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HYPOTHESIS: 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.

Vincent P. Dole, Jr., MD; Marie Nyswander, MD; and Mary Jeanne Kreek, MD

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:
   *(also recorded in the Association of American Physicians meeting transcription of discussion)*

2) **1965**: Translational applied clinical research performed at Manhattan General Hospital:
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

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

Methadone Maintenance Treatment for Opiate (Heroin) Addiction – 2013

Number of patients currently in treatment: ~1 million worldwide

- USA: ~260,000
- Europe: ~500,000
- Rest of world: ~250,000

Efficacy in “good” methadone treatment programs using adequate doses (80 to 150mg/d):

Voluntary retention in treatment (1 year or more) 50 – 80%
Continuing use of illicit heroin 5 – 20%

Actions of methadone treatment:

- Prevents withdrawal symptoms and “drug hunger”
- Blocks euphoric effects of short-acting narcotics
- Allows normalization of disrupted physiology

Mechanism of action: Long-acting medication (24h half-life for racemate in humans) provides steady levels of opioid at specific receptor sites.

- Methadone found to be a full mu opioid receptor agonist which internalizes like endorphins (beta-endorphin and enkephalins)
- Methadone also has modest NMDA receptor complex antagonism

Kreek, 1972; 1973; 2013
1981-1983: Discovery of Second Risk Group for HIV-1 and Effectiveness of Methadone Treatment for Prevention

- Dr. M.J. Kreek, working with two methadone maintenance treatment programs associated with her Laboratory at The Rockefeller University (headed by Dr. Elizabeth Khuri and the late Dr. Aaron Wells) evaluated and cared for maintenance patients who also developed unexplained lymphadenopathy, profound weight loss, and often death, frequently attributed to hepatitis B or hepatitis B+Delta.

- In 1983, Dr. Don Des Jarlais, a colleague, then with the New York State Division of Substance Abuse Services, approached Dr. Kreek as a colleague, aware of the fact that she had prospectively collected, anonymized, and stored blood specimens from subjects coming in for treatment or neurobiological research from 1969 onward, and requested that she share those unique specimens with the CDC, then developing an antibody test for this “wasting disorder.”

Kreek, THS 2013

Percent of IV Drug Users Infected with HIV-1

Des Jarlais et al., 1984-1989-present; Kreek et al., 1984-1990-present; THS 2013
Untreated, street heroin addicts: Positive for HIV-1 antibody

Methadone maintained since before 1978 (beginning of AIDS epidemic in New York City), and staying in continuous treatment: less than 10% positive for HIV-1 antibody
**Effect of Drug Abuse Treatment (Methadone Maintenance) on “LAV” (HIV-1) Seropositivity Rates in IV Drug Users – 1985**

All subjects were male, heterosexual IV drug users in New York City. Treatment provided was methadone maintenance.

**HIV Seropositivity Rates**

- **Not in Treatment (Tx):** 47%
- **Currently in Tx:** 23%
- **In Tx 5 Years:** 17%
- **No Needle Use Since Admission to Tx:** 12.5%
- **In Tx 5 Years & No Needle Use Since Admission to Tx:** 6%

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Antibodies to a Retrovirus Etiologically Associated with Acquired Immunodeficiency Syndrome (AIDS) in Populations with Increased Incidences of the Syndrome

HIV-1 Infection Among Intravenous Drug Users in Manhattan, New York City, From 1977 Through 1987

Don C. Des Jarlais, PhD; Samuel R. Friedman, PhD; David M. Novick, MD; Jo L. Sotheran, MA; Pauline Thomas, MD; Stanley R. Yancovitz, MD; Donna Mildvan, MD; John Weber, RPA; Mary Jeanne Kreek, MD; Robert Maslansky, MD; Sarah Bartelme, RN; Thomas Spira, MD; Michael Marmor, PhD
“Antibody to LAV, the putative agent of AIDS, in parenteral drug abusers and methadone-maintained patients: Abstract of clinical research findings: Therapeutic, historical, and ethical aspects.”

Acquired immunodeficiency syndrome and infection with hepatitis viruses in individuals abusing drugs by injection

D. M. NOVICK
The Rockefeller University and Beth Israel Medical Center, New York, N.Y., United States of America
I. KHAN
Division of Mental Health, World Health Organization, Geneva, Switzerland
M. J. KREEK
The Rockefeller University, New York, N.Y., United States of America

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1983-1986-present: Sharing of Discovery of Second Risk Group for HIV-1 and Effectiveness of Methadone Treatment for Prevention

- Sharing of discovery of second risk group for HIV-1 infection and effectiveness of methadone maintenance treatment for opiate addiction to prevent further cases (cessation or marked reduction of illicit drug use and information about importance of not sharing blood-tinged needles, syringes, and related paraphernalia).

- **Summer 1984** – Information shared in Washington and in Geneva (MJ Kreek with D Des Jarlais and MJ Kreek alone)

- **Summer 1985** – Information shared with Sweden, along with strong recommendation to reopen and enlarge methadone maintenance treatment (MJ Kreek, *Stockholm* and *Uppsala*)

- **1986-1989** – Training two physician-scientists from Israel at the Laboratory of the Biology of Addictive Diseases at The Rockefeller University and our affiliated treatment clinics (and meetings in *Jerusalem* and *Tel Aviv*, MJ Kreek, Miriam Ochshorn (Adelson (1986-89) and Gershon Bodner (1989-92))
Methadone Maintenance Programs in Sweden

To the Editor.—I write this letter as the medical director of one of the two methadone maintenance treatment programs currently active and caring for former heroin addicts in Sweden. I was invited to give the keynote address at the opening session of the 5th Annual Northeastern Regional Methadone Maintenance Conference in New York on November 28, 1988. I was deeply concerned when my audience in New York showed me the article in the November 25 issue of JAMA stating that Sweden “has effectively banned it, after closing the country’s single program,” referring to methadone maintenance treatment. ¹

The facts are that our (then sole) methadone maintenance program in Uppsala, Sweden, was closed temporarily for admittance of new patients from 1979 to 1984, which was disastrous to the 98 heroin addicts on the waiting list: 39 (40%) died during that period (drug-related deaths). Conversely, the patients who had been admitted to treatment prior to 1979 were allowed to stay in treatment. A recent study, conducted by our group at Uppsala and presented in June 1988 at the International AIDS Meeting at Stockholm, Sweden, showed that these fortunate former heroin addicts in continuous effective methadone maintenance treatment escaped human immunodeficiency virus infection, a finding similar to that made by Novick et al. ² Recently, the methadone maintenance program was officially allowed to expand from one national program divided into three regional programs. Our original program remains in Uppsala, a second regional program is in Stockholm, and a third is currently in the process of opening in the south of Sweden.

Olof Blix, MD, PhD
University of Uppsala (Sweden)

Swedish Methadone-Assisted Rehabilitation Program (MARP) – 1966 to 1986; 2013

Special study of 34 subjects fulfilling MARP admission criteria:
17 received methadone, 17 were followed on no medication.
6-year follow-up showed:

- 6 of 17 controls died within 5 years (73x expected death rate of controls compared to that expected for age group [20-24 years])
- 8 of control group applied and entered methadone treatment after 2 years of study; 2 applied later
- 81% of methadone-treated group became free of illicit drug use

Study of all 174 heroin addicts admitted to MARP in 20 years:

- 75% retained in treatment one year or more; stopped illicit drug use
- 25% expelled from program—violation of rules
- 6% after long-term treatment became and remained medication and illicit drug-free

Currently – 2013 – approximately 4500 patients are in the combined methadone/ buprenorphine programs in Sweden.

Gronbladh & Gunne, Drug Alcohol Depend. 24: 31-37, 1989; THS 2013
### AIDS and IV Heroin Addicts: The Preventive Effect of Methadone Maintenance in Sweden

<table>
<thead>
<tr>
<th></th>
<th>New Patients</th>
<th>HIV+</th>
<th>Refusal of Testing</th>
<th>HIV+%</th>
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</thead>
<tbody>
<tr>
<td>Admitted before 1983</td>
<td>67</td>
<td>2</td>
<td>2</td>
<td>3%</td>
</tr>
<tr>
<td>Limited number of persons admitted to Methadone Treatment, 1983-1987 (government mandate)</td>
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<tr>
<td>Admitted 1984-1986</td>
<td>32</td>
<td>5</td>
<td>0</td>
<td>16%</td>
</tr>
<tr>
<td>Treatment programs reopened</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Admitted 1987</td>
<td>60</td>
<td>34</td>
<td>0</td>
<td>57%</td>
</tr>
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*Blix and Gronbladh, 1988; THS 2013*
# International Prevention Efforts Using Methadone Maintenance Treatment

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Replication of an Effective Opiate Addiction Pharmacotherapeutic Treatment Model: Minimal Need for Modification in a Different Country

Miriam O. Adelson, MD
Rachel Hayward, MEd
Gershon Bodner, MD
Avi Bleich, MD
Marc Gelkopf, MA
Mary Jeanne Kreek, MD

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ABSTRACT. Objective: To determine whether we can replicate, with a similar success, an effective USA model clinic for opiate addiction in another country in spite of major geographical, linguistic and cultural differences.

Design: Prospective data on demographic and other factors relating to addiction and treatment were collected, since the establishment of the clinic in July 1993.

Setting: New outpatient model methadone maintenance and research clinic for 120-150 patients, affiliated with a major university hospital in Tel Aviv, Israel.

Patients: A total of 212 patients with opiate addiction were admitted to clinic and followed from July 1, 1993 until July 1, 1997.

Main Outcome Measures:

1. The overall retention and one year retention rate for all patients admitted since July 1993.
2. The prevalence of patients with no evidence of illicit opiate use, after both one and one and a half years in treatment.

Results: The overall retention in treatment, irrespective of time in treatment, is 67.9%. The one-year retention rate for all patients admitted since the clinic was opened in July 1993 is 72.5%. After one year in treatment 58.8% (n = 131) of our patients had no further evidence of illicit use of opiates in urine, and after one and a half years of treatment 71.2% (n = 104) had no evidence of illicit opiates use.

Conclusion: We have succeeded in replicating a model clinic from the USA in Israel, as shown by the high retention rate and the significant reduction in the use of illicit opiates, in spite of the geographical, linguistic and cultural differences between the countries.
Figure 48

Acquired immunodeficiency syndrome (AIDS) including HIV carriers

Number of cases and rates per 100,000: 1986-2010

1993
Opening of Adelson Clinic in Tel Aviv
Methadone Maintenance Treatment Experience in Macao – Prospective Follow-up for Initial 4.5 Years

Miriam Adelson, M.D.\textsuperscript{a,b,c}; Hon Wai Wilson, B.A.\textsuperscript{d}; Vong Yim Mui Celeste, B.A.\textsuperscript{e}; Shirley Linzy, R.N., M.S.\textsuperscript{b}; Mary Jeanne Kreek, M.D.\textsuperscript{c} & Einat Peles, Ph.D.\textsuperscript{a}

Abstract — The initiation of the first methadone maintenance treatment program (MMT) in Macao was founded in collaboration between MMT clinics in the USA and Israel. All patients admitted into treatment between October 2005 and October 2008 were prospectively followed through March 2010. Of the 163 patients, 81\% were male, the mean age on admission was 39.5 (sd = 10.2). Seventy-three percent (n = 119) were hepatitis C sera positive, and 4.9\% (n = 8) were HIV sera positive. One-year treatment retention rate was 59.5\%, with 52.6\% of the 95 patients who stayed in treatment having an opiate-negative urine test at the 10-month evaluation. Four and a half years of follow-up showed mean long-term retention (Kaplan Meier analyses) of 2.2 years. Higher methadone dose (\geq 80mg/day) and hepatitis C sera positive status were predictors for longer treatment retention. This study describes an effective model of MMT that supports the expansion of addiction treatment in other countries.
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- HCV-/HIV+: 0.5%
- HCV+/HIV+: 25.9%
- HCV+/HIV-: 40.8%
- HCV-/HIV-: 32.8%

Piccolo...Kreek, J. Addict. Dis. 21:55-66, 2002; THS 2013
Genetic Variants of the Human Mu Opioid Receptor: Single Nucleotide Polymorphisms in the Coding Region Including the Functional A118G (N40D) Variant

HYPOTHESIS

Gene variants:

- Alter physiology
  "PHYSIOGENETICS"

- Alter response to medications
  "PHARMACOGENETICS"

- Are associated with specific addictions

Bond, LaForge… Kreek, Yu, PNAS, 95:9608, 1998; Kreek, Yuferov and LaForge, 2000
### Association Between a Functional Polymorphism in the mu Opioid Receptor Gene and Opiate Addiction in Central Sweden

<table>
<thead>
<tr>
<th>Genotype</th>
<th>All Subjects</th>
<th>Swedish with Both Parents Swedish</th>
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<tbody>
<tr>
<td></td>
<td>Controls (n=170)</td>
<td>Opiate Dependent (n=139)</td>
</tr>
<tr>
<td>A/A</td>
<td>147 (0.865)</td>
<td>98 (0.705)</td>
</tr>
<tr>
<td>A/G</td>
<td>21 (0.123)</td>
<td>39 (0.281)</td>
</tr>
<tr>
<td>G/G</td>
<td>2 (0.012)</td>
<td>2 (0.014)</td>
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RR = 2.86 $\chi^{2} (1) = 13.403$ P = 0.00025* RR = 2.97 $\chi^{2} (1) = 8.740$ P = 0.0031*

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<tr>
<th>Genotype</th>
<th>Opiate Dependent (n=139)</th>
<th>Control (n=170)</th>
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<tr>
<td>G/G; A/G</td>
<td>41</td>
<td>23</td>
</tr>
<tr>
<td>A/A</td>
<td>98</td>
<td>147</td>
</tr>
<tr>
<td>118G Allele Frequency</td>
<td>0.155</td>
<td>0.074</td>
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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%)

Association of the A118G variant with change in viral load since admission to study and prior to start of HAART therapy (medical care without or with monotherapy)

Rs1799971 (118A>G)  
\( p \approx 0.395 \)

Study Points
- Admission to WIHS
- Start HAART

- AA (66 subjects)
- GA (35 subjects)
- GG (4 subjects)

Human prodynorphin gene: Chr 20pter-p12
Exon / intron organization and single nucleotide polymorphisms

- Three 3’UTR SNPs (rs910080, rs910079, and rs2235749) are in complete linkage disequilibrium (LD), and comprise two haplotype blocks: T-T-C or C-C-T;

- The haplotype C-C-T was significantly associated with cocaine dependence and cocaine/alcohol codependence (OR=2.32, experiment-wise p=0.015) in Caucasians.

Yuferov et al, Neuropsychopharmacology, 34:1185, 2009
Influence of the genotypes of a PDYN variants on change of viral load from admission to study (WIHS) to prior to start of HAART (medical care without or with monotherapy)

Rs6035222 (189C>T)

p=0.0014

Admission to WIHS

Start HAART

Study Points

## The Laboratory of the Biology of Addictive Diseases

### 2013

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<th>Laboratory Scientists</th>
<th>Postdoctoral Fellows</th>
<th>Adjunct Faculty/ Collaborators</th>
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<tr>
<td>Eduardo Butelman</td>
<td>Keiichi Niikura</td>
<td>Miriam Adelson*</td>
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<td>Yan Zhou</td>
<td>Derek Simon</td>
<td>Gavin Bart*</td>
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<td>Orna Levran</td>
<td>Marta Valenca</td>
<td>Lawrence Brown*</td>
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<td>Vadim Yuferov</td>
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<td>Yong Zhang</td>
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<td>Brian Reed</td>
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<td>Roberto Picetti</td>
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<td>Brenda Ray</td>
<td>Devon Collins</td>
<td>Virginia Pickel*</td>
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<td>Ellen Unterwald*</td>
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<td>Jurg Ott</td>
<td>Kitt Lavoie</td>
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<td>Joel Correa da Rosa</td>
<td>Hillary Briggs</td>
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<td>*Adjunct Faculty</td>
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