# Drug Abuse and Addictions: Some Scientific Approaches to a Global Health Problem

**Mary Jeanne Kreek, M.D.**
**Professor and Head**
**The Laboratory of the Biology of Addictive Diseases**
**The Rockefeller University**

**NIH-NIDA P60 Center**
**"Treatment of Addictions: Biological Correlates"**

**February 21, 2006**

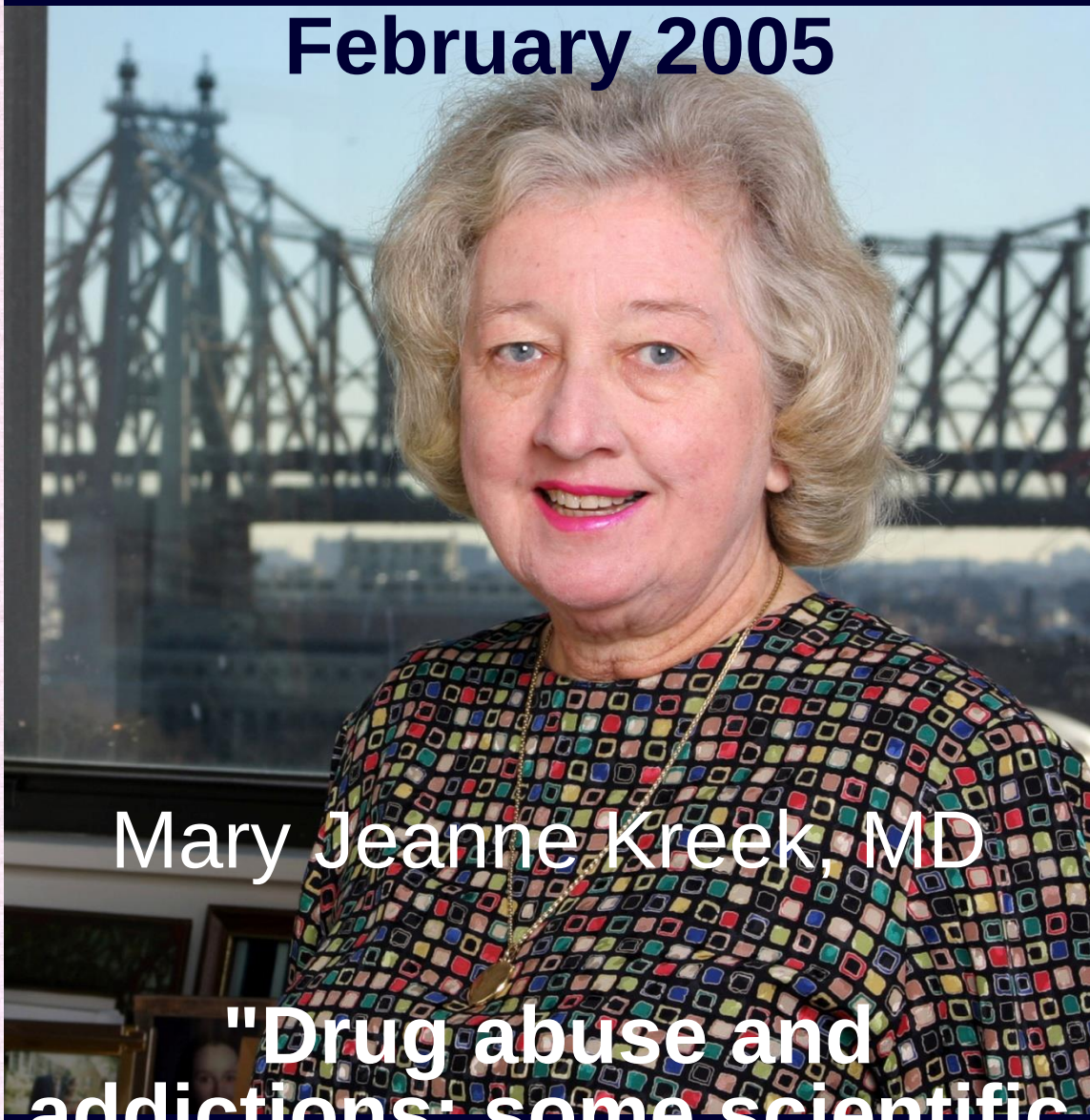
**GRENDIN**
***Host – Dave Alexander***

***funded primarily by NIH-NIDA, NIHCRR and NYS OASAS***

WINDWARD ISLANDS RESEARCH & EDUCATION FOUNDATION

# 6th Annual Lecture

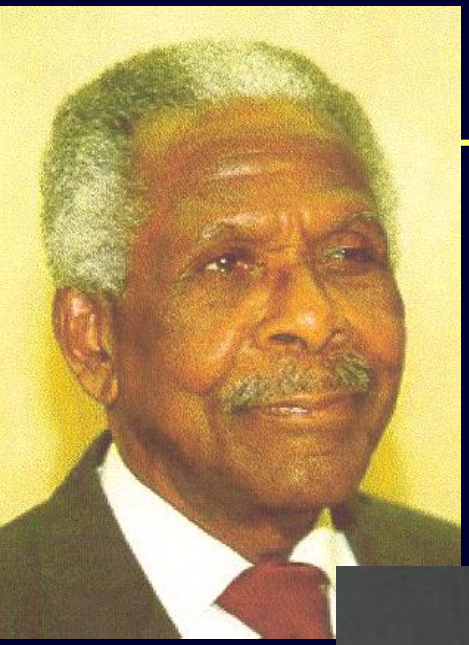
## February 2005



Mary Jeanne Kreek, MD

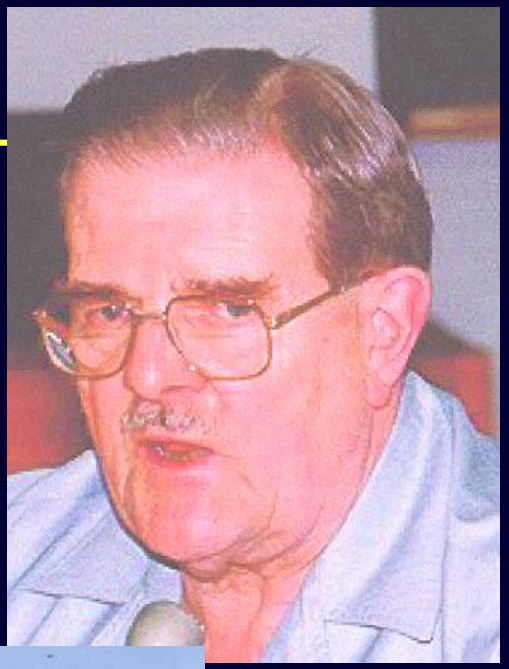
**"Drug abuse and addictions: some scientific approaches to a global**

# Previous WINDREF Speakers



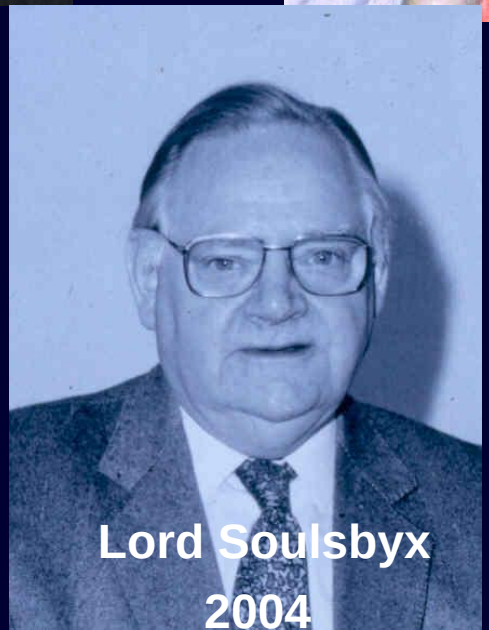
Sir Kenneth Stuart, 2000

Prof Ade Lucas 2001



Lord Walton 2002

Prof David Molyneux 2003



Lord Soulsbyx 2004

# Schaefer-Kreek Family in 1979

# Our 25th Anniversary at St. George's Medical College St. Vincent Campus – 1980-2005

**Robert A. Schaefer, MD**

**Spring Term – 17 Years – 1980 to 1999**
**(1989 school closed; 1994 schedule did not work out)**
**Gastroenterology and Hepatic Diseases**
**10 Lectures (10 days to 2 weeks– February and March)**

**Mary Jeanne Kreek, MD**

**Spring and Fall Terms – 2000 to present**
**Biology, Diagnosis, and Treatment of Addictive Diseases**
**2 campuses – St. Vincent and Grenada (5 to 8 days)**

**30th Anniversary of first visit to Grenada – January, 1970**

# Prevalence of Specific Drug Abuse and Vulnerability to Develop Addictions

**National Household Survey and Related Surveys – 1996 – 2002**

| | |
|---|---|
| Alcohol Use – ever | ~ 177 million |
| Alcoholism | ~ 15 million |
| Cocaine Use – ever | ~ 26 million |
| Cocaine Addiction | ~ 2 to 3 million |
| Heroin Use – ever | ~ 2.5 to 3 million |
| Heroin Addiction | ~ 0.5 to 1 million |
| Illicit Use of Opiate Medication – ever | ~ 4.4 million |
| Resultant Opiate Medication Addiction | ? |

**Development of Addiction After Self Exposure**

| | |
|---|---|
| Alcoholism | ~ 1 in 8 to 1 in 15 |
| Cocaine Addiction | ~ 1 in 8 to 1 in 15 |
| Heroin Addiction | ~ 1 in 3 to 1 in 5 |

*NIDA, SAMHSA Reports, 1998-2005*

To M J Kreek MD
8/22/02
by Mr Dave Alexander

# SITUATION ANALYSIS OF THE DRUG PROBLEM IN GRENADA

*Researched and Written by:*
*Dave Alexander,*
*Drug Avoidance Officer,*
*Drug Control Secretariat,*
*August 2002*

# Types and Quantity of Drugs Confiscated by the Royal Grenada Police Force – 2002

Confiscation of drugs is done both by the Royal Grenada Police Force and the Customs and Excise Department. Drugs confiscated were:

- Cannabis (marijuana)
- Cocaine
- Crack

The following types and quantities of drugs were confiscated:

- Cannabis (marijuana) trees: 247,194
- Cured marijuana: 7,990.57 kgs
- Marijuana cigarettes: 19,788
- Cocaine: 724.74 kgs
- Crack: 8,871 blocks

*Dave Alexander, Drug Avoidance Officer, Drug Control Secretariat, Grenada, 2002*

# Development of Methadone Maintenance Treatment – 1964 Onward

Initial clinical research on mechanisms and treatment using methadone maintenance pharmacotherapy at The Rockefeller Hospital of The Rockefeller Institute for Medical Research (by the mid-1960s, The Rockefeller University) performed by the team of:

**Vincent P. Dole, Jr., M.D.**

Professor & Head of the Laboratory of Physiology and Metabolism (now Professor Emeritus)

**Marie Nyswander, M.D.**

Guest Investigator – Joined Dole Lab in Winter 1964 (now deceased)

**Mary Jeanne Kreek, M.D.**

Guest Investigator – Joined Dole Lab in Winter 1964 (now Professor & Head of Laboratory)

## First publications describing methadone maintenance treatment research

1) 1964: Initial clinical research on development of treatment using methadone maintenance pharmacotherapy and on elucidating mechanisms of efficacy performed at The Rockefeller Hospital of The Rockefeller Institute for Medical Research:
   Dole, V.P., Nyswander, M.E. and Kreek, M.J.: Narcotic blockade. Arch. Intern. Med., 118:304-309, 1966.
   *(also recorded in the Association of American Physicians meeting transcription of discussion)*

2) 1965: Translational applied clinical research performed at Manhattan General Hospital:
   Dole, V.P. and Nyswander, M.E.: A medical treatment for diacetylmorphine (heroin) addiction. JAMA, 193:646-650, 1965.

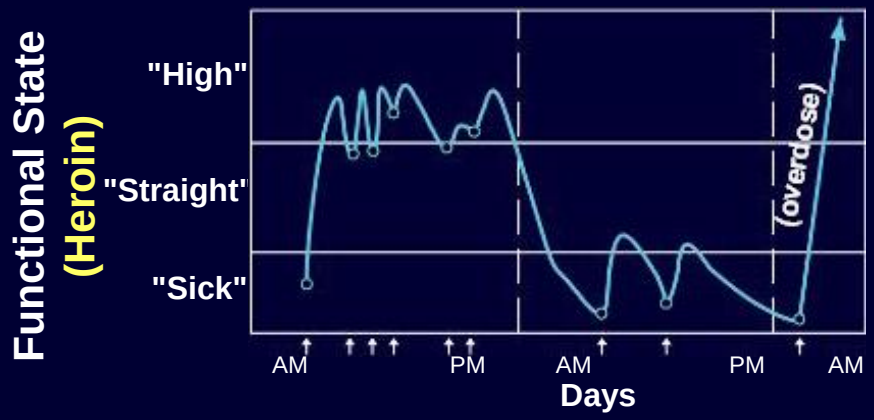
# Hypothesis (1963–1964)

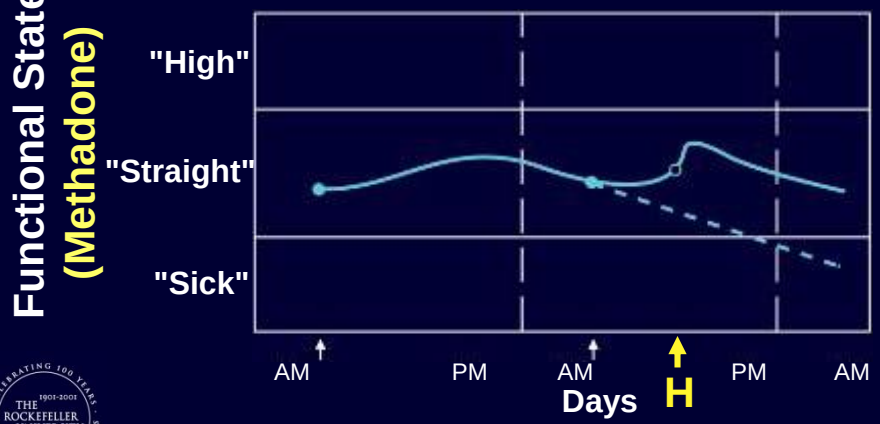
**Heroin (opiate) addiction is a disease – a "metabolic disease" – of the brain with resultant behaviors of "drug hunger" and drug self-administration, despite negative consequences to self and others. Heroin addiction is not simply a criminal behavior or due alone to antisocial personality or some other personality disorder.**



*Dole, Nyswander and Kreek, 1966*

# Impact of Short-Acting Heroin versus Long-Acting Methadone Administered on a Chronic Basis in Humans - 1964 Study and Opioid Agonist Pharmacokinetics: Heroin Versus Methadone



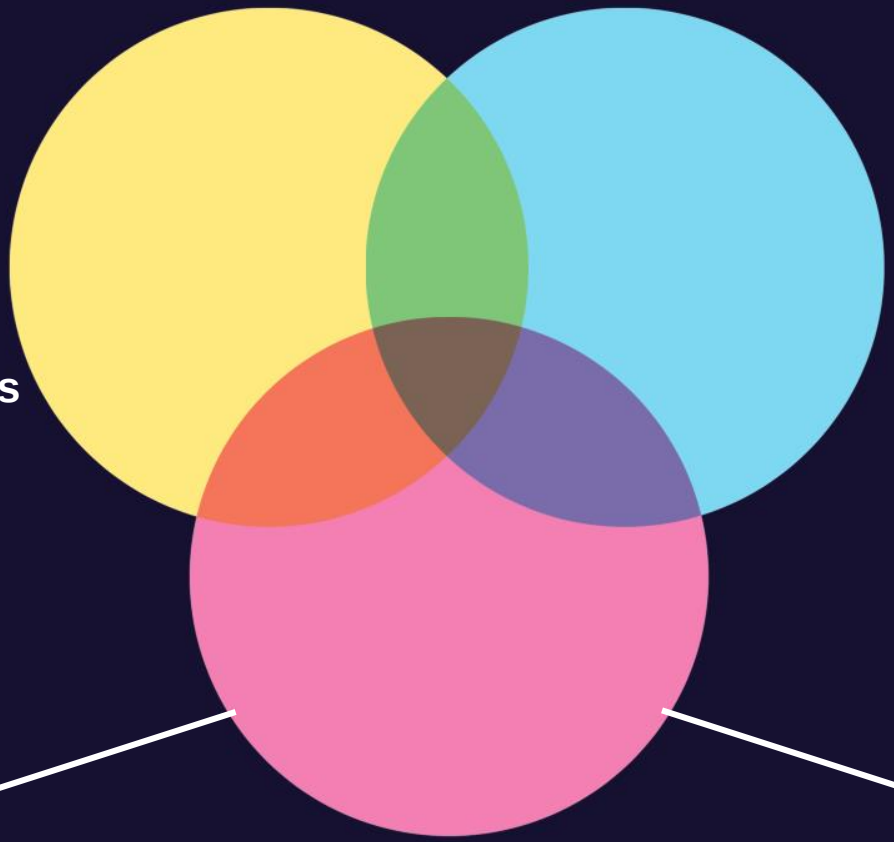




| Systematic Bioavailability After Oral Administration | Apparent Plasma Terminal Half-life ($t_{1/2}$ Beta) | Major Route of Biotrans-formation |
|---|---|---|
| Limited (<30%) | 3m (30m for active 6-acetyl-morphine metabolite) (4-6 for active morphine-6-glucuronide metabolite) | Successive deacetylation and morphine glucuronidation |
| Essentially Complete (>70%) | 24h (48h for active [R](l)-enantiomer) | N-demethylation |

*Dole, Nyswander and Kreek, 1966; Kreek et al., 1973; 1976; 1977; 1979; 1982; Inturrisi et al, 1973; 1984*

# Factors Contributing to Vulnerability to Develop a Specific Addiction

use of the drug of abuse essential (100%)



**Genetic (25-60%)**
- DNA
- SNPs
- other polymorphisms

**Environmental (very high)**
- prenatal
- postnatal
- contemporary
- cues
- stress and stressors

- mRNA levels
- peptides
- proteomics

**Drug-Induced Effects (very high)**

- neurochemistry
- behaviors

*Kreek et al., 2000*

# Primary Site(s) of Major Drugs of Abuse

| | | |
|---|---|---|
| **Heroin** | ***Depressant*** | • **Acts primarily on endogenous opioid system**<br>• **Also affects dopaminergic system** |
| **Cocaine** | ***Stimulant*** | • **Acts primarily on dopaminergic system, as well as on serotonergic and noradrenergic systems**<br>• **Also affects opioid system** |
| **Alcohol** | ***Stimulant & Depressant*** | • **Undefined primary site of action**<br>• **Affects dopaminergic, serotonergic and opioid systems** |



***Kreek, 1978, 1987, 2003***

# "Craving" or "Drug Hunger": Hypothesis
## (with or without drug seeking and drug self-administration)

### Neurochemical mediators of "rewarding" or "reinforcing" effects of drugs of abuse

- Dopamine acting at dopamine $DA_1$-like and $DA_2$-like receptors
- Mu opioid receptor agonists acting at mu opioid receptors (e.g., beta-endorphin and enkephlins)
- CRF and ACTH in stimulant and stimulant-depressant addicts only (e.g., cocaine and alcoholism)
- +/- serotonin, +/- norepinephrine

### Neurochemical counter-modulators of "rewarding" or "reinforcing" effects

- Kappa opioid receptor agonists acting at kappa opioid receptors (e.g., dynorphins)
- Orphanin/nociception acting at orphan opioid-like receptors
- CRF and ACTH in opiate addicts (e.g., heroin)
- +/- GABA, +/- glutamate

**Chronic drug use leads to persistent neurochemical and neurobiological changes, with blunting of the "rewarding" components and persistence of the counter-modulatory components (lowered dopaminergic tone and relative "endorphin deficiency"), which, when coupled with learning and memory, contribute to the resultant "drug craving" and "drug hunger."**

*Kreek, 2003*

# Hypothesis: Genetic Variability and the Opioid System

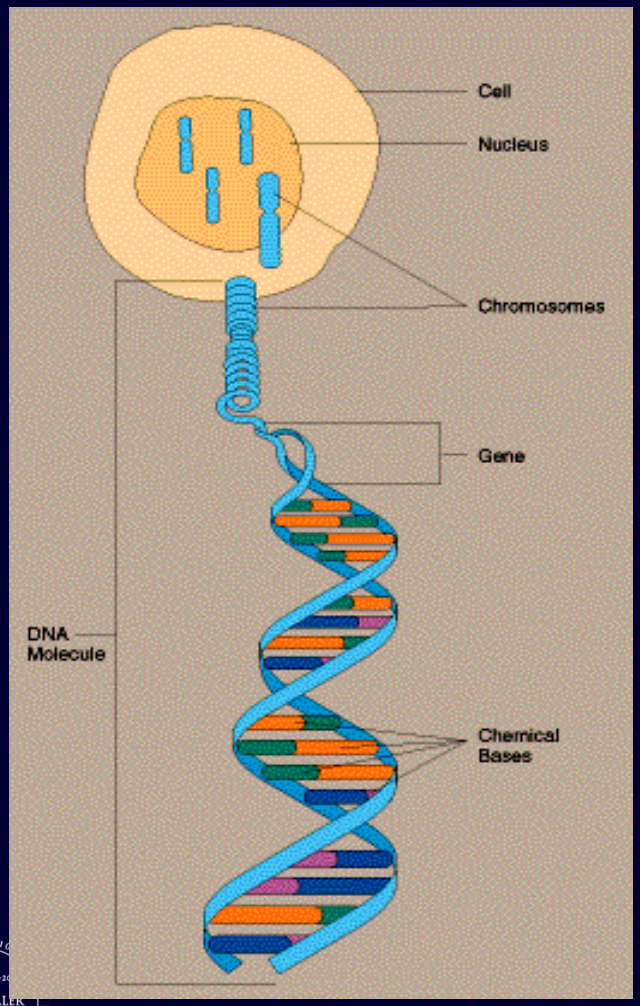
**Some of the individual genetic variability in susceptibility to the development and persistence of, or relapse to, opiate addiction may be due to polymorphisms of the mu opioid receptor.**

**Also, individual differences in responses to endogenous opioids ("physiogenetics") or pharmacotherapies ("pharmacogenetics") may be mediated by variant forms of the mu opioid receptor.**



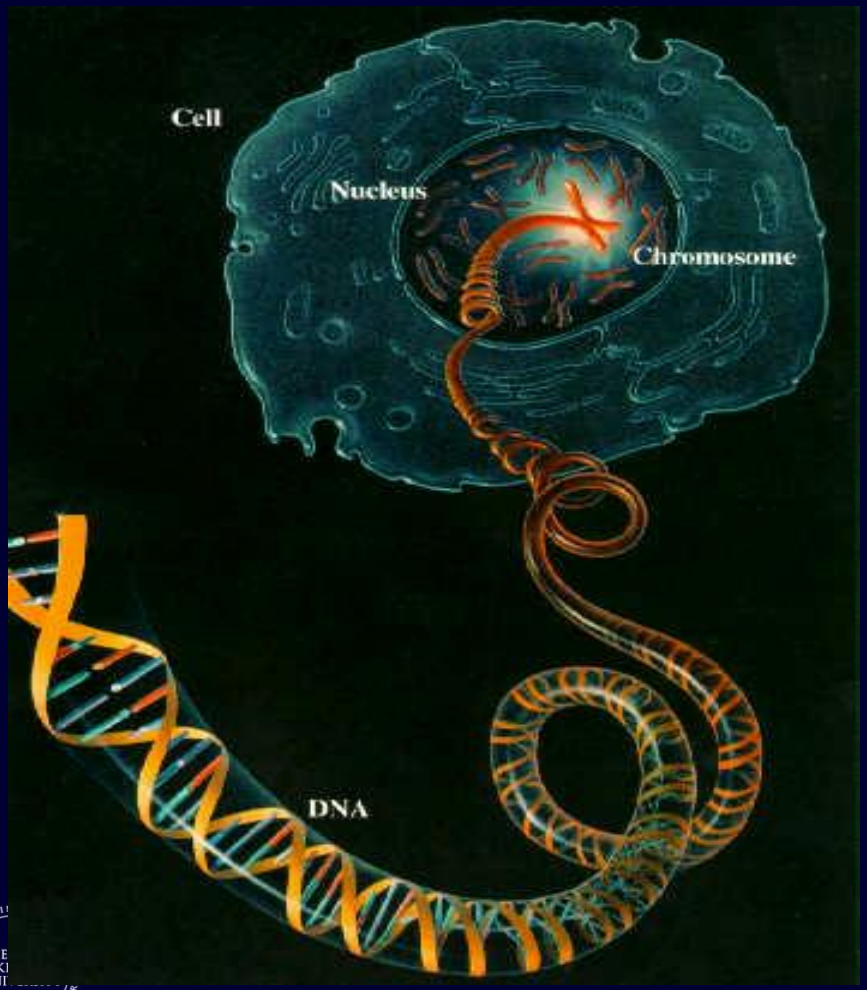
*LaForge, Yuferov and Kreek, 2000*

# Basic Principles: Genes




- Genes are functional units of DNA. Most genes contain the information for making a specific protein.
- Proteins are the basic structural and functional molecules of living things. They may differ somewhat from person to person, resulting in individual variation.
- Gene variants determine the form of a protein that a person has.
- Genes for specific proteins have specific locations on the chromosomes.

# The Human Genome
## (as currently understood)




- In the human genome, there are ~3 billion bases (nucleotides)
- In humans, there are estimated to be ~25,000 genes (many but not all identified and annotated)
- Each gene is a sequence of bases or nucleotides

# Human Gene Diversity is One Basis of Variations and Differences in Humans

**SNPs and Other Polymorphims (i.e., allelic variants of genes):**

- **Usually neither "good" nor "bad"**
- **May (or may not) have any functional significance (e.g., yield different peptides and proteins; alter levels of gene expression)**
- **May (or may not) contribute to altered response to therapeutic agents, i.e., medications, "pharmacogenetics" and "pharmacogenomics" or altered response to endogenous peptides (e.g., hormones, enzymes)– "physiogenetics" and "physiogenomics"**



*Kreek, 2000*

# Association Between a Functional Polymorphism in the mu Opioid Receptor Gene and Opiate Addiction in Central Sweden

| Genotype | All Subjects | | Swedish with Both Parents Swedish | |
|---|---|---|---|---|
| | Controls (n=170) | Opiate Dependent (n=139) | Controls (n=120) | Opiate Dependent (n=67) |
| A/A | 147 (0.865) | 98 (0.705) | 104 (0.867) | 46 (0.687) |
| A/G | 21 (0.123) | 39 (0.281) | 15 (0.125) | 19 (0.283) |
| G/G | 2 (0.012) | 2 (0.014) | 1 (0.008) | 2 (0/030) |

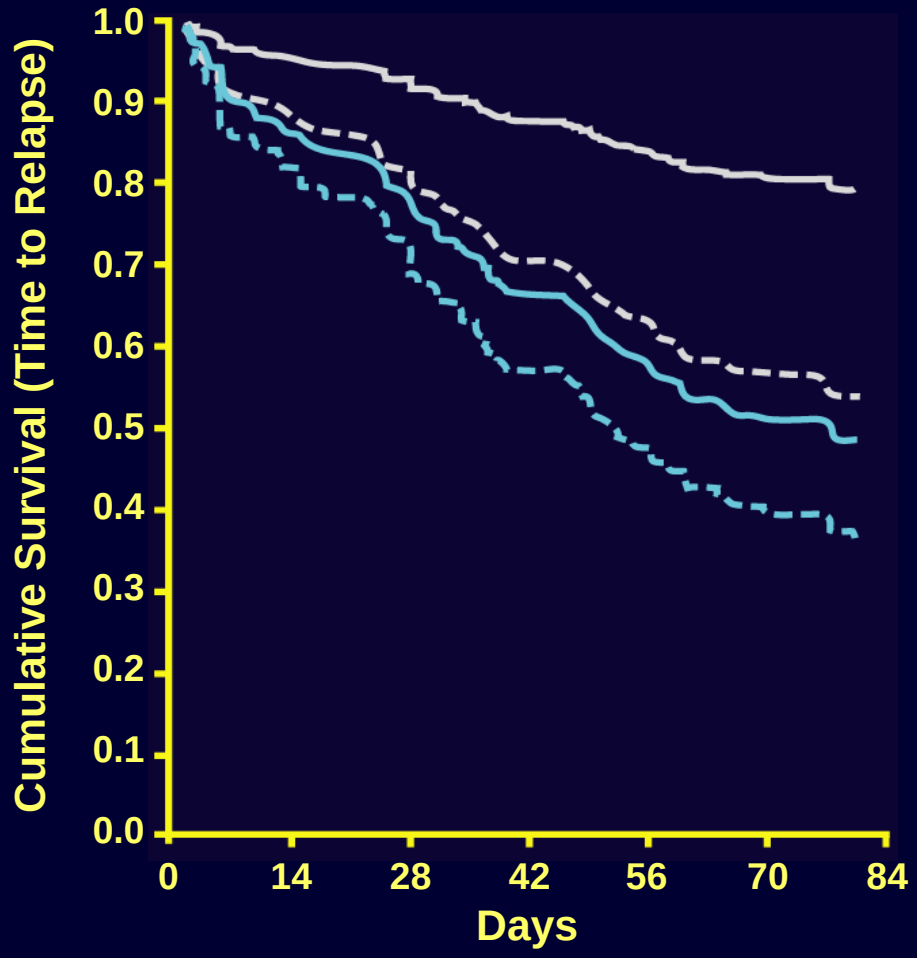
RR = 2.86 $\chi^2_{(1)}$= 13.403 P = 0.00025* RR = 2.97 $\chi^2_{(1)}$= 8.740 P = 0.0031*

| | Opiate Dependent (n=139) | Control (n=170) |
|---|---|---|
| G/G; A/G | 41 | 23 |
| A/A | 98 | 147 |
| 118G Allele Frequency | 0.155 | 0.074 |

Thus, in the entire study group in this central Swedish population,
Attributable Risk due to genotypes with a G allele in this population: 18%
Attributable Risk due to genotypes with a G allele in Swedes w/ Swedish parents: 21%
(with confidence interval ranges from 8.0 to 28.0%)

*Bart G , Heilig M, LaForge KS… Ott J, Kreek MJ, et al., Molecular Psychiatry, 9:547-549, 2004*

# "Pharmacogenetics"— Naltrexone Treatment Response: Survival Analyses for Time to Relapse in Subjects With One or Two Copies of the Asp40 Allele vs. Those Homozygous for the Asp40 Allele by Medication Group




Naltrexone/
Asp40 Allele (A/G, G/G) (n=23)

Naltrexone/
Asn40 Allele (A/A) (n=48)

Placebo/
Asp40 Allele (A/G, G/G) (n=18)

Placebo/
Asn40 Allele (A/A) (n=41)

*Oslin, Berrettini, Volpicelli, Kranzler, O'Brien, et al., 2003*

# Association Between a Functional Polymorphism in the mu Opioid Receptor Gene and Alcoholism in Central Sweden

| | Swedish with two Swedish parents | | Non-Swedish without Swedish Parents | |
|---|---|---|---|---|
| | Alcohol Dependent (n=193) | Control (n=120) | Alcohol Dependent (n=196) | Control (n=50) |
| A118 | 158 | 104 | 141 | 43 |
| A118G, G118G | 35 | 16 | 55 | 7 |

OR=1.92 $\chi^2_{(1)} = 7.18$, p = 0.0074

| | Alcohol Dependent (n=389) | Control (n=170) |
|---|---|---|
| G/G; A/G | 90 | 23 |
| A/A | 299 | 147 |
| 118G Allele Frequency * | 0.125 | 0.074 |

** Overall 118G Allele Frequency = 0.109*

**Thus, in the entire study group in this central Swedish population:**

**Attributable Risk due to genotypes with a G allele: 11.1%**

**(with confidence interval ranges from 3.6 to 18.0%)**

*Bart G , Kreek MJ, LaForge KS… Ott J, Heilig M, et al., Neuropsychopharmacology, 2004*

# Opioid System Polymporphisms in Relation to Specific Addictive Diseases

| Opioid Receptor Genes | Opioid Peptide Genes |
| --- | --- |
| Mu Opioid Receptor | Dynorphin |
| Kappa Opioid Receptor | Enkephalin |



*Kreek, 2003*

# Genetics Research—
# ? Why Grenada
# (? Why St. Vincent)

**Unique Patterns of Exposure to Drugs of Abuse:**

**Alcohol/ Nicotine**
- worldwide
- legal
- omnipresent

**Cannabis**
- worldwide
- illegal
- local/regional culture

**Cocaine**
- worldwide
- illegal
- trafficking through SE Caribbean

**BUT:**

**NO Heroin**

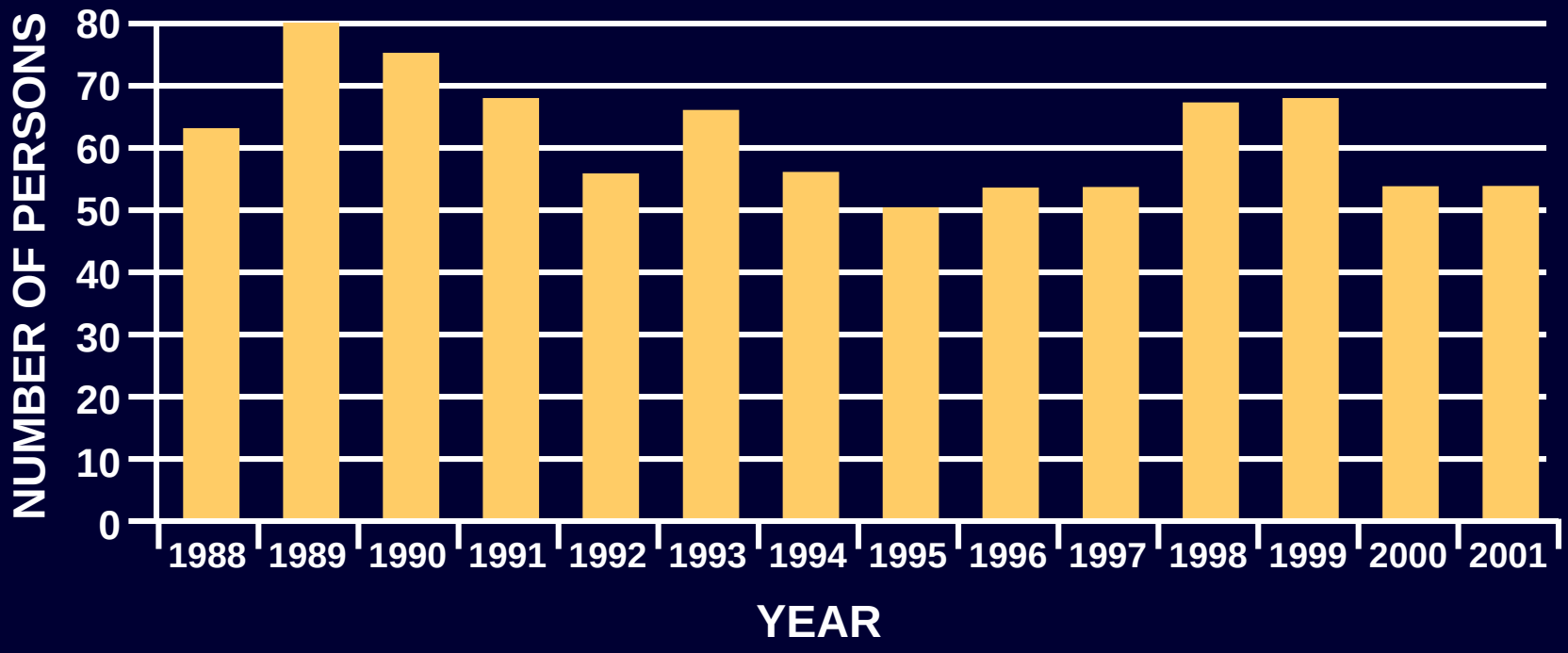
**NO Illicit Prescription Opiate Abuse**

**NO Other Illicit Opiate Use/ Access**

*Kreek, 2004*

# Outside Cartlon House
# August 30, 2004

# Number of Persons Admitted to Carlton House, 1988 to 2001




*Dave Alexander, Drug Avoidance Officer, Drug Control Secretariat, Grenada, 2002*

# Carlton House Treatment Centre 2002; 2004

- Males: 791
- Females: 58
- 93% of admissions were males.
- 7% of admissions were females.
- The drugs of choice for these patients were:
  - Alcohol (2004 – 11)
  - Marijuana (2004 – 3)
  - cocaine/crack (2004 – 5)
- Poly drug use (combinations of above) by many of these patients prior to admission to treatment is prevalent (2004 – 19).

*Dave Alexander, Drug Avoidance Officer, Drug Control Secretariat, Grenada, 2002*

# Human Molecular Genetics Research in Grenada – WINDREF

**P.I.Mary Jeanne Kreek, MD**
Professor and Head
The Laboratory of the Biology of Addictive Diseases
The Rockefeller University
**Co-P.I. Calum Macpherson, PhD (DIC)**
**Co-P.I. Trevor Noel, BSc (Ireland), MPH (St. George's)**
**Co-P.I. Mr. Dave Alexander, Drug Avoidance Officer for Grenada**

(facilitated by Dr. Ed Johnson, Dr. Hans Baer, Dr. Al Pensick, Dr. Jeff Johnston)

| | |
|---|---|
| Planning Phase | 2000-2003 |
| Ethics and IRB Review | 2003 |
| Final Approval | January, 2004 |
| Scheduled to Begin | September 20, 2004 |

# Collaborators in Grenada

**Mary Jeanne Kreek, MD**
Professor and Head of Laboratory
The Rockefeller University

**Dr. Calum Macpherson, PhD**
Director, WINDREF

**Mr. Trevor Paul Noel, BSc, MPH**
Assistant Director, WINDREF

**Mr. Dave Alexander**
Drug Avoidance Officer

**Hon. Ann David Antoine**
Minister of Health

**Mr. Thorne Roberts**
Former Director of Carlton House

**Research Nurses from the Granada School of Nurses**
**Staff of the Ministry of Health**
**Staff of the Ministry of Education**

# Hurricane Ivan
# September 7, 2004

# Genetics Research—
# ? Why Grenada

There was/ is (?) a wonderful facility, Carlton House, for the treatment of drug addiction, but it was destroyed when Hurricane Ivan hit Grenada on September 7, 2004. It now needs to be rebuilt.

Amendment – move to Rathdune, January, 2005

Until the facility is rebuilt, we must start our work now:

? in hospitals

? on parole groups

? other

# MT. GAY HOSPITAL, GRENADA (Rathdune Psychiatric Unit)

# Genetics Research 2005-2006

- Studies now conducted at Rathdune at Mt. Gay
- 24 volunteer subjects ascertained to date.

# LABORATORY OF THE BIOLOGY OF ADDICTIVE DISEASES, 2005

## Mary Jeanne Kreek, MD – Professor and Head

***BACK ROW:*** *Matthew Swift, Lauren Bence, Jason Choi, Laura Nunez, Jannese Rojas, Kitt Lavoie, Susan Russo, Nicole Dankert, Julie Allen, Johannes Adomako*

***MIDDLE ROW:*** *Matthew Randesi, Alexis Bailey, Brian Reed, Scott Kellogg, Heather Hofflich, Charles Lilly, Kathy Bell, Elizabeth Ducat*

***FRONT ROW:*** *Stefan Schlussman, Eduardo Butelman, K. Steven LaForge, Ann Ho, Mary Jeanne Kreek, Vadim Yuferov, Gavin Bart, Dmitri Proudnikov, Yan Zhou*

***NOT PICTURED:*** *David Nielsen, Lisa Borg, Yong Zhang*