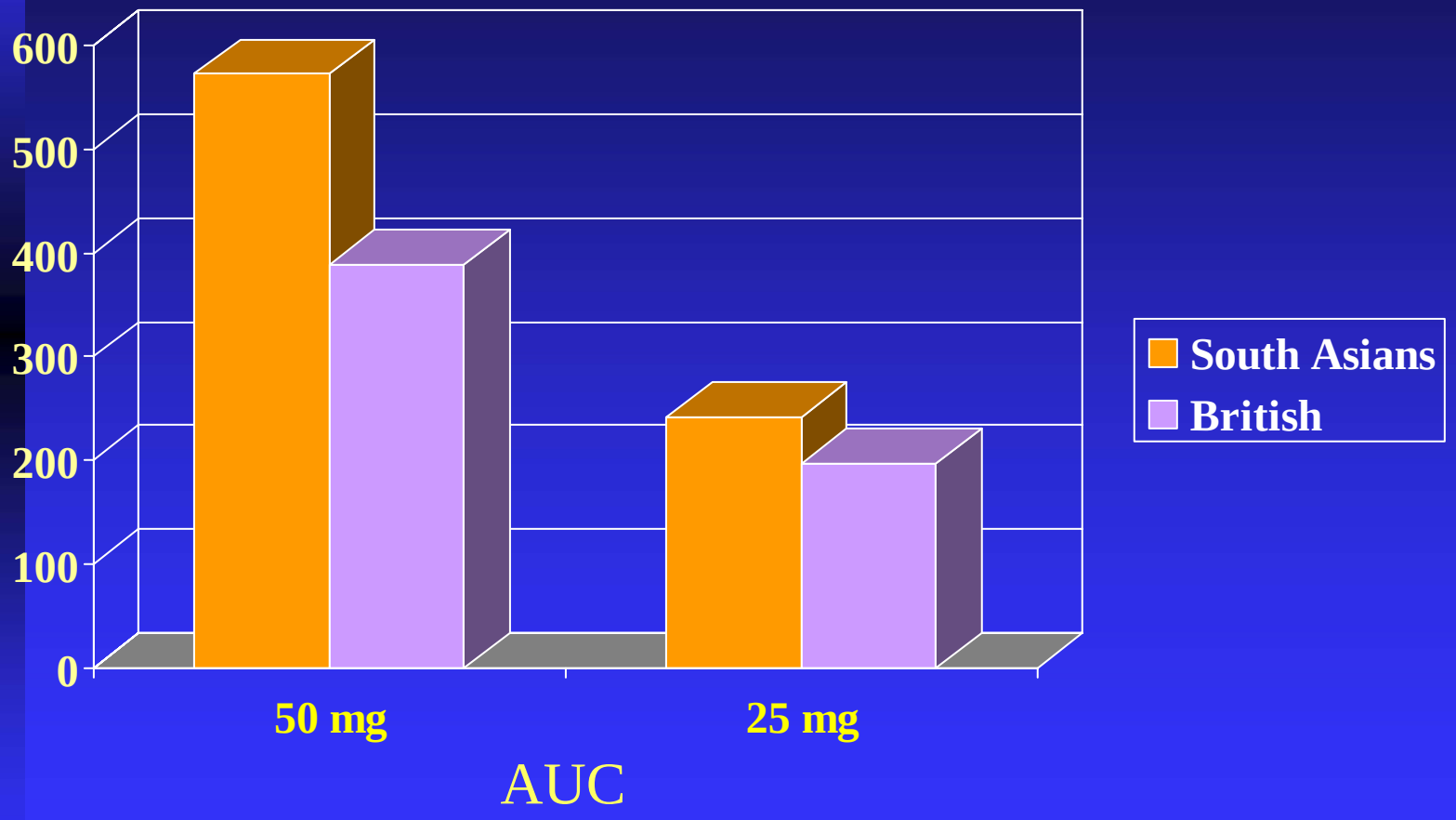
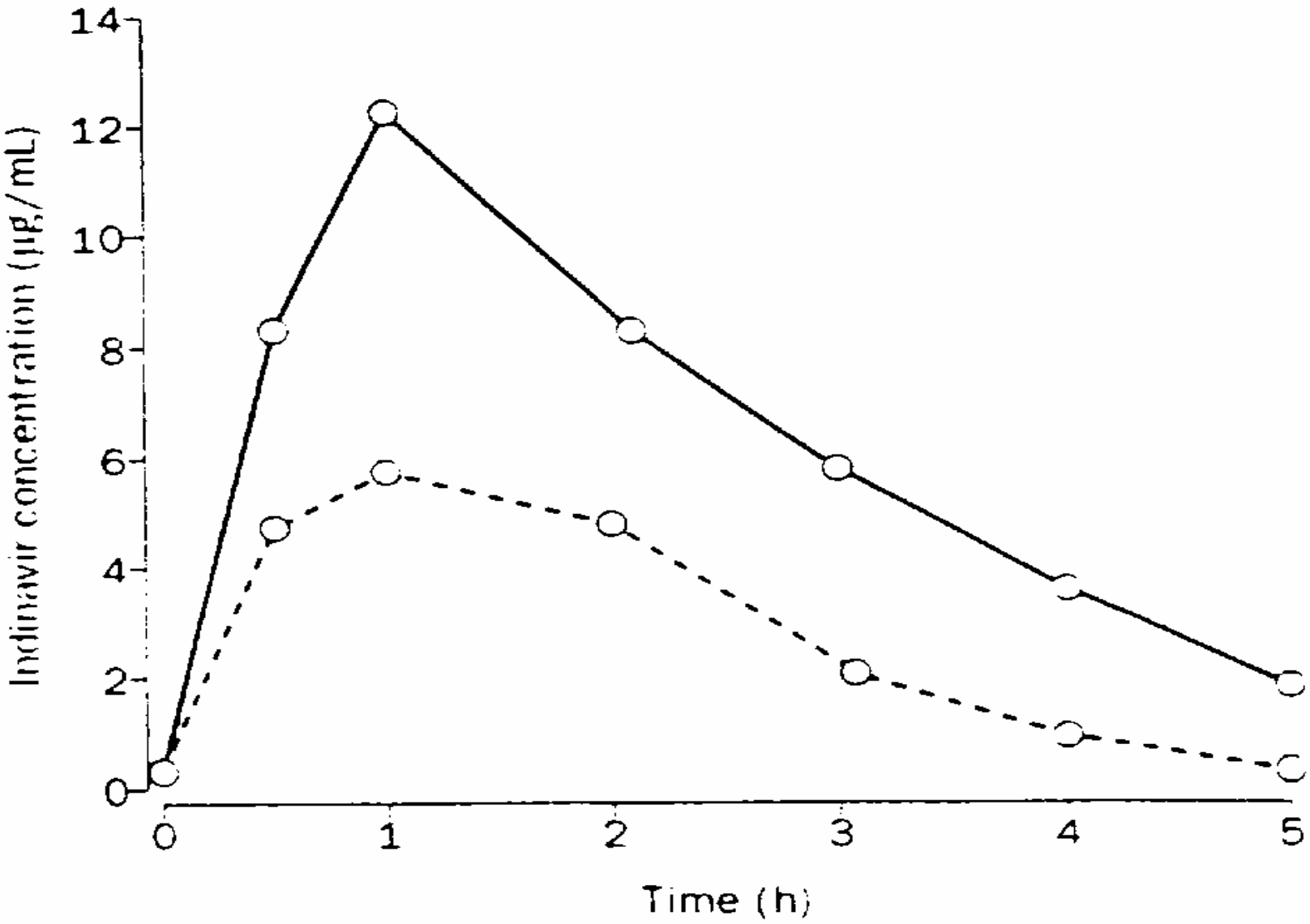


Fig. 2. Distribution of values for area under the plasma concentration–time curve (A nifedipine in Caucasian subjects *(hatched bars)* and in South Asian subjects *(solid bars)*.

Clomipramine Concentration: South Asians vs British Whites

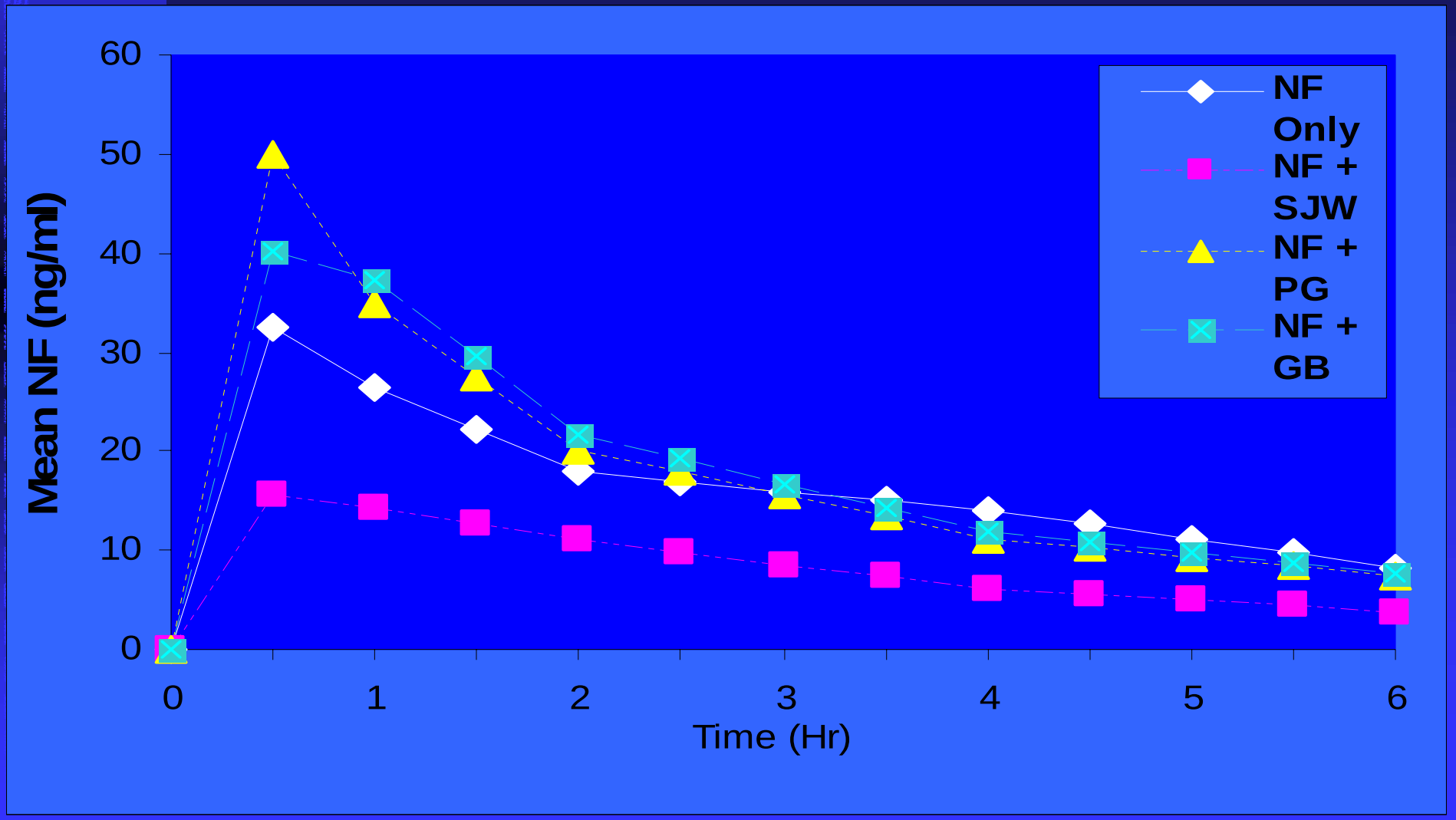


Lewis P, Rack PH, Vaddadi KS, Allen JJ (1980) Postgraduate Medical Journal 56 (Suppl. 1): 46-49

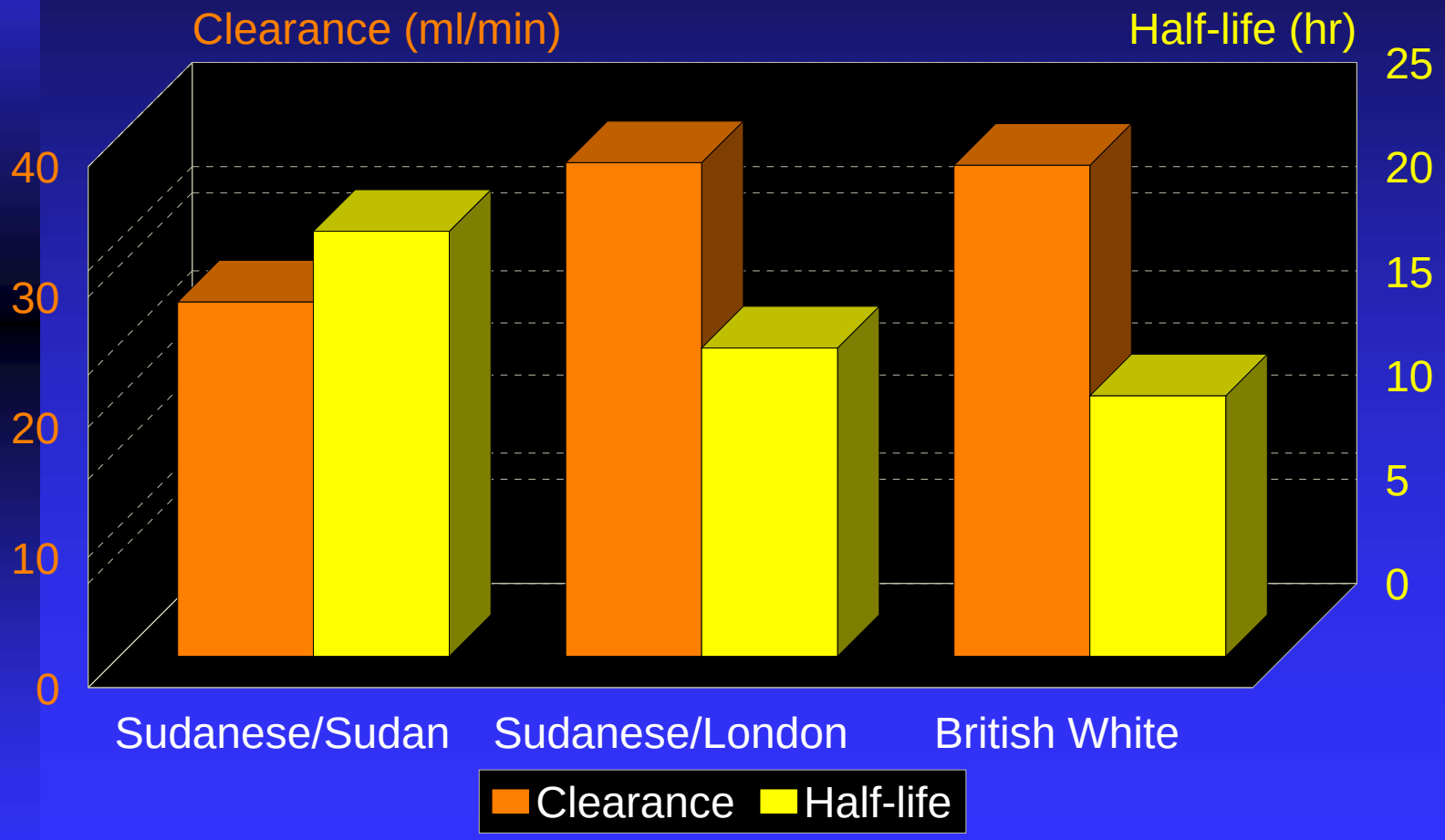


Mean concentration-time of indinavir alone (solid line) and with concomitant St John's wort (dotted line)

Nifedipine-Herb Interactions: Nifedipine Plasma Levels (ng/ml)



PHARMACOKINETICS OF ANTIPYRINE: SUDANESE AND BRITISH



Paroxetine
Citalopram, etc

Reboxetine
Desipramine, etc

Serotonin
Transporter

Norepinephrine
Transporter

Serotonin system

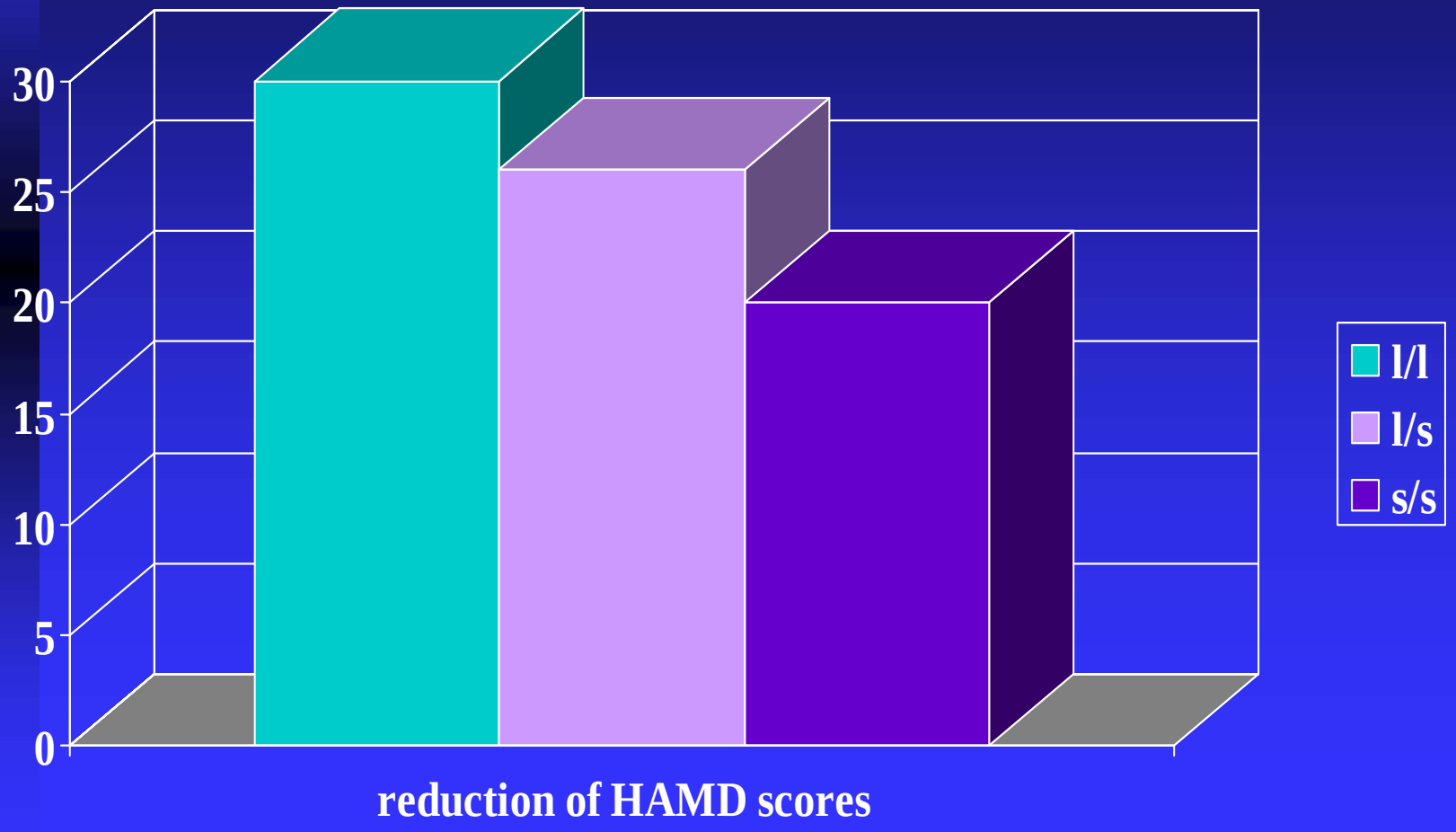
Norepinephrine system

Relationship between Serotonin Transporter (SERT or 5-HTT; SLC6A4) Polymorphism and Antidepressant Response

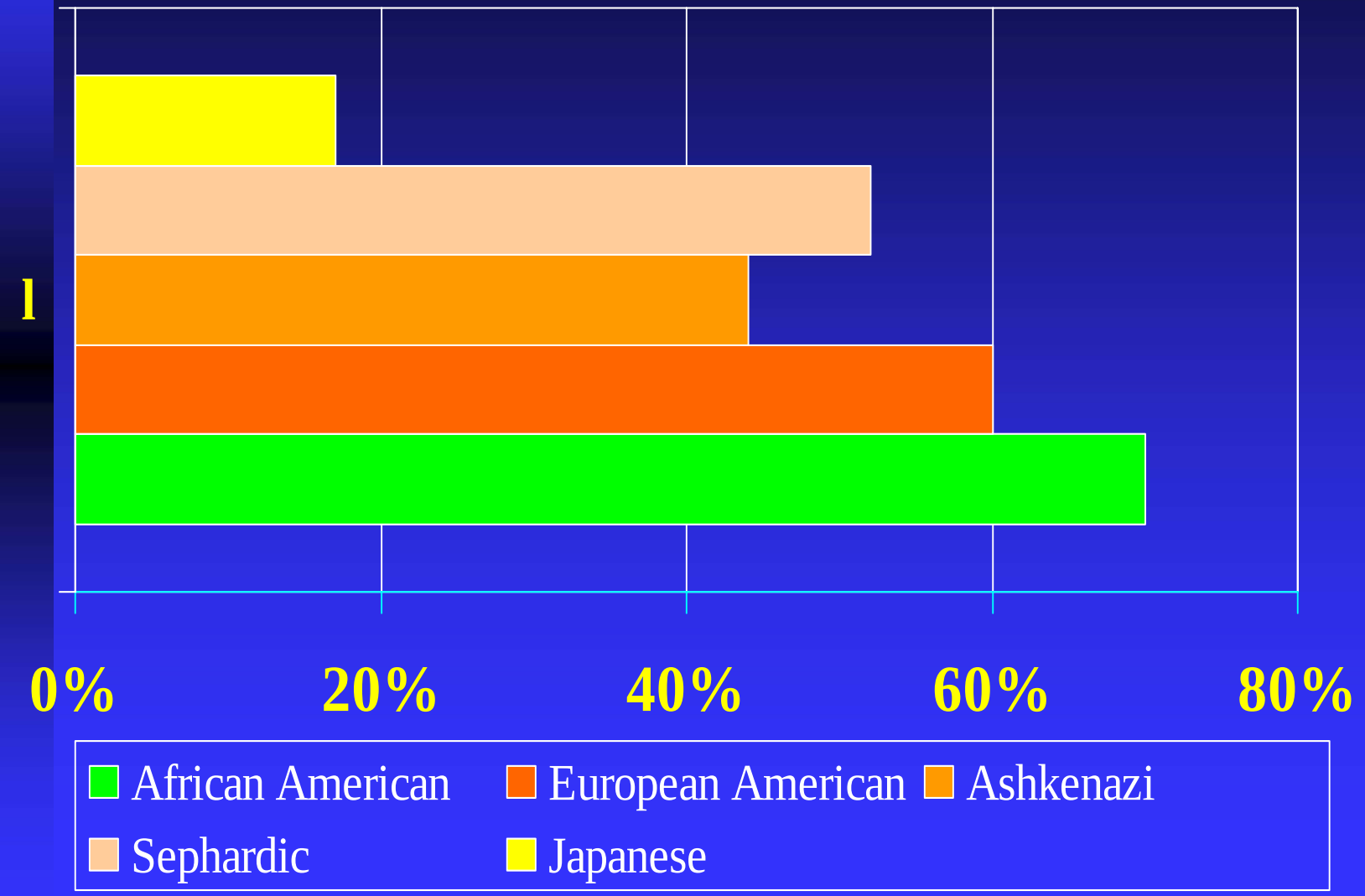
Diallelic promoter polymorphism (*l* and *s* alleles)

- Subjects with long variant (*l*) showed twice the basal transcriptional activity
- In Caucasians, long variant (*l*) is associated with better and faster response to SSRI's, such as paroxetine and fluvoxamine

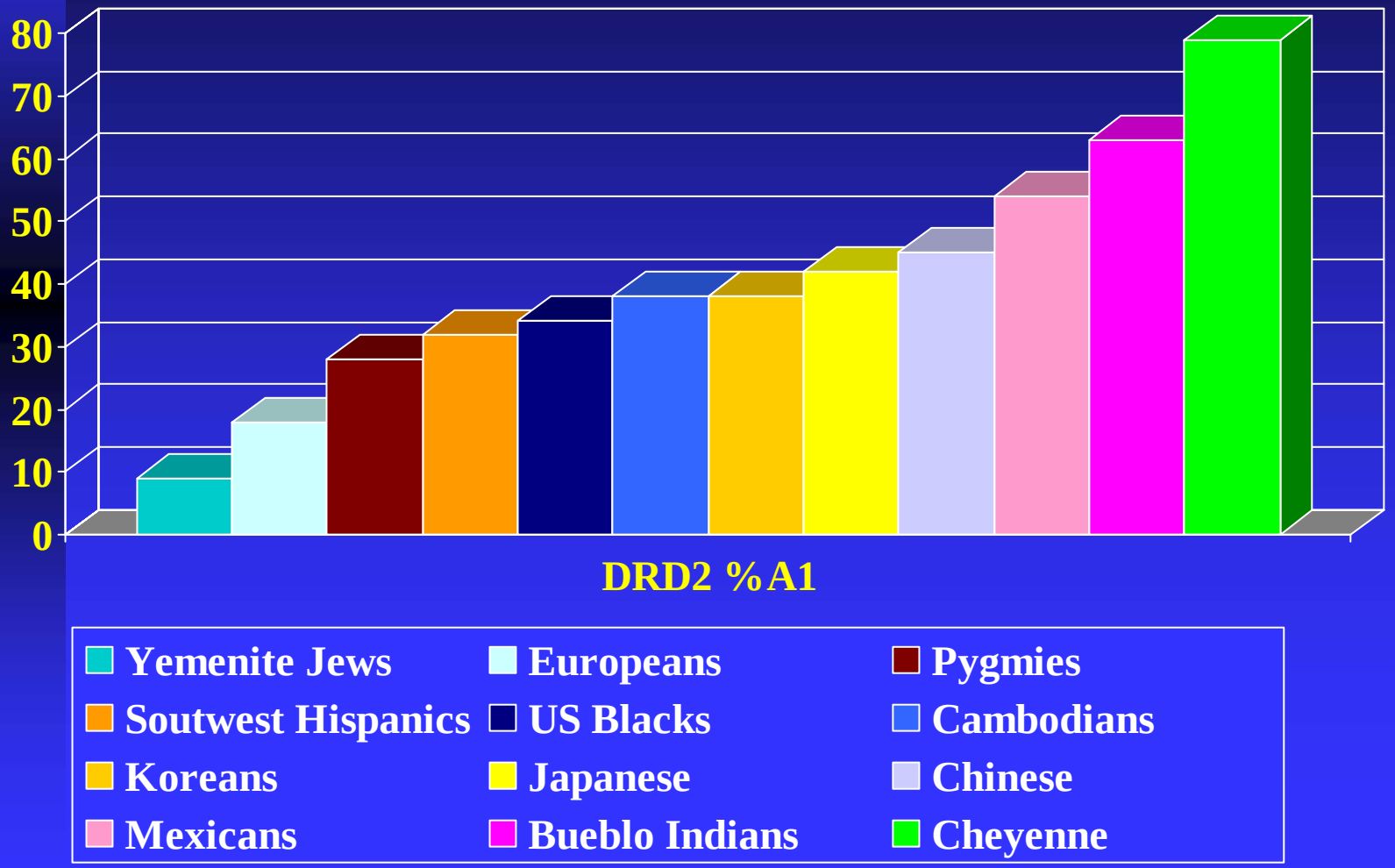
5HTT POLYMORPHISM AND RESPONSE TO FLUVOXAMINE



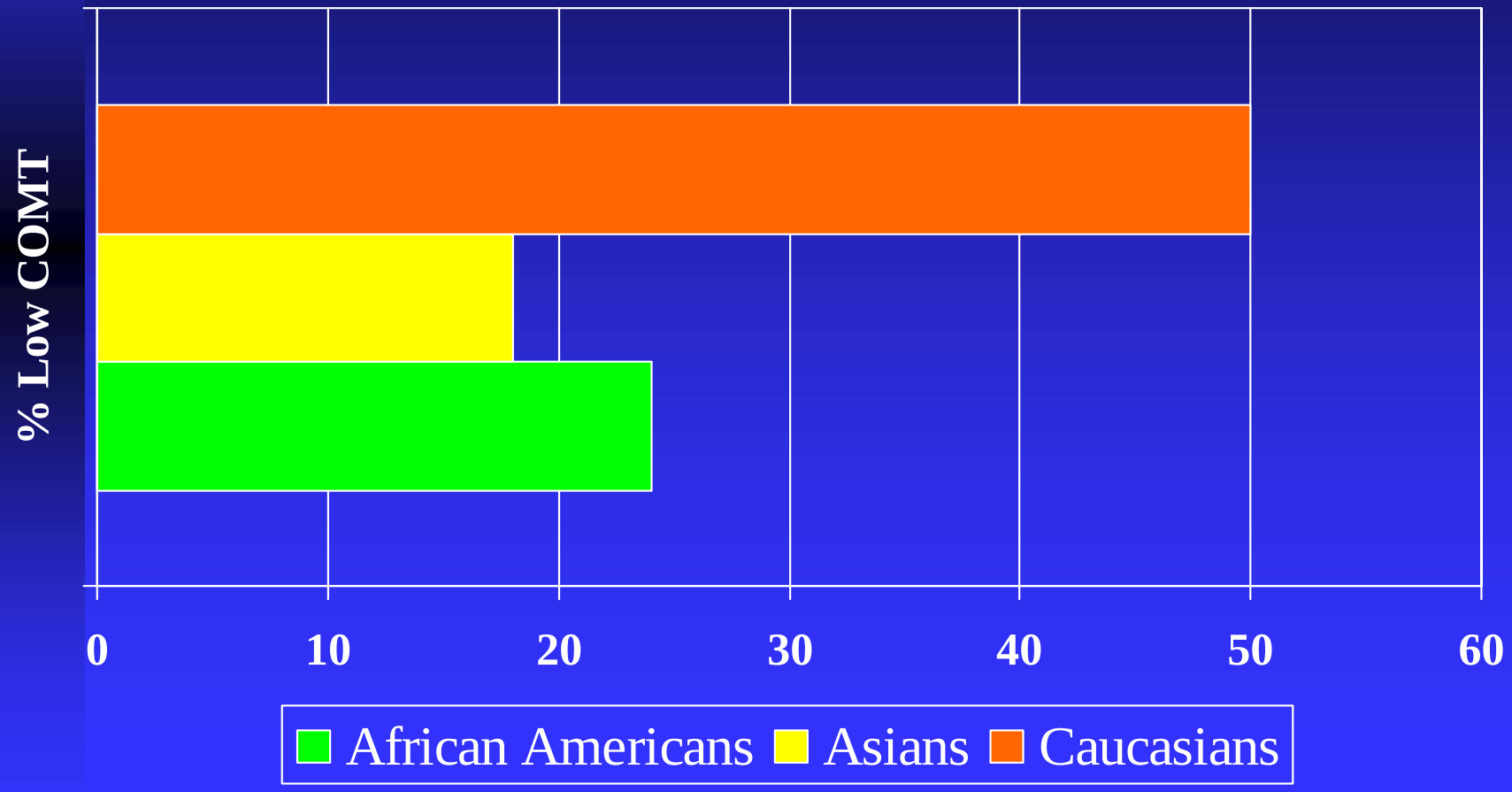
Serotonin Transporter Gene (SLC6A4) Polymorphism



Dopamine D2 Receptor Gene Polymorphism



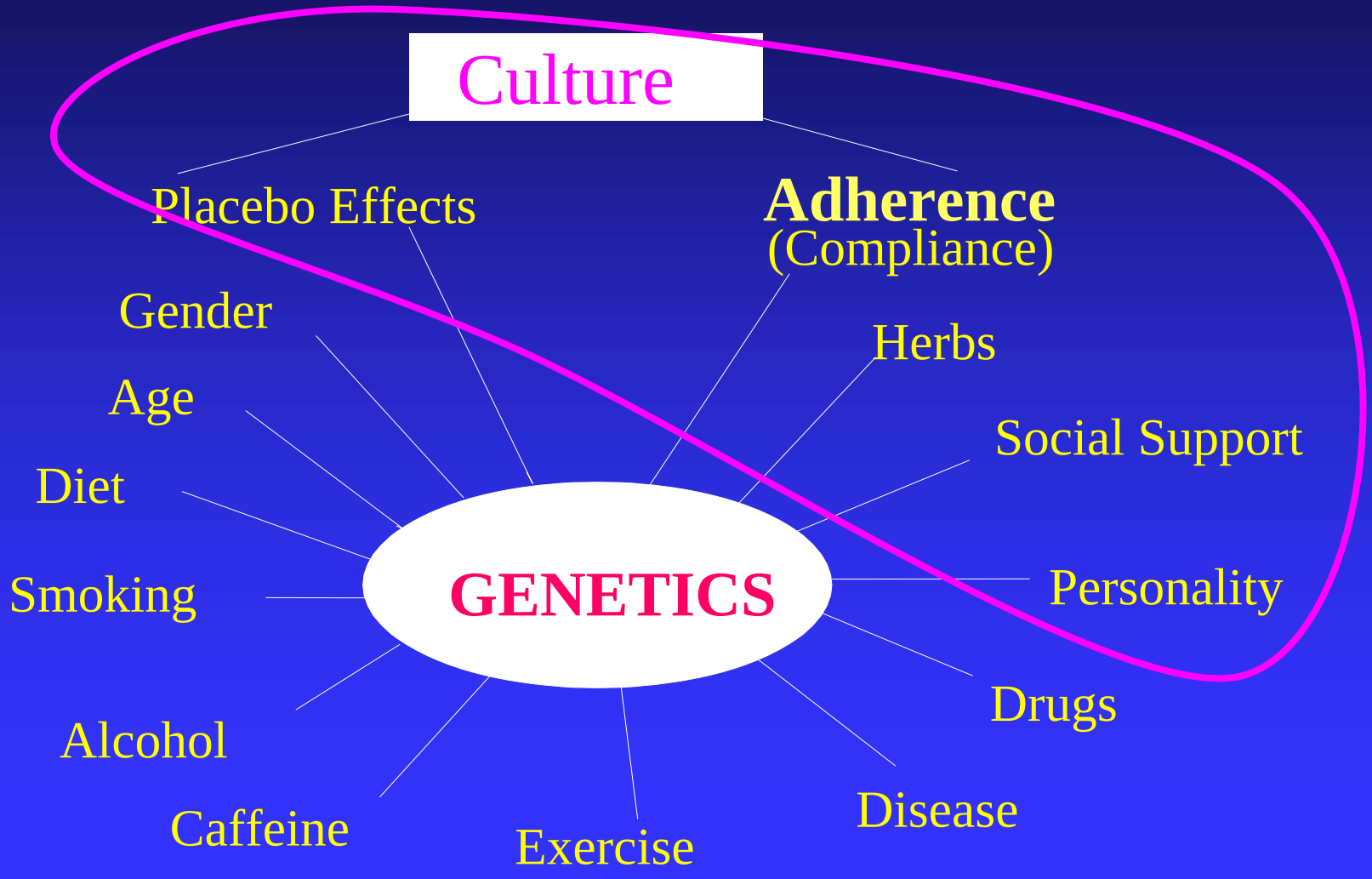
CATECHOL-*O*-METHYLTRANSFERESE (COMT) POLYMORPHISM



Genetic Variations within and across Populations

- Variations extremely prevalent
- Responsible for inter-individual and cross-ethnic variations in biological and behavioral traits
- Responsible for the risks of all complex health problems, including all psychiatric conditions, as well as most of the chronic medical problems, such as diabetes and hypertension
- These associations may be ethnically specific. Thus, findings from one ethnic group can not be applied to other groups until proven
- Determines pharmacological treatment response

FACTORS AFFECTING DRUG RESPONSE



PSYCHOPHARMACOLOGY IN THE SOCIOCULTURAL CONTEXT

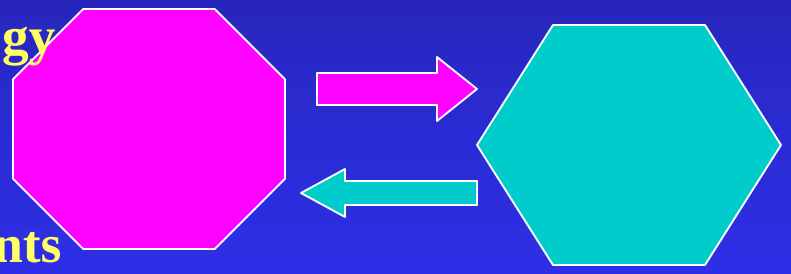
Clinician **Patient**

Professional Ideology

Institutional Policies

Financial Constraints

Influence from the Industry



Cultural Beliefs

Family and Friends

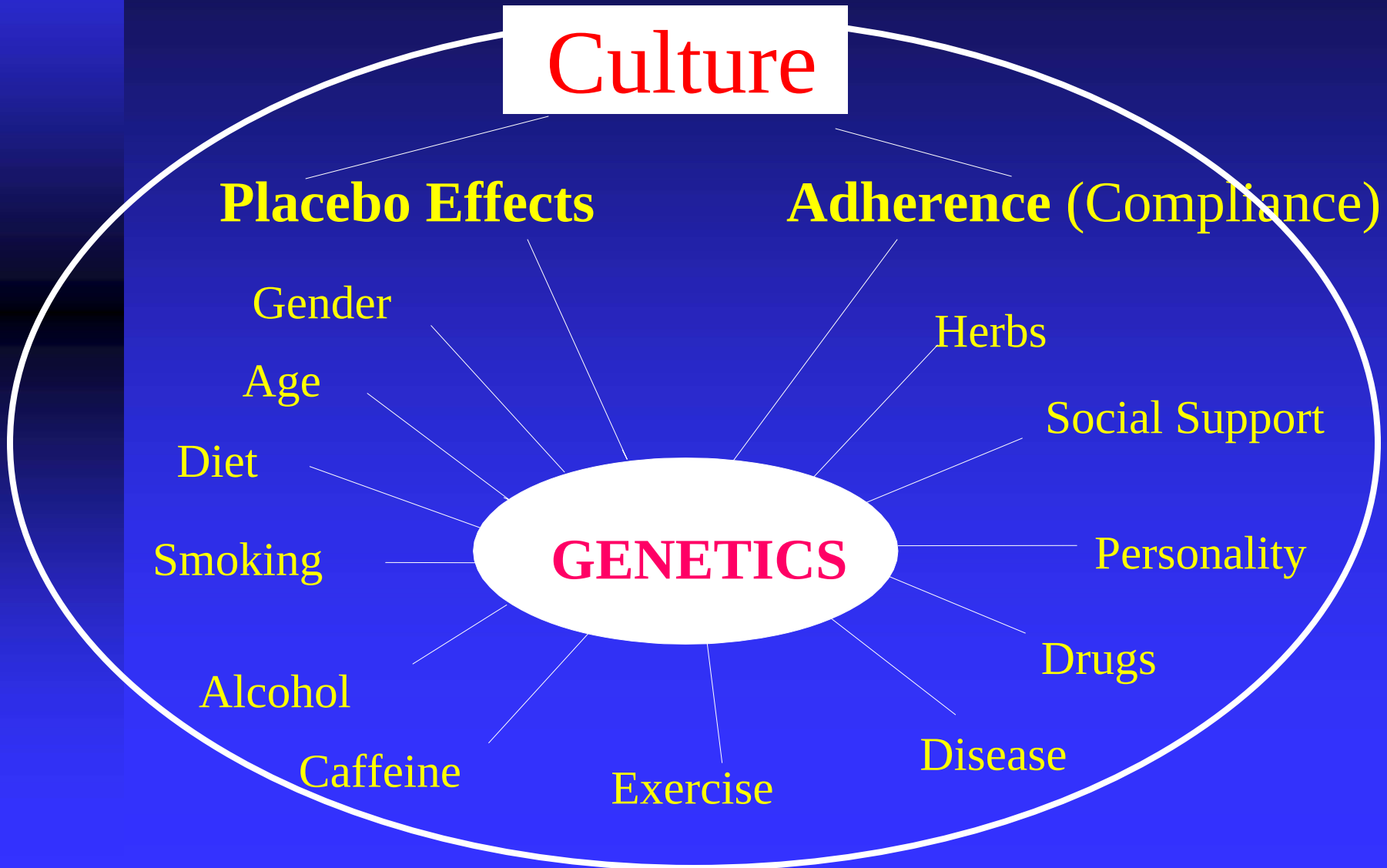
Past Experiences

Psychopathology

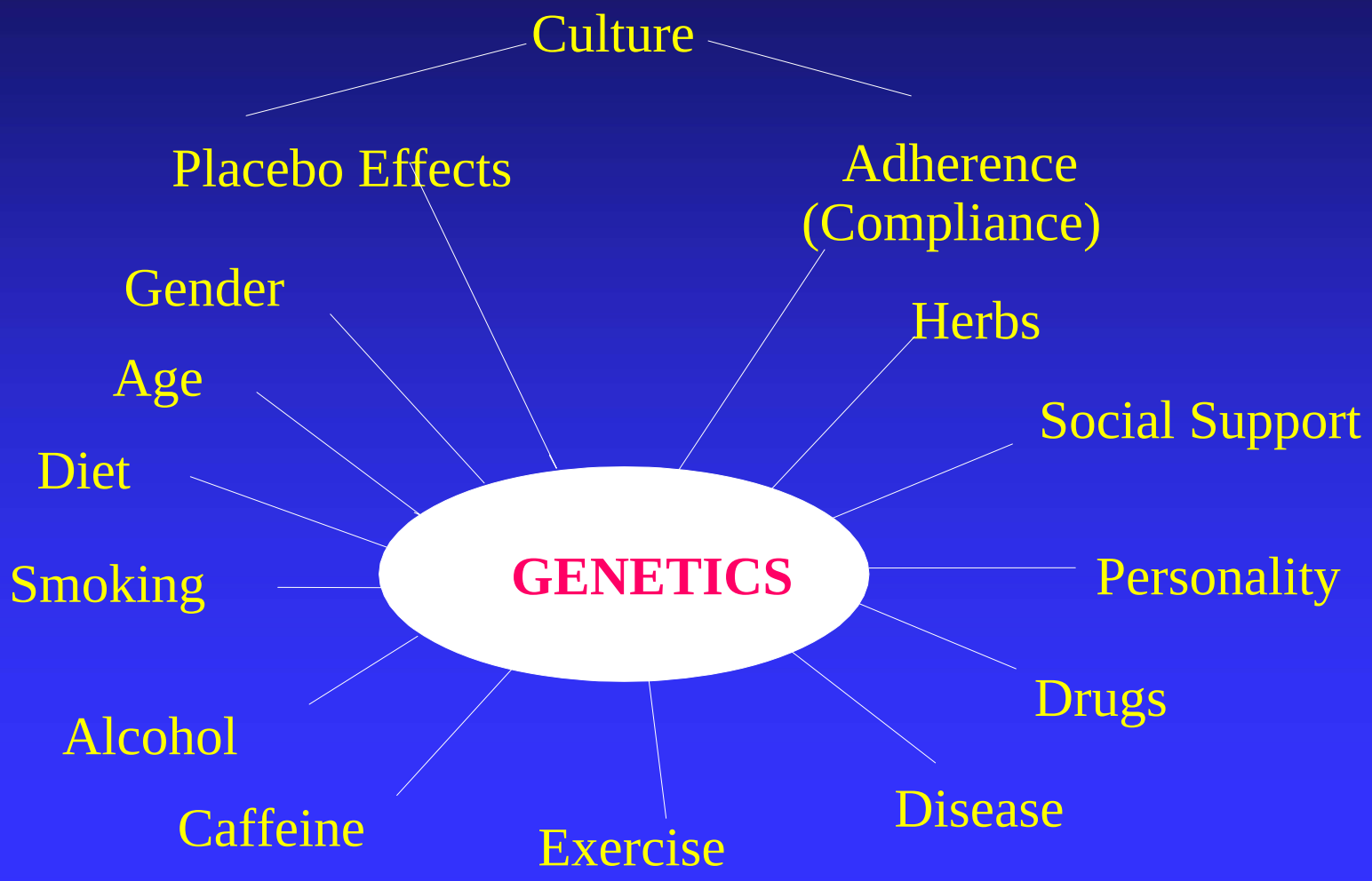
Future Directions

- **Technological advances**
  - Gene array methodologies
  - Cell biology
  - Neuroscience
- **Clinical advances**
  - Alternative ways for conceptualizing clinical phenomena
  - Assessment of individual differences
- **Research on the Socio-cultural Context of Psychopharmacological Practice**

FACTORS AFFECTING DRUG RESPONSE



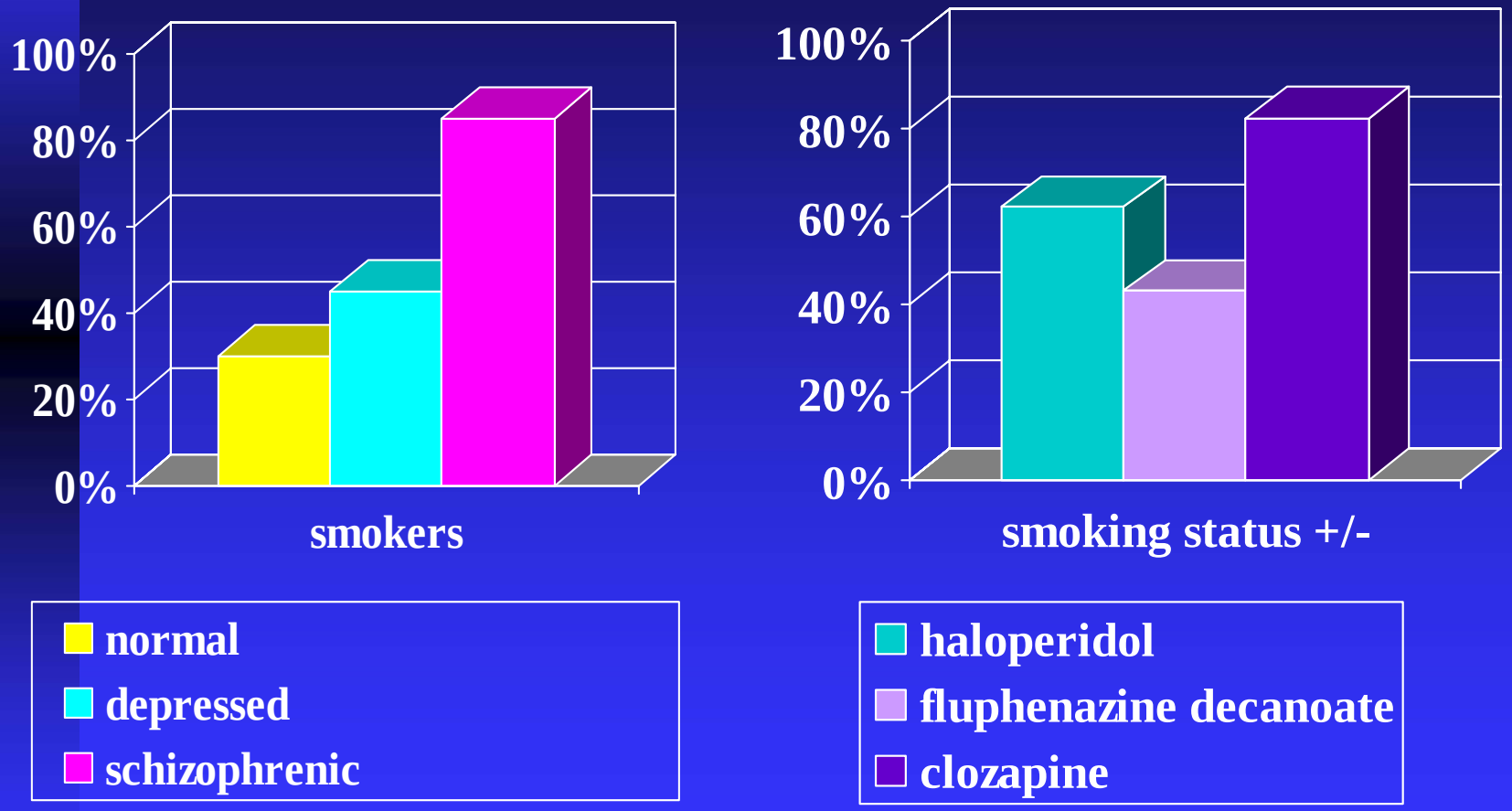
FACTORS AFFECTING DRUG RESPONSE



Ethnic Variations in Antidepressant Response

- A three site collaborative RO1 project (2001-2006)
- Subjects recruited from three sites with identical criteria and treated with identical protocol
  - Harbor-UC LA Medical Center
  - King-Drew Medical Center
  - Cedars-Sinai Medical Center
- 400 subjects with DSM-IV major depression: 200 African Americans vs 200 Caucasians
- Patients treated with citalopram for 8 weeks
- Pharmacogenetic profiles as predictors of response
  - Serotonin transporter polymorphism
  - CYP2C19 and CYP3A4

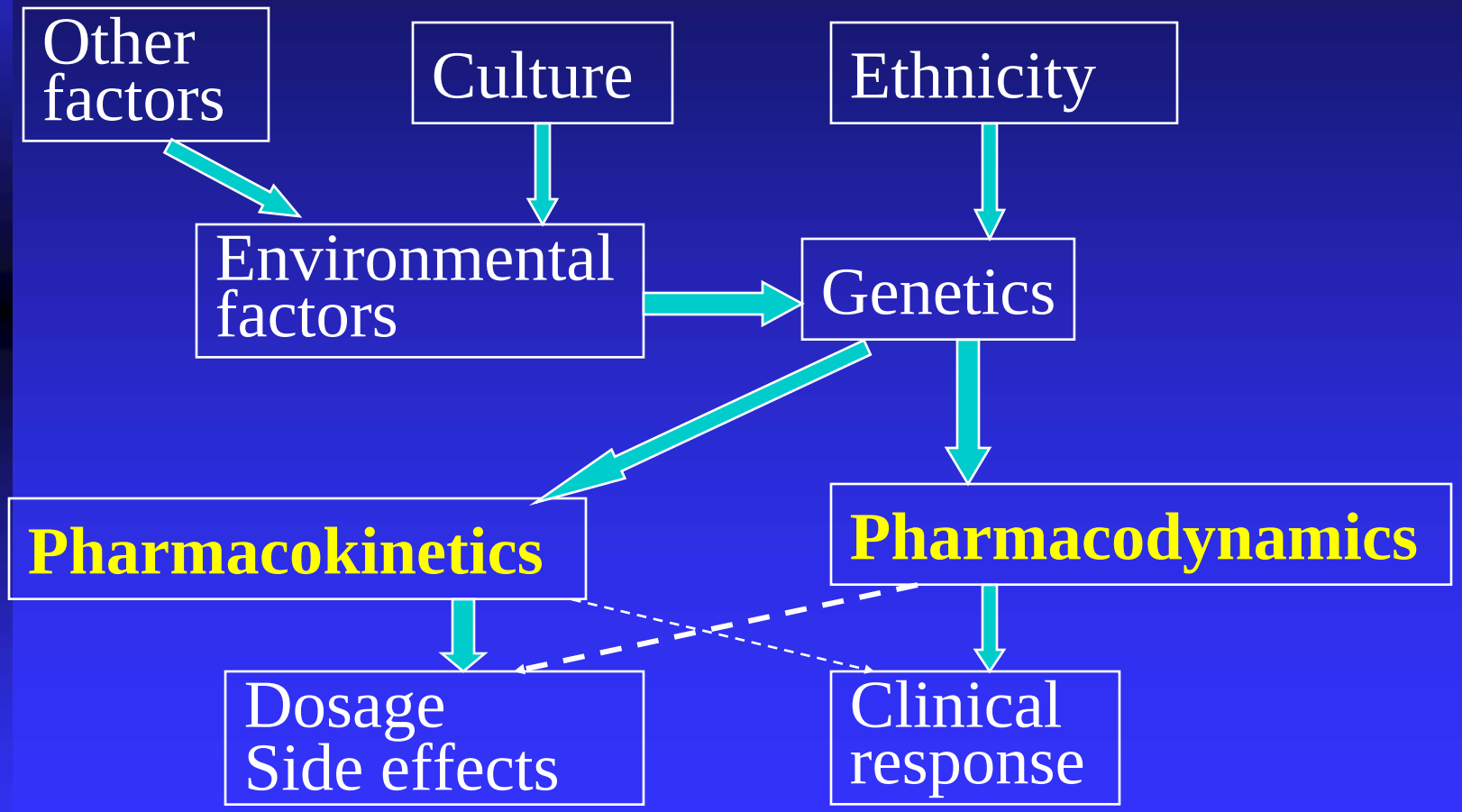
SMOKING AND ANTIPSYCHOTIC RESPONSES



Monoamine Hypothesis for Mood Disorders

- Neurotransmitters
  - Serotonin, Norepinephrine, Dopamine, etc
- Systems Involved in the Regulation of the Effects of Neurotransmitters
  - Transporters (e.g. Serotonin Transporter)
  - Receptors
  - Monoamine synthesis and removal (e.g., **CATECHOL-*O*-METHYLTRANSFERESE [COMT]**)

Factors Determining Pharmacological Response



CYTOCHROME P450 ENZYMES

- Most psychotropics metabolized by one or more of the following four:
  - CYP2D6
  - CYP3A4
  - CYP1A2
  - CYP2C19
- Dramatic individual and ethnic variations in all, caused by differences in the frequency of functional alleles
- Inhibition common with all
- Induction common with CYP3A4 and CYP1A2

Variations in pharmacogenetic profiles across populations of “African” origin

Ethnic Variations in Antidepressant Response

- A trial of citalopram in African-American and European-American Patients with DSM-IV Major Depression
- Clinical outcome assessed 8-week trial
  - Measures of depression: HAM-D and BDI
  - Side effect profiles: TESS and ASEX
  - Others: CGI, PGI
- Harvest leukocytes
  - Creating immortalized cell lines
  - Extraction of DNA
- Determination of genotypes
  - SERT
  - CYP2C19
- Serum drug levels

Genetic Variations within and across Populations

- Variations extremely prevalent
- Responsible for inter-individual and cross-ethnic variations in biological and behavioral traits
- Responsible for the risks of all complex health problems, including all psychiatric conditions, as well as most of the chronic medical problems, such as diabetes and hypertension
- Determines pharmacological treatment response

The Role of Ethnicity in Determining Pharmacological Responses

- Three classical examples
  - “Primaquine hemolysis”
  - Isonizid toxicity
  - “Flushing response” to alcohol
- More recent studies

Hemolytic Anemia and Glucose-6-Phosphatase Dehydrogenase Deficiency

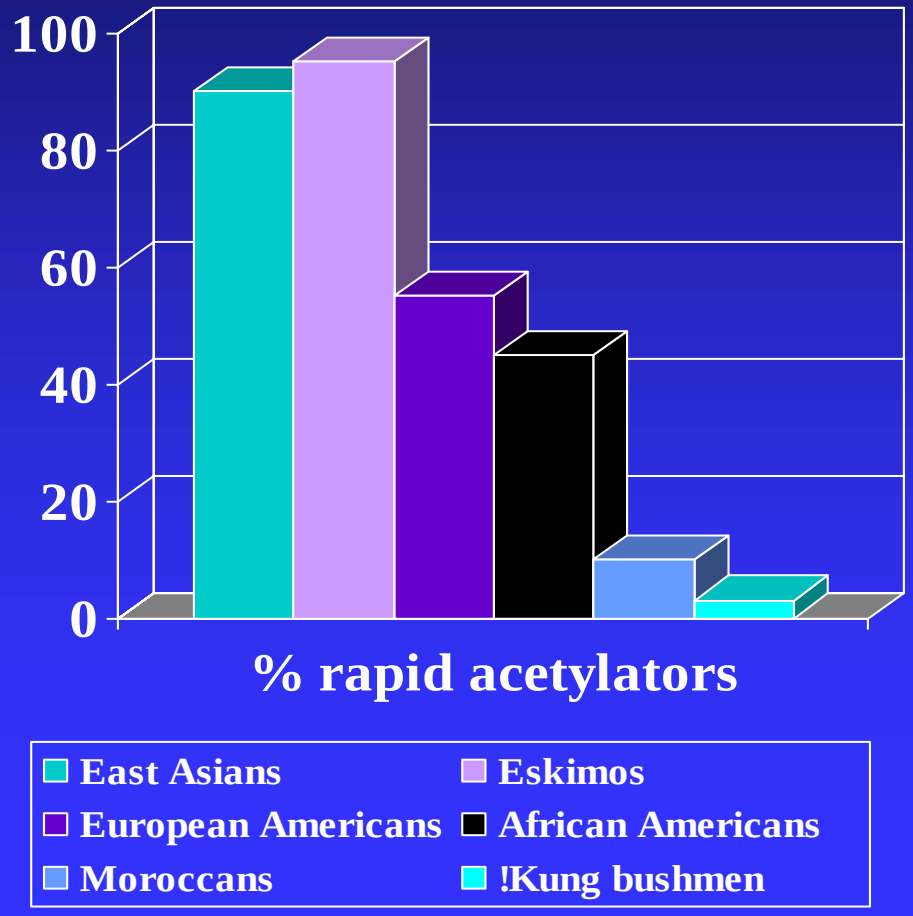
- "Primaquine hemolysis"
- Other oxidant drugs
- Fava beans
- Caused by hemoglobin variants
- Prevalent in people of African, Mediterranean and Southeast Asian origins

Isoniazid Toxicity

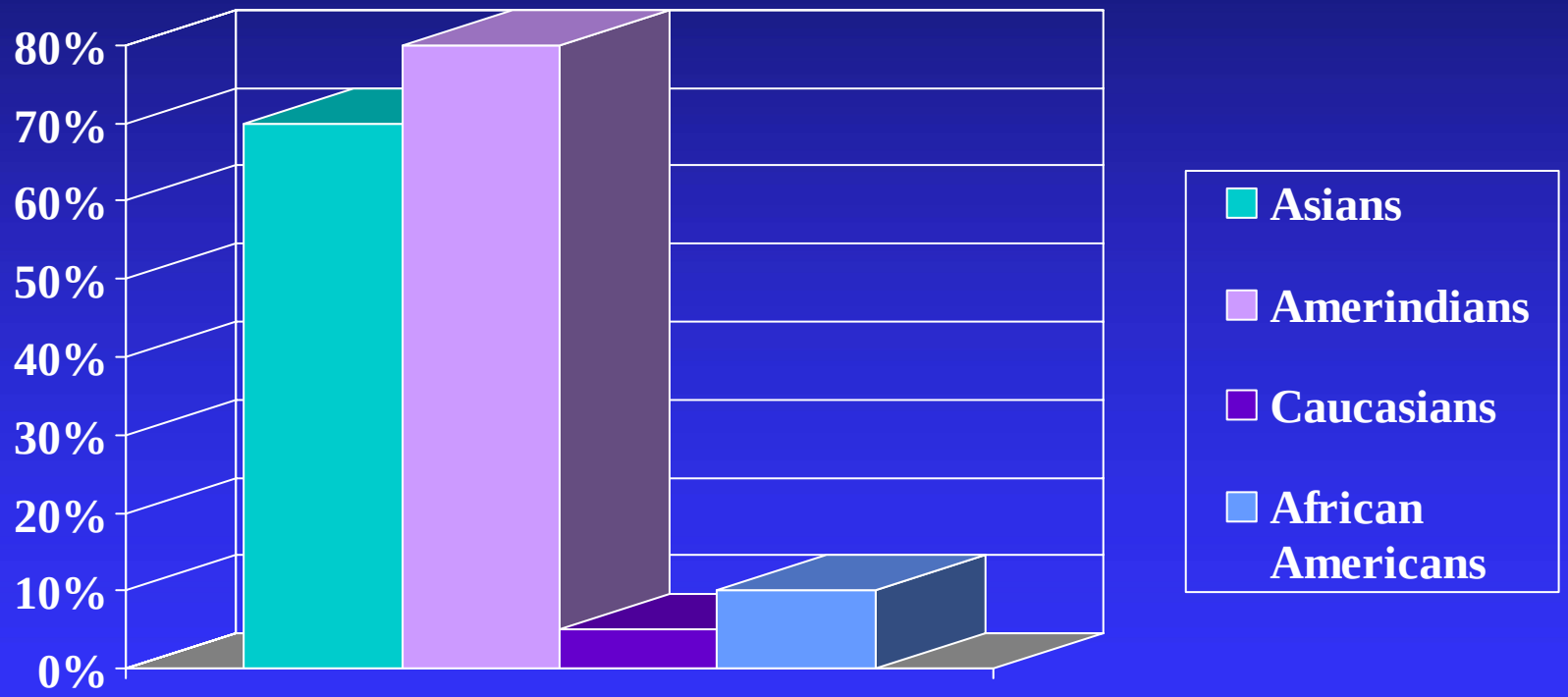
- Acetylation status is associated with different types of side effects
  - Hepatotoxicity - rapid acetylators
  - Peripheral neuritis - slow acetylators
- The distribution of the acetylation status varies significantly across ethnic groups:

Isoniazid Toxicity

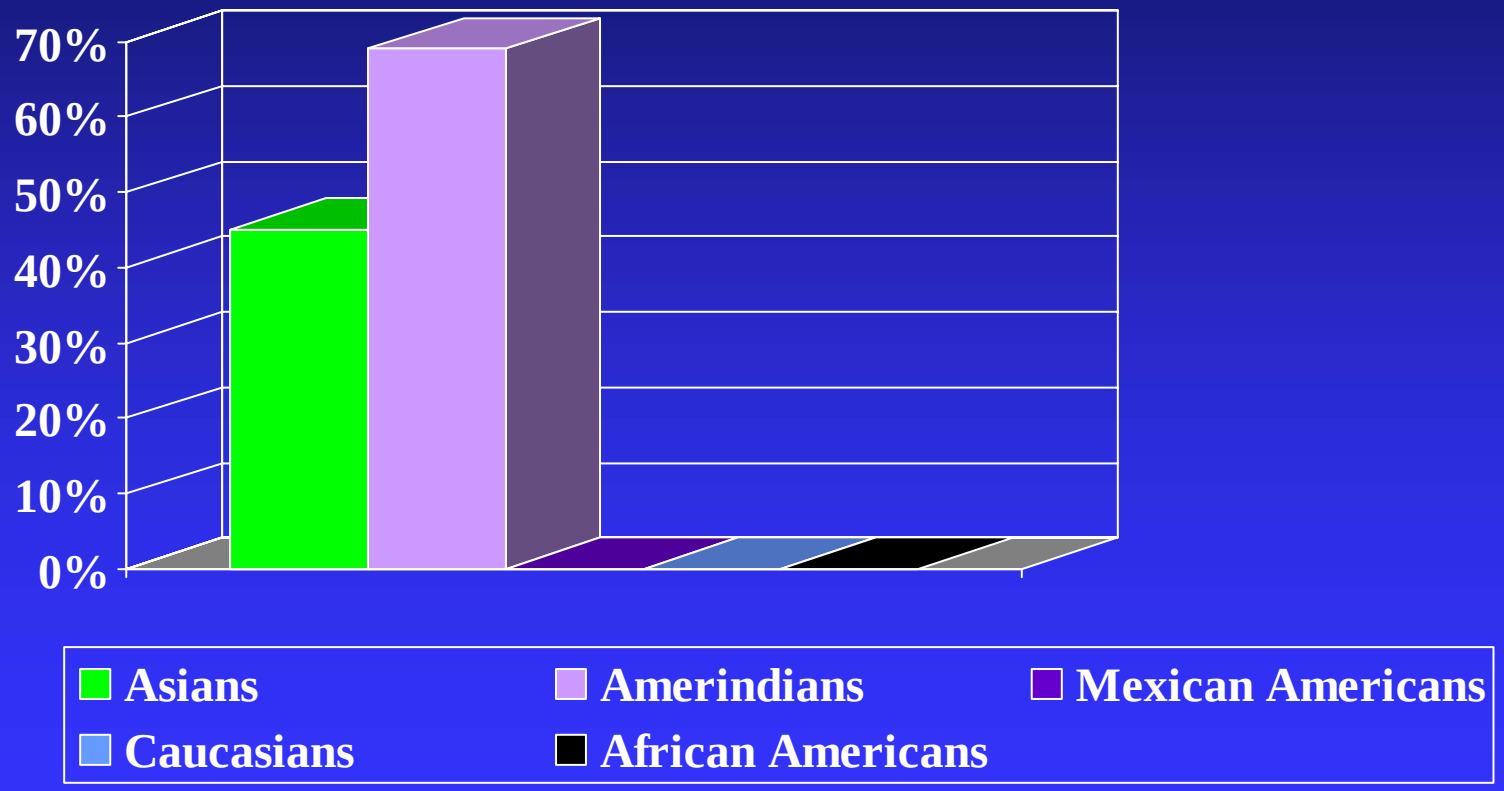
- Acetylation status associated with different types of side effects
  - rapid acetylators: Hepatotoxicity
  - Peripheral neuritis: slow acetylators



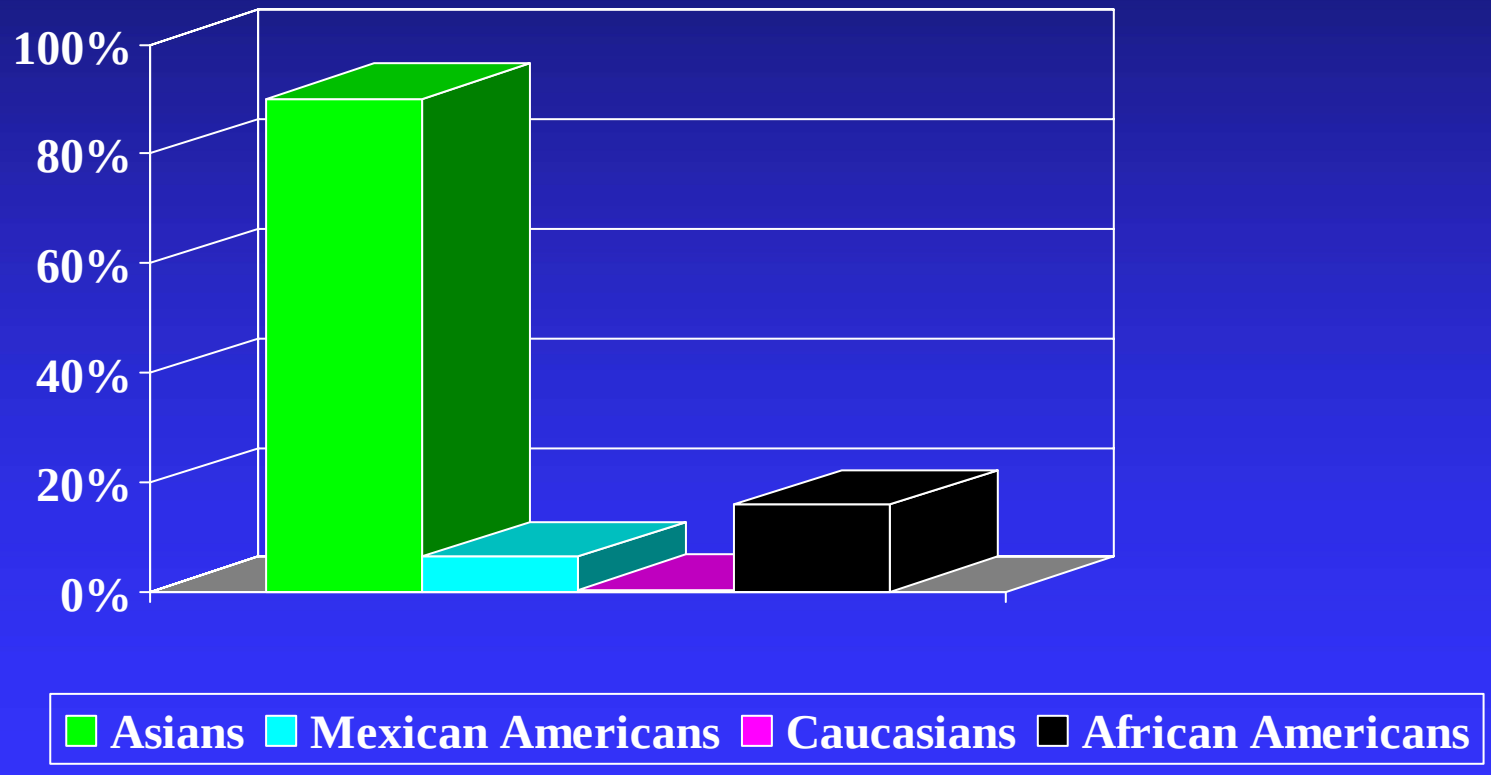
PREVALENCE OF FLUSHING RESPONSE BY ETHNCIITY



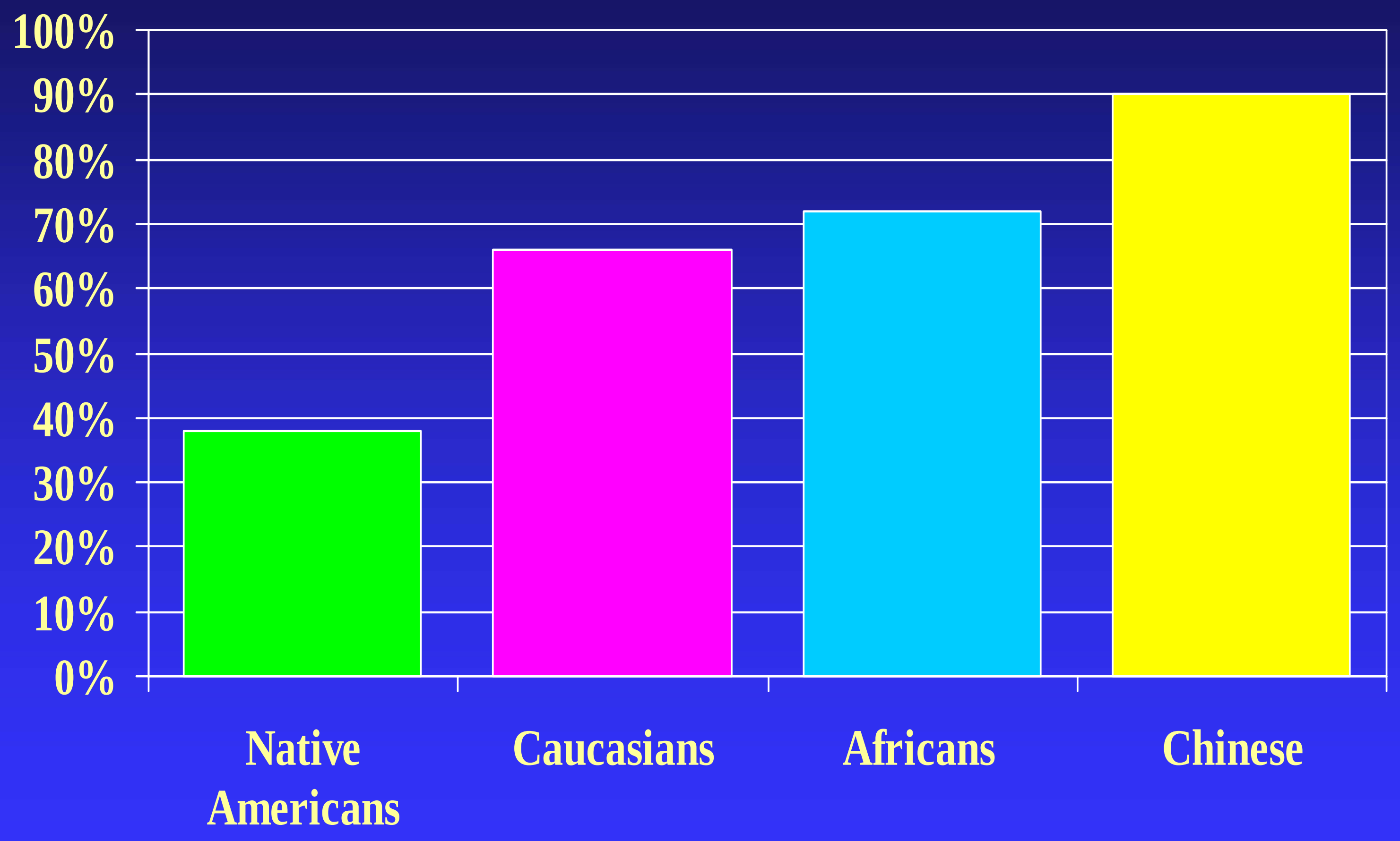
PREVALENCE OF ACETALDEHYDE DEHYDROGENASE (ALDH) BY ETHNCIITY



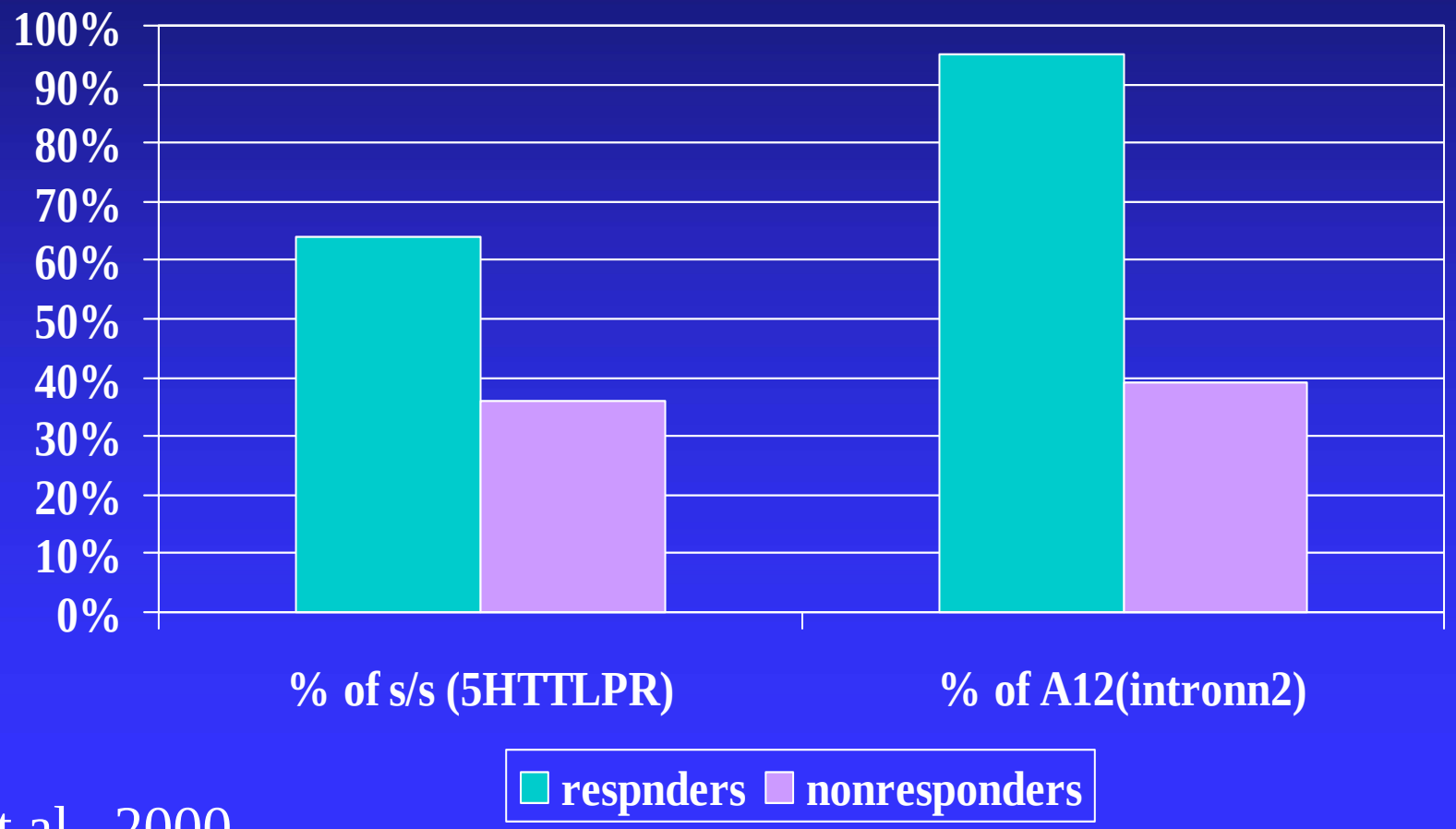
PREVALENCE OF ALCOHOL DEHYDROGENASE (ADH) BY ETHNCIITY



Frequency of the A12 Allele in Intron 2 of the Serotonin Transporter (SERT) in Normal Volunteers

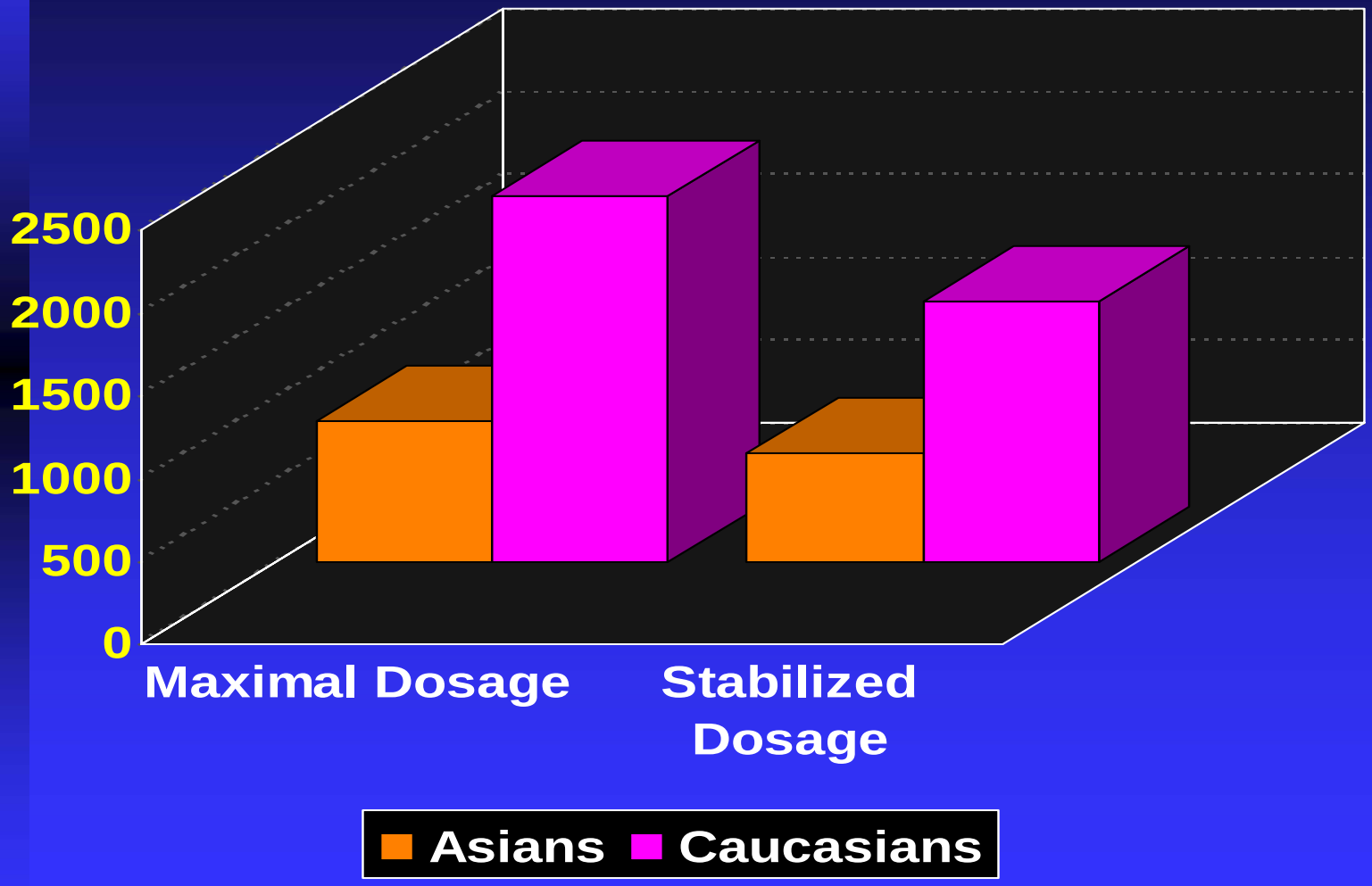


Serotonin Transporter (SERT) and Antidepressant Response in Asians



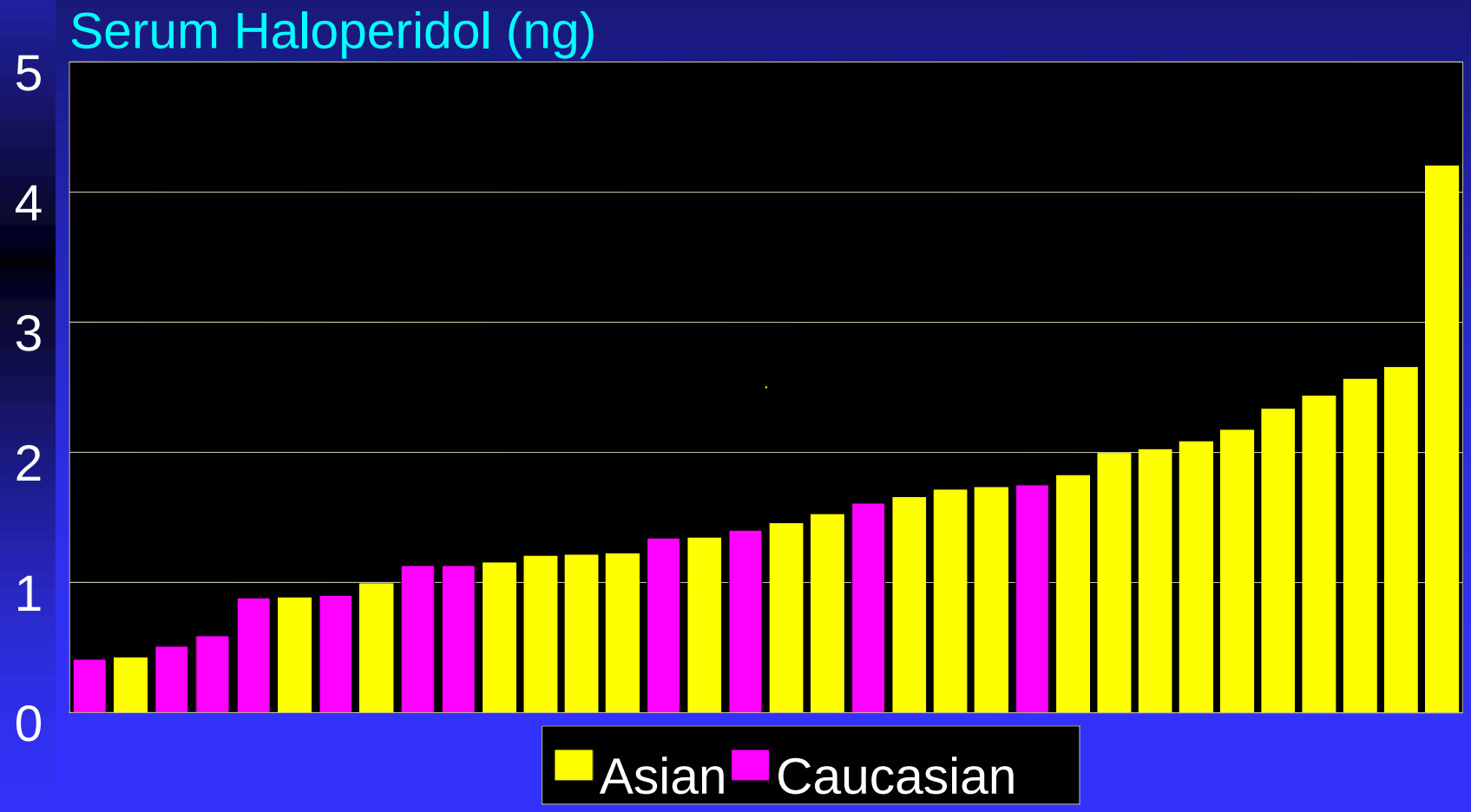
Kim et al., 2000

NEUROLEPTIC DOSAGE FOR HOSPITALIZED PATIENTS: ASIANS VS CAUCASIANS

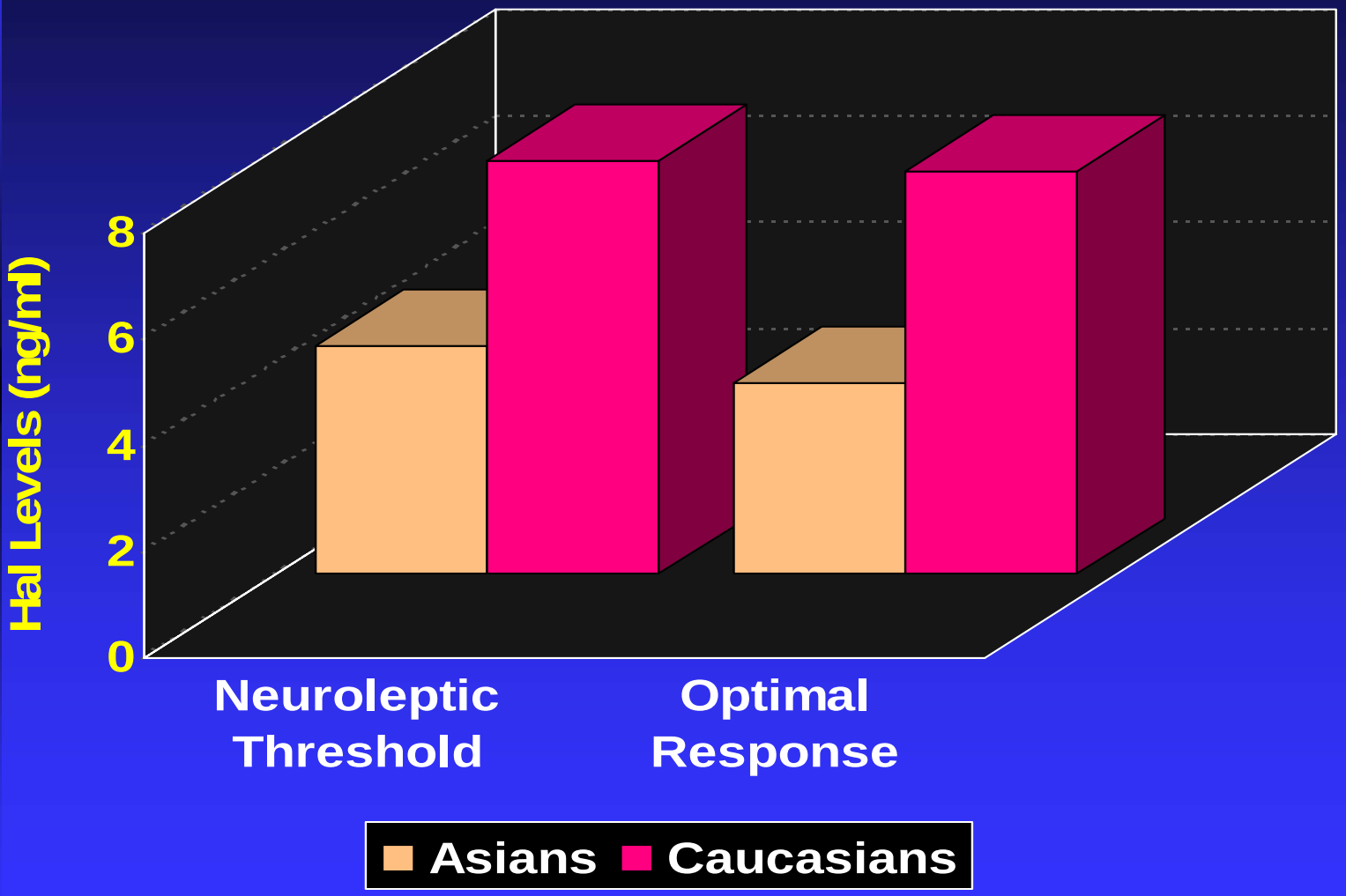


Lin & Finder, Am J Psychiatry 140:490-491, 1983

Maximal Haloperidol ConcentrationAfter 0.5 mg i.m. Haloperidol

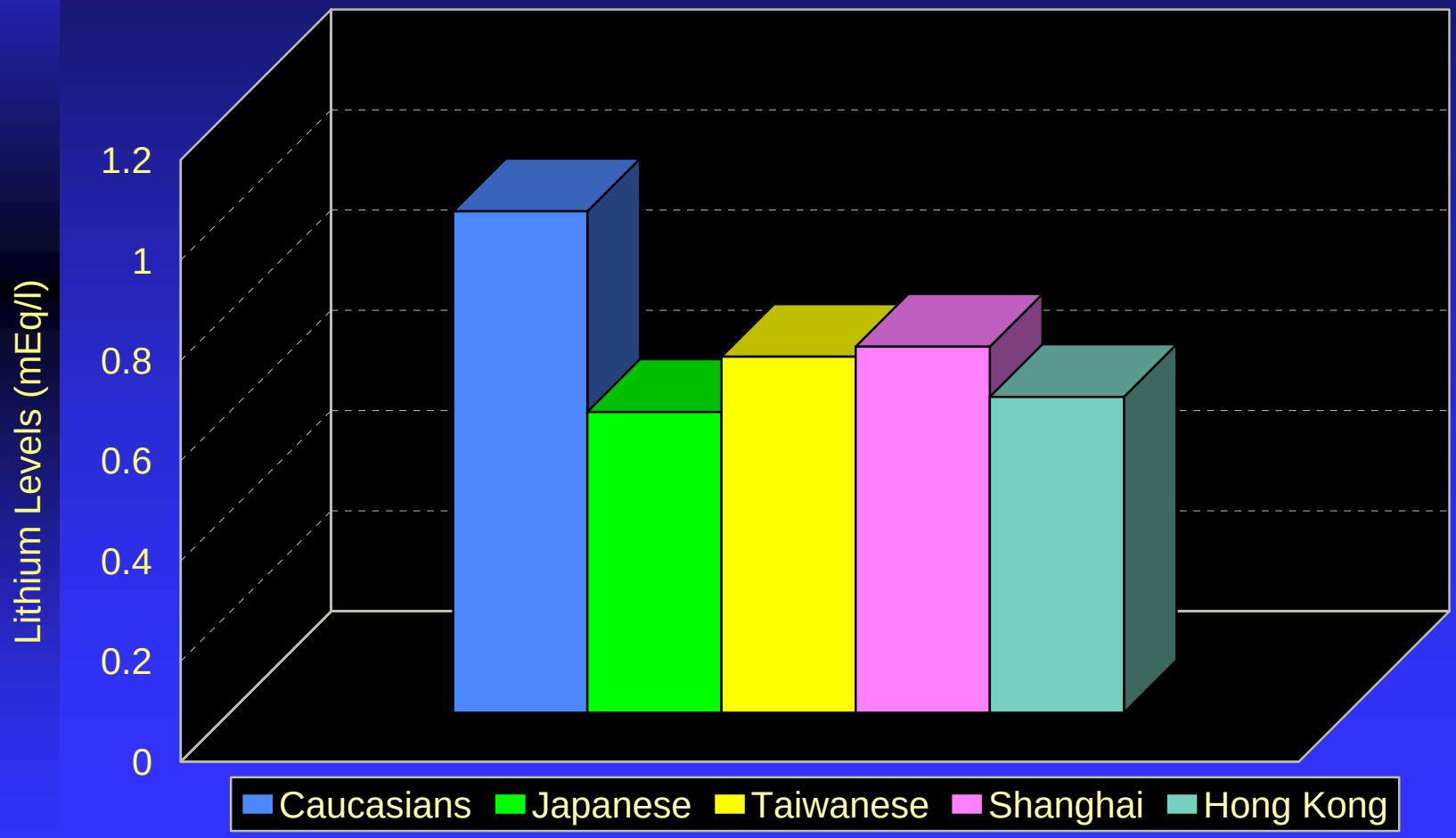


Neuroleptic Dose and Level at the Neuroleptic Threshold and Optimal Response Points for Asian and Caucasian Patients

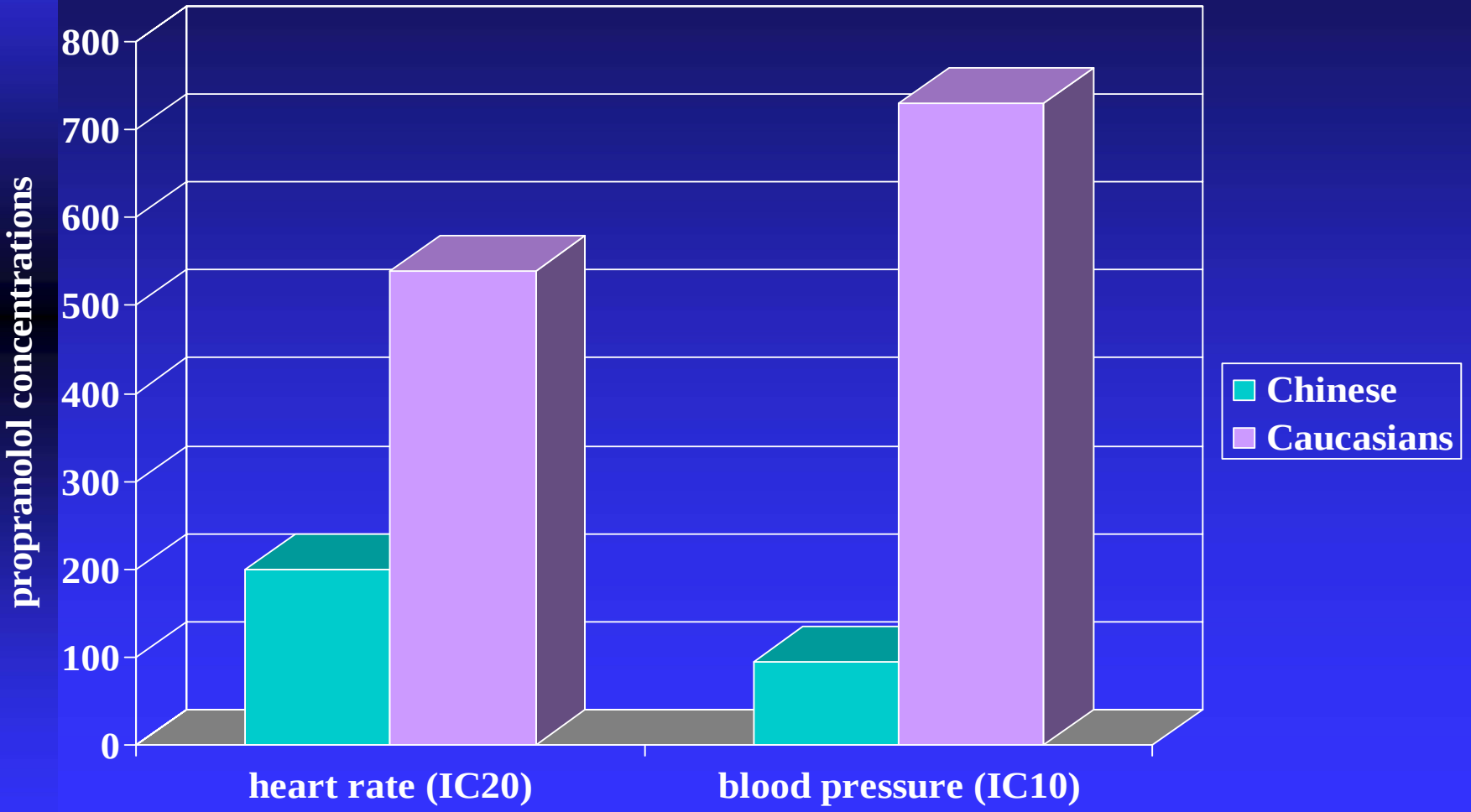


Lin et al. Am J Psychiatry, 146:1307-1311, 1989

Therapeutic Lithium Concentrations



Propranolol Response: Chinese vs Caucasians



Zhou et al., NEJM 320:565-70, 1989

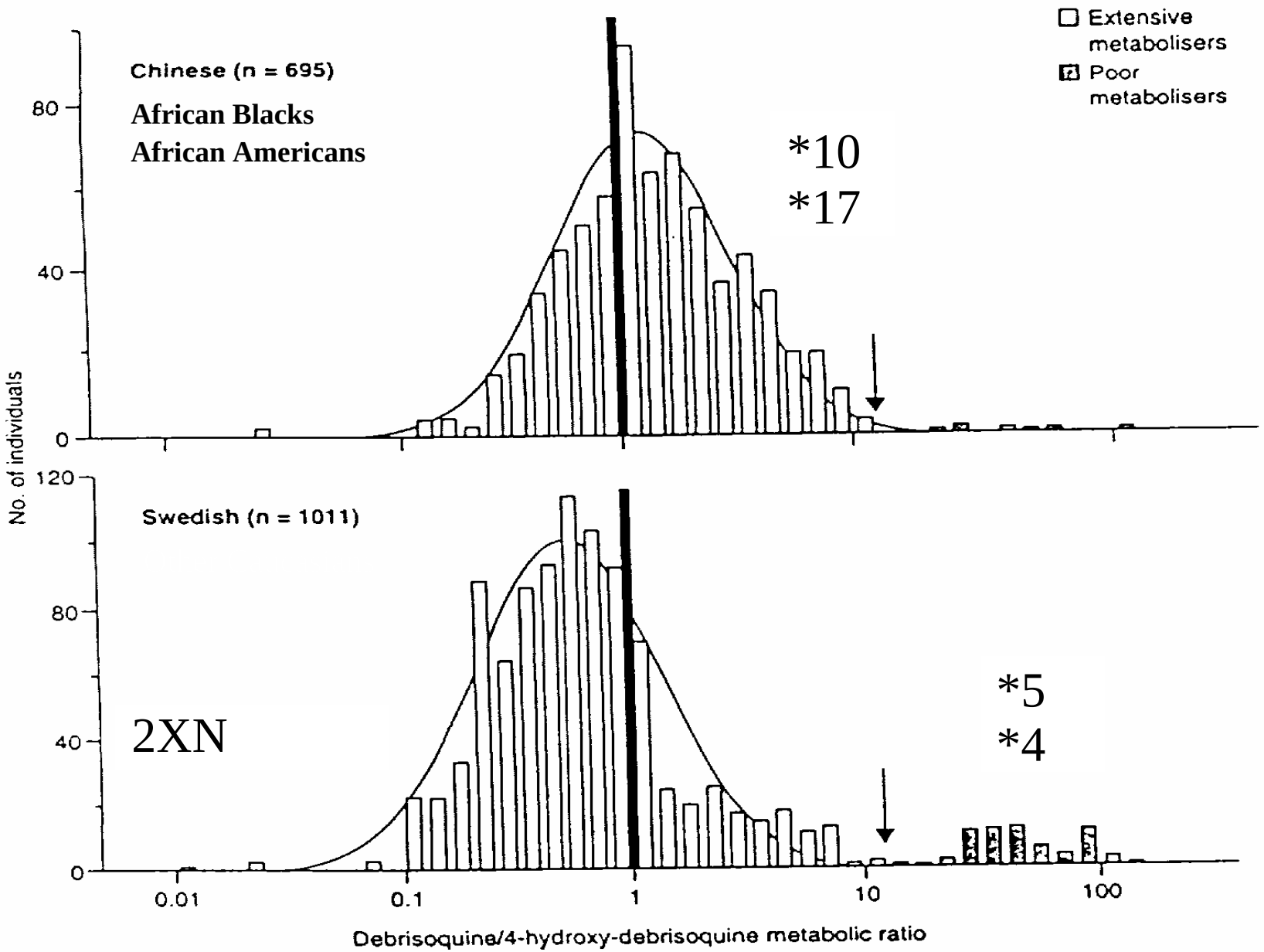


Fig. 2. Distribution of the urinary debrisoquine/4-hydroxy-debrisoquine metabolic ratio (MR) in 695 Chinese and 1011 Swedis Caucasian healthy individuals. The arrows indicate a MR of 12.6, the antimode between extensive metabolisers and poor metab olisers as established in Caucasian populations. A line is drawn at a MR of 1.0. Most Chinese extensive metabolisers have a MI >1, while most Swedish extensive metabolisers have a MR <1 (reproduced from Bertilsson et al.,[14] with permission).