I. Neural Control of Arousal
   A. Neuromodulators
      i. ACh from the pons and basal forebrain
         1. Behavioral activity levels correlate with the ACh levels
         2. Desynchronize the EEG
         3. Controls neural excitability
         4. ACh is high in REM sleep
      ii. NE from the locus coeruleus: vigilance, attention
         1. Amphetamines (NE agonists) produce arousal
      iii. 5HT from the raphe nuclei (in the pons)
         1. Correlates with sleep stages
         2. Active during the transitions out of REM sleep
      iv. Histamines (tuberomammillary nucleus, hypothalamus): activate the cortex directly, and indirectly (through basal forebrain ACh)
         1. Anti-histamines promote drowsiness
      v. Orexin (Hypocretin, from the lateral hypothalamus): excitatory projections to cortex and many neuromodulatory centers
         1. Wakefulness promoting, accessing causes you to be more alert
         2. Indirect arousal effects
         3. When damaged, narcolepsy occurs
      vi. Central Question: What makes us go/transition to sleep?
         1. Adenosine Hypothesis - Adenosine accumulation during the awake period; adenosine is a 'sleep promoting substance'
      vii. The awake state:
         1. Astrocytes provide energy to neurons
         2. Astrocytes --> adenosine --> neurons
            a. Astrocytes also give glycogen (the fuel) to neurons
         3. Glycogen depletion --> increase in adenosine --> progressive increase in general inhibition --> increase in sleep tendency
      viii. Sleep state: Restorative Process
         1. Glycogen --> Astrocytes

II. Neural Bases of Sleep: SWS
   A. Ventrolateral PreOptic Area (vLPOA)
      i. Destruction --> no sleep --> death
      ii. Stimulation --> drowsiness and delayed sleep
      iii. Mutual inhibition: vLPOA sends inhibitory projections to Histamine, NE, 5HT, ACh systems
         1. These systems in turn inhibit the vLPOA
      iv. "Flip-Flop circuitry"
         1. In the "ON" position, the brainstem is activated, meaning the arousal systems are activated and you are in the awake state
2. In the "OFF" position, the vLPOA is activated in the brain stem, which results in slow-wave sleep

B. Turning the Flip-Flop "ON": Orexin neurons
   i. Orexin neurons are active during the awake state and project to the arousal systems
   ii. ON: "motivation to remain awake", "stimulus driven", mediated by external signals: biological clock, hunger signals, etc.

C. Turning the Flip-Flop "OFF": Adenosine Hypothesis
   i. Active state: glucose consumption from blood
   ii. When blood glucose is not sufficient, use glycogen
   iii. Glycogen --> (local) glucose + adenosine (nucleoside transmitter)
   iv. Adenosine accumulate in those parts of the brain that were the most active
   v. Adenosine is inhibitory --> decrease brain stem activity --> increase vLPOA --> SWS
      1. SWS = slow-wave sleep
   vi. OFF: also related to food consumption, satiety signals inhibit orexin neurons
   vii. Are there any therapeutic manipulations of SWS?
      1. Prolonged total sleep deprivation leads to loss of body weight, temperature deregulation, and eventual death
      2. However, one night sleep deprivation (total, or second half of the night) this has an antidepressant effect

III. Neural Control of Sleep
   A. REM
      i. Dreams = windows to the 'psyche'
         1. 65% sad, angry; 20% happy excitement; 1% sexual
      ii. Executive mechanism (switch, flip-flop)
         1. ACh levels are high during REM (and awake)
            a. From pons
      iii. REM flip-flop
         1. Mutual inhibition: sublaterodorsal nucleus (SLD) and ventrolateral PAG (vPAG)
         2. Orexin neurons also influence the REM flip-flop
a. Cataplexy

B. SLD Projections
i. SLD projections explain the normal features of REM sleep
   1. Cortical activation: thalamus (dream content), Medial Pontine Reticular Formation (dream intensity)
   2. REM: Tectum (superior colliculi)
   3. Genital activity: lateral preoptic area (sexual preparedness ?)
   4. Atonia: medulla, prevents the "acting out" of dreams
      a. Lesion of "paralysis neurons" (in medulla) yield Rem without atonia
   ii. When orexin neurons are damaged, emotional stimuli take over (cataplexy)
      1. Amygdala and hypothalamus

IV. Biological Rhythms
A. Internal Clocks
i. InfraDian (less than one day)
ii. Circadian (one day)
   1. Sleep/wake cycle
   2. Roughly 25 hours free running
iii. SupraDian (more than one day)
   1. Ex: menstrual cycle
iv. Circannual (one year)
   1. Hibernation

B. SupraChiasmatic Nucleus: Circadian/Supradian
i. Time scale: day --" month
ii. Small (8600 cells) within the hypothalamus
iii. Reset by light (retino-hypothalamic tract)
   1. Melanopsin in "special" retinal ganglion cells projecting to SCN
      a. Light is a 'zeitgeber' or 'giver of time'
iv. Intrinsic and network rhythmic phenomena: SCN neurons by themselves, or as a group in a dish, have a circadian rhythm
v. Transplantation studies indicate the SCN uses chemical non-synaptic connection to affect its targets

C. Biological Rhythms
i. SCN sends inputs to the SWS flip-flop
   1. Inhibits vLPOA (decrease drowsiness)
   2. Excite orexin neurons (promote wakefulness)
ii. SCN Ticking = slow production of a self-inhibiting protein
iii. 'normal' sleep onset: 10-11pm
   1. Average length of 8 hours
iv. Advanced sleep phase syndrome: sleep onset 6-7pm, wakeup at 3-4am
   1. Genetic mutation
v. Delayed sleep phase syndrome: sleep onset 2-3am, wakeup 10-11am
   1. Genetic mutation
vi. Normal genetic variations may explain 'normal' variations in sleep onset time and sleep duration

D. Circadian Rhythms
i. Pineal Gland: Circadian/Circannual
1. In midbrain, near cerebellum
   a. Secretes melatonin during the night

2. Melatonin has slow cumulative actions in the periphery (sympathetic system)
   a. Seasonal time keeper in most animals
   b. Melatonin - highest levels just before bedtime
   c. Melatonin helps jet-lag
      i. Take before adjusted bed-time
      ii. Side effects: depression, low sex drive, weight loss
   d. Melatonin helps blind people to sleep better