1. **Introduction of Pain (neural systems, NTs)**
   
   tissue damage --- activates **free nerve endings** = “nociceptors”

   signal from body (FNEs) --- dorsal horn of sp. cord --- increased release of NTS:
   
   - substance P (a neuropeptide)
   - nerve growth factor
   - neurotropic factors
   - glutamate (aminoacid)
   
   **endogenous opioids** (which opioid agonists mimic)
   
   --- act on presynaptic neuron to **decrease release of sub.P**
   called “endorphins”

   why would lowering release of sub.P help reduce pain?
   
   because normally increased sub. P release activates small spinal cord neurons, which is the basis of the rapid transmission of the pain signal to the brain

   these incoming signals go through **brain stem** --- to **thalamus** --- to **limbic system** (where the “suffering” message occurs) and to the **somatosensory cortex** (where the non-affective sensation of pain occurs)

   thalamic nuclei: **parafascicular nucl. & intralaminar nucl.**

   brainstem area: PAG (periaqueductal gray) in tegmentum rich in **opioid RSs** (where exogenous opioids could have their effects)

   **descending pain-inhibition systems:**
   
   descending brainstem neurons --- spinal cord --- increased activity in interneurons of dorsal horn --- inhibit release of sub. P in primary afferent nociceptive neurons

   placebo-induced analgesia
   hypnosis-induced analgesia
2. **History of Opium Use**

Opium obtained from **poppy plant** (*Papaver somniferum*)
- Milky sap from opium poppy seed pod, turns darker at it ages ("tar")
- Active ingredient (morphine) extracted --- into heroin

Long history (dates from B.C.) of use for tx. for diarrhea, for sleep
recreational use & addiction were common

Plant originated in **Mesopotamia**, then spread to Asia by Portugese
now also grown in so. amer. (esp. Colombia)

Established use of **hypodermic needle & syringe** (**1856**)
- 1843 Dr. Alexander Wood (Edinburgh) invented
- Used in Civil War in USA for pain control
- "soldier’s disease" referred to heroine addiction in self-injecting abuser

**Harrison Narcotics Act (1914)**
- Fed. legislation to strictly control use of most opiates/narcotics
- Required physicians, pharmacists, & others who prescribed narcotics
to register with feds and to pay a tax
- None the less, as with all other drugs of abuse, opiates are not only
used medically, but they continue to be used recreationally & abused

**Drug Enforcement Agency** (DEA), under Fed Justice Department
established by Nixon in **1973**

**1996 data on opium:**
- 10 tons of raw opium tar --- becomes 1 ton of heroine
- 4,300 tons of raw opium tar produced/year --- 430 tons heroine/year
- 2,500 tons from Burma (biggest producer, followed by Thailand,
  and then Laos)
- 50% of this imported into USA/year
3. Terminology: NTs & RSs

Both morphine and codeine are found in “tar” from poppy juices. Heroine is a semisynthetic compound made from morphine.

Endogenous opiates (“endorphins”) include:
- Enkephalins
- Dynorphins
- Beta-endorphins

There are so far three opioid RSs:
- Mu – strongest analgesia, strongest addiction
  - Mu1 – responsible for analgesia
  - Mu2 – found throughout CNS, responsible for decreased respiration, spinal analgesia, decreased HR, physical dependence, euphoria

Morphine is a mu1 and mu2 agonist

Acts in thalamus & in striatum (basal ganglia: caudate+Putamen) to produce relaxation, euphoria.
Acts in brainstem to decrease respiration, increase nausea/vomiting.
Acts in spinal cord to produce analgesia.

Kappa – modest analgesia, little/no effect on respiration, miosis, little/no dependence.
But does produce strong dysphoric response (which limits its use).
May antagonize the mu RS actions in brain.

Delta – may also modulate action of mu RS.
Little dependence, little/no analgesia.

All opioid RSs belong to a group of G-protein coupled RSs, with seven membrane-spanning regions (similar to all G-proteins).
3. **Terminology: NTs & RSs** (cont.)

opoid RS (G-protein coupled)

when RS is activated, it inhibits (via presynaptic, axoaxonal synapse) cell by increasing the efflux of K+ and closing Ca++ ion channels

--- **hyperpolarization** of neuron & blocking any release of NTs

--- **pain signaling neurons are kept shut** off (see p. 258, Fig. 9.6, Julien, 9th Ed.)

4. **Classification of Opioid Analgesics**

   a. **“pure agonists”**
      
      their affinity for RSs = ligand’s affinity for the same RSs

      e.g. morphine, methadone, fentanyl (a pure *mu* agonist)

   b. **“pure antagonists”**
      
      has affinity for RS, but produces no effect (blocks RS)

      e.g. naltrexone

   c. **“mixed agonist-antagonist”**
      
      produces an agonistic effect at one RS (e.g. *kappa*), but also produces an antagonistic effect at another RS (e.g. *mu*)

      e.g. Talwin (pentazocine) which is a weak, less efficacious analgesic (agonist at *kappa*, blocks *mu*)

   d. **“partial agonist”**
      
      binds to RSs, but does not produce as much of an effect vs. ligand low efficacy

      and since it does bind to RS, the natural ligand cannot bind --- can result in w/d-like effects

      e.g. Buprenex (buprenorphine) – does produce some analgesic effects, but does not depress respiration as much…a good thing
5. **Morphine**
   a pure opioid agonist
   the most potent & efficacious analgesic we have today still

**Pharmacokinetics:**
administered PO, rectal suppository (avoids nausea/vomiting), IV, 
or into spinal cord (subdural space)(which avoids SEs such as 
respiratory depression, increased euphoria, increased constipation, 
& increased sleepiness)

can also be inhaled (smoked)
   Julien says of this route “…rarely abused when smoked”, why?

**Morphine fairly slowly crosses BBB** (much more water soluble than fat soluble), only 20% reaches CNS by usual clinical routes (note: heroin & fentanyl cross BBB much more rapidly)

crosses the placenta too, so neonate is born opiate dependent
neonate will show w/d effects, which require extensive support th.
no teratogenic effects
may retard fetal growth rates
may increase paranatal birthing problems

distributed to all body tissues (esp. muscle)

**Metabolized by liver enzymes**
some active metabolites
e.g. morphine --- morphine-6-glucoronide (a potent analgesic)
morphine ½ life is 3-5 hours, m-6-g ½ life is 3-5 hours
urine drug screen can detect morphine/codeine/heroine use for 2-4 days after use

does show dependence & tolerance (see later notes)
5. Morphine (cont.)

**Pharmacological effects:**
- Analgesia
- Sense of tranquility
- Pupillary constriction
- Relaxation
- Decreased apprehension
- Calm euphoria
- Respiratory depression
- Sedation
- Reduced cough reflex

**Analgesia** w/o loss of consciousness & w/o loss of appreciation of senses especially blunted “suffering/affective” part of pain awareness, even though can still feel touch, and non-hurtful part of “pain” via blocking mu RS

Naloxone (Narcan) reverses this analgesic effect

Note: in NCs, naloxone does **not** --- pain, dysphoria, or any other noticeable effects

**Euphoria** response probably the result of more than mu RS, probably also DA RSs in nucl. Accumbens, etc.

Opioids (via mu RSs) --- inhibits GABA neurons in ventral tegmental area --- disinhibition of DA release in nucl. Accum.

Does show **tolerance** with repeated use

**Sedation & anxiolysis** (reduced anxiety) not as deep a sedation as that produced by sed-hyps (e.g. ETOH, barbs, BZDs)

A marked lack of concern, “What, me worry?” attitude, “dreamy” lack of concentration, cognitive impairment

**Depressed respiration** decreased sensitivity to increased CO2 levels, to the point of not breathing at all in O.D.

Dangerous to combine with other sed-hyps., although would be a painless death…
5. Morphine (cont.)

**pharmacological effects** (cont.)

**cough suppression**
useful clinically, but now have non-opioids to do this too

**pupillary constriction**
via mu & kappa agonists --- extreme miosis (“pin-point pupils”)

**nausea & vomiting**
morphine stimulates area postrema = “chemoreceptor trigger zone”
in medulla --- N&V
may also affect gastric RSs of some sort

**GI tract effects**
increased muscle tone, decreased motility --- increased fecal
dehydration & increased cramping --- constipation
Imodium (loperamide), Lomotil (diphenoxylate) are both opioids
that do not cross BBB, used to tx. diarrhea w/o “buzz” or abuse

**histamine agonist** effects
(can --- hives, severe allergic reactions, bronchoconstriction)

**I.S. antagonist/suppressant**

**Tolerance & dependence**
all opioids build up tolerance with repeated use, & show dependence
thus, clinical use of all opioids (for analgesia, to reduce diarrhea, to
reduce coughing) is limited by:
tolerance for main effects
increasing SEs if dose levels are increased
potential for compulsive use (abuse, dependence)
5. Morphine (cont.)

Tolerance & Dependence (cont.)

tolerance seems to occur via glutamate/NMDA RSs

as opioid use continues, see increasing activity in glutamate/NMDA RSs

note: Ketamine blocks glutamate NMDA RSs --- blocks tolerance

thus, glutamate/NMDA system must somehow regulate opioid mu RSs

note: an unfortunate clinical aspect of opioid tolerance

after opioid use for analgesia, if D/C opioids --- S becomes super-sensitive to pain ("hypergesia") for long period of time…why?

(note: this hypergesia or decrease in pain threshold is blocked by ketamine)

note: rates at which tolerance to morphine develops depends on how it is used

note: tolerance with one opioid drug --- cross-tolerance with other opioids, but not with sed-hypn. drugs

physical dependence occurs, marked w/d Sxs:

marked reduction in DA release in nucl. Accumbens

marked increase (x3) release of NE in hippocampus, nucl. accumb. and locus coeruleus

Sxs of w/d are not life-threatening, but are very unpleasant:

motor restlessness   insomnia   increased respiration

dysphoria           anxiety      rate, “panting”

drug cravings       depression   aches, pains

sweating            irritability (see p.270, Table 9.4, Julien, 9th ed.)

retching, vomiting   fever, chills

cramping            explosive diarrhea
OPIOID ANALGESICS (p.9)

5. **Morphine** (cont.)

   **Dependence** (cont.)

   **“Rapid Opioid Detoxification”** (RAAD = Rapid Anesthesia-Aided Detoxification)

   S placed under general anesthesia for several hours while unconscious, S is given naloxone/naltrexone.

   S does through blunted w/d Sxs while unconscious.

   S comes out of general anesthetic state, presumably now over any w/d Sx, and is then maintained on naloxone (to reduce cravings for opiates) and goes into relapse prevention drug counseling.

   a great idea, but still very controversial, more risky (gen anesthetic), often not covered by insurance.

   **“protracted abstinence syndrome”** (PAS)

   seen after end of acute w/d, lasts at least 6 months or so

   Sxs: depression

   abnormally sensitive to stress

   strong drug cravings

   lowered sense of self-esteem

   anxiety

   various physiological disturbances (in bowels, sleep, etc.)

   increased sensitivity to pain

   note: abnormal brain activity, esp. while experiencing cravings will this ever normalize?...maybe not…

   note: many (estimate of 47%) of opiate users had a **premorbid/comorbid Dx**

   depression (15%)

   affective disorders (unipolar depression, bipolar)

   personality disorders (antisocial)(25%)
6. Other Opioid Substances
(See Julien for more extensive material)

a. Codeine
is a commonly prescribed analgesic (often combined with aspirin or acetaminophen)
about 40% of Ss repeatedly using medically prescribed codeine meet criteria for codeine dependence
many of these repeat users are showing comorbid Sxs of endogenous depression
codeine is metabolized by CYP2D6 into morphine & some of the effects presumably from codeine are actually due to morphine
note: some SSRIs will block the conversion of codeine --- morphine via liver enzyme inhibition, and will block/lessen the analgesic effects of codeine therefore

b. Heroin
x3 more potent than morphine
intense “rush” esp. if smoked or used IV
legal for clinical used outside USA, not inside USA
when used along with free-base cocaine (“crack”) --- increased euphoria, decreased anxiety & paranoia, & decreased depression if the cocaine use if D/Cd…very difficult to treat this combination addiction…

c. Dilaudid (hydromorphone), Numorphan (oxymorphone)
x6-10 mor potent than morphine
slightly less sedating, about same degree of respiratory depression

d. Demerol (meperidine)
synthetic opioid, structurally unlike morphine
is as prone to abuse as is morphine
1/10\textsuperscript{th} the potency of morphine, but produces euphoria like morphine
different SEs: tremors, delirium, increased reflexes, convulsions (more excitatory) vs. morphine, produced by active metabolite
OPIOID ANALGESICS (p. 11)
6. Other Opioid Substances (cont.)

e. Dolophine (methadone)
   synthetic mu agonist, analgesic
   can be used PO…why is this important?
   long ½ life (24 hours)
   little tolerance with repeated use
   little/no “rush”, euphoria
   used to maintain heroin addicts, controlled by feds
      blocks cravings for heroin (at > 50mg/day doses)
   note: some Ss metabolize methadone more rapidly (33%), need b.i.d.
      dosing, or could use LAAM (longer ½ life)
   some Ss may bee 80-100 mg/day, in b.i.d. split doses

f. LAAM (levo-alpha-acetylmethadol)
   related to methadone
   can take PO
   slow onset of effects, long ½ life (up to 3 days)
   active metabolites
   helps to control cravings for both heroine and cocaine

g. Darvon (propoxyphene)
   structurally similar to methadone
   analgesic for mild-mod pain
   potency: aspirine < Darvon < codeine
   when taken PO there is little abuse potential; injected --- more
   not available legally in injectable form

h. ultra-short acting opioids
   Sublimaze (fentanyl), Sufenta (sufentanil), Ultiva (remifentanil)
   used IV usually, can be given by transdermal patch or “lollypop”
   used during/after short surgeries
   x80-100 more potent than morphine, profound respiratory depression
   Ultiva ½ life is 10-20 minutes (metabolized by plasma enzyme)
OPIOID ANALGESICS (p.11)

7. **Partial Opioid Agonists**
   See Julien (Buprenex/buprenorphine; Ultram/tramadol)

8. **Mixed Opioid Agonist-Antagonists**
   See Julien (Talwin/pentazocine; Stadol/butorphanol; Nubaine/nalbuphine; Dalgan/dezocine)

9. **Opioid Antagonists**
   Narcan (naloxone); Trexan, ReVia (naltrexone); Revex (nalmefene)
   structurally related to Numophan (oxymorphone)
   a pure opiate agonist
   strong affinity for mu RS, but blocks RS
   note: if Narcan is injected into non-opiate user --- no effects
   but into opiate user --- opiate w/d effects
   **cannot** give PO (is injected)
   fast duration of effects – ¼ to ½ hour
   can be used to reverse respiratory depression in opiate OD or neonates

   note: Trexan, ReVia can be given PO
   longer duration of action, can be given once a day
   used to reduce opiate cravings in former abusers **not on methadone**
   SEs: nausea & liver toxicity
   also used to tx. cravings for ETOH in former abusers
   may also help to reduce SIBs in autistic Ss
   may be helpful in tx. of borderline personality disorder…

   note: Revex has a ½ life of 8-10 hours
   must be injected
   used to tx. respiratory depression in opiate OD
   used to tx ETOH cravings in former alcohol abusers
10. **Pharmacotherapy of Opioid Dependence**
   use LAAM and/or Buprenex for treatment-resistant Ss (who must be maintained on an opiate substitute)

   use **opiate antagonist** to also reduce opiate cravings
   in patients not able to use substitute opiate (Methadone, LAAM)
   blocks euphoria if does relapse
   e.g. ReVia, Trexam

   **treatment of any comorbid Dxs** (esp. affective disorders)

   non-pharmacological **support therapy**
   outpatient treatment programs (vs. inpatient intensive programs)
   focused on relapse prevention & cognitive/behavioral changes
   e.g. change environment, associates, activities

   note: total abstinence need not be the objective for each/all abusers
   hence, methadone maintenance programs
   and movement to let MDs prescribe methadone in private practice

   note: must change societal attitudes (incl. government & politicians)
   about these issues, and adopt Harm Reduction Model (vs. abstinence)
   more money for prevention than “cure”
   more money for treatment vs. drug interdiction