Clinical Characterization of Compound at the Addiction Research Center
1929

- NAS strategy
- USPHS Hospitals Authorized
  - Research division–Addiction Research Center at Lexington Hospital
- Lyndon Small at University of Virginia
- Nathan Eddy at University of Michigan
that further sociological studies are not likely, at this point, to help in the solution of drug addiction;
that research at the beginning should be confined to the study of one drug (after consultation with many men, including those in charge of the narcotic divisions of the U.S. Public Health Service and of the Treasury Department, morphine was selected as the most important drug of the group);
that since there are many specific uses of morphine in therapeutic practice and since no one drug can function for all of these uses, it is necessary to replace the legitimate uses of morphine with a number of substitutes;
that, if at all possible to substitute for all legitimate uses of morphine other chemical compounds without addiction properties, it should render morphine an unnecessary commodity in international commerce, and a definite step forward will have been taken.
That, if any success from the researches planned develops, it will come:

a) From some base line chemical and biological study such as is described hereafter,

b) From the provision of new implements for the use of those charged with control of drug addiction, (and)

c) From the provision of substitutes for every legitimate use of morphine first, and thereafter of other drugs, in order that the use of habit-forming drugs may be outlawed.
Clinical Research Program

- Federal prisoner volunteers
- 1933 to 1976
  - Leavenworth
  - Lexington 1935
- 1979
  - Move to Baltimore
  - Establish program in free living volunteers
State of Knowledge
State of Knowledge

- Strong vs. Weak opiates
- No concept of relative potency
Clifton Himmelsbach

“Look for the bee without the sting”
Abstinence deviations

- **Intensity of abstinence**
- **Temperature**
- **Blood sugar**
- **Respiratory rate**
- **Systolic blood pressure**
- **Diastolic blood pressure**
- **Sleep**
- **Caloric intake**
- **Basal metabolic rate**

- Significant abstinence deviations
- Nonsignificant abstinence deviations
- Abstinence intensity (points)
- Abstinence intensity (degree)

Abscissae = Days of abstinence
Himmelsbach’s Substitution Hypothesis

Diagram showing the comparison of withdrawal symptoms from Morphine and Substituted Drugs.
Himmelsbach Studies

- “Agent that would sustain physical dependence would produce it”
- Eighteen compounds assessed including codeine and dihydromorphine (Dilaudid)
Figure 7. Reproduced in part from Himmelsbach and Andrews [18].
Changes

- NIH program suspended during WWII
- Harris Isbell became director in 1945
  - Abraham Wikler
  - Frank Fraser
- Methadone
  - Highly euphoric
  - Suppressed morphine abstinence for 24 hours
  - Led to interest in subjective effects of opiates
Formal Abuse Potential Responsibilities

- Meperidine and methadone synthetics
- Law change to include addiction sustaining or addiction forming similar to morphine
Analgesia in pathologic pain
Subjective effect for pain relief
Bioassays
  ◦ Double blind
  ◦ Cross-over
  ◦ Dose response
  ◦ Positive control -- morphine 5 and 10 mg
  ◦ Negative control – placebo
  ◦ Test drug in two doses
Analgesia expressed in morphine equivalent units
Studies of subjective effects

- Abusers discriminate morphine in a dose related manner
- Single dose opiate Questionnaire
- Dose response curves
- Bioassays
  - Pupils
  - Liking scales
  - Symptoms
- Addiction Research Center Inventory
- Bioassay data on 38 drugs
Methods for bioassays of morphine like activity

- Single dose studies
  - Subjective scales including liking
  - Pupils
- 24 substitution studies in dependent subjects
- Direct addiction studies
Selectivity

- Similar relative potencies
  - Post addicts
  - Pathologic pain
  - Respiratory depression
- No advantage over morphine
Fig. 2. Dose effect curves using 5-h total scores for pupillary change, opiate signs, observers' liking, MBG, opiate symptom and subjects' liking scores for the comparison of intravenously administered heroin, morphine and placebo. Morphine (M) (---); methadone (ME) (ΔΔ--ΔΔ); heroin (H) (■■--■■); placebo (---); 95% confidence limits/mean placebo response (-----).
Compounds judged to have low abuse potential

- dextromethorphan
- diphenoxylate
- d- propoxyphene
nalorphine

- 1915 Pohl demonstrated morphine antagonism
- 1941 Hart synthesized and studied
- 1943 Merck studied
- 1950 initial studies in addicts indicate low abuse liability and possible analgesia
- 1951 Eckenhoff demonstrated morphine antagonism in man
- 1953 Wikler demonstrated precipitated abstinence
- 1954 Lasagna and Beecher demonstrated analgesia
Consequences

- Synthesis of a large number of N substituted opiates
- First in laboratory of Eddy by May in 1959
- Pentazocine, cyclazocine and naloxone
Nalorphine and cyclazocine withdrawal without drug seeking
Subjective effects valid measure
Multiple receptors
  ◦ Mu, Kappa, Sigma
Receptor dualism
Partial agonism
Naloxone

- Little or no agonist effects
  - Acute and chronic administration
- Antagonize both mu and kappa agonists
- Support concept of competitive antagonism
- Tool
Morphine receptors are finite
Saturation seen in chronic administration in doses of 240 mg morphine daily or greater
Partial agonists
  - Substitute at low levels of morphine dependence such as 60 mgs of morphine daily
  - Precipitate at higher levels of dependence 240 mg morphine daily
opioids

- Mu agonists
  - Full
  - Partial
- Mixed agonist antagonists
  - Full and partial kappa agonists
- Competitive antagonists
Agonist antagonists

- Nalorphine
- Naloxone
- Nalbuphine
- Butorphanol
- Cyclazocine
- Naltrexone
## Opioid Drugs studied in humans at the ARC from 1933 through 1976

<table>
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<tr>
<th>Drug class</th>
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<tr>
<td>morphine and congeners</td>
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<td>Miscellaneous</td>
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Last drug studied at Lexington
Before relocation to Baltimore

buprenorphine
Subsequent studies

- Baltimore 1979 to 1985
- Johns Hopkins 1985 to 2010
- tramadol
No opiate like effects in im or iv studies

Oral studies
- delayed opiate-like effects
- ? M1 metabolite
- larger doses required

Consistent with pre-clinical pharmacology
- mixture of opiate and non opiate effects
- therapeutic doses predominately non opiate
Conclusions

- Lesser abuse potential than d-propoxyphephene or pentazocine
  - no parenteral effects
  - therapeutic effect non opiate like
  - dissociation of analgesia and opiate like effects
- No pharmacologic basis for Scheduling under CSA
Accomplishments

- Treatment drugs
  - Naloxone
  - Naltrexone
  - Methadone
  - Buprenorphine

- Tolerance and dependence
  - Morphine and methadone
  - Primary and secondary withdrawal
NAS goal of opiate substitutes

- Anti-diarrheal – loperamide
- Antitussive – dextromethorphan
- Weak oral analgesic – tramadol
- Injectable opioid – nalbuphine