# SmartTots: what you should know right now

Andrew S Triebwasser, MD
Assistant Professor of Surgery (Clinical)
Hasbro Children's Hospital

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# Faculty Disclosures

- no commercial relationships to disclose

# Objectives

*upon completion of this lecture participants should be able to*


- delineate basic science driving concern that sedatives may harm the developing brain
- describe recent epidemiologic evidence of potential postoperative neurotoxicity
- identify SmartTots and its role in addressing scientific and clinical gaps regarding the safe use of anesthetics in young children

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# SmartTots:
## Scientific Background

- animal studies w/anesthetics *unequivocally* demonstrate developmental neurotoxicity
- some epidemiologic evidence links surgery in small children with later learning disabilities and developmental disorders

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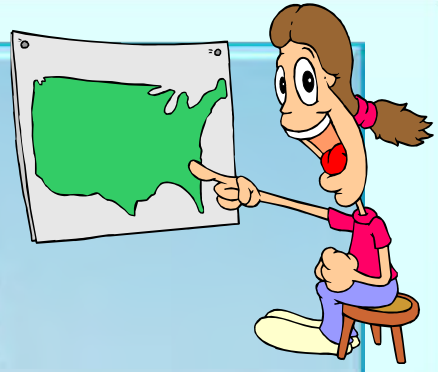
# SmartTots:
## Epidemiologic Background



- US – estimated 1M surgical anesthetics < 4
  - ↑↑↑ in the use of anesthesia* for children
- AIDN (anesthetic-induced developmental neurotoxicity) is therefore a major health issue of concern to the public, government agencies and the medical community

* spectrum of sedation (imaging, procedures, ICU)

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# Doctor, is the anesthesia safe for my child?

YES!

- assessment through institutional audits, closed claims, cardiac arrest registry [1]
- major morbidity exceedingly rare
  - 1990's → monitoring, ↓ halothane
- minor morbidity increasingly on our radar

1 Paterson N . *Pediatric Anesthesia* 21:848;2011

# Leap of faith: complete anesthetic reversibility

- coma → assume brain emerges unscathed BUT
- changes in gene & protein expression beyond emergence suggest the possibility of more durable effects, both positive and negative [1]

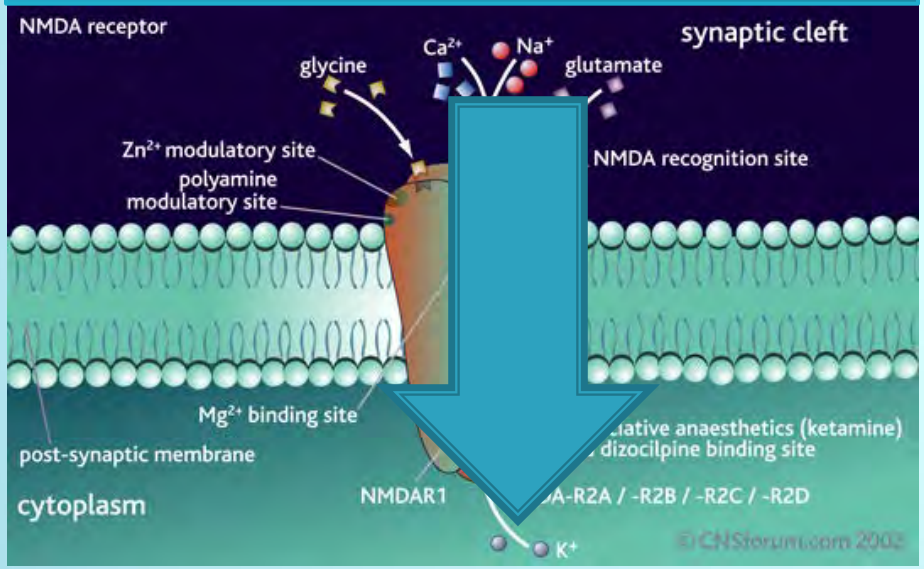
1 Hudson AE. *Br J Anaesth* 107:30;2011

# Anesthesia is complex and incompletely understood

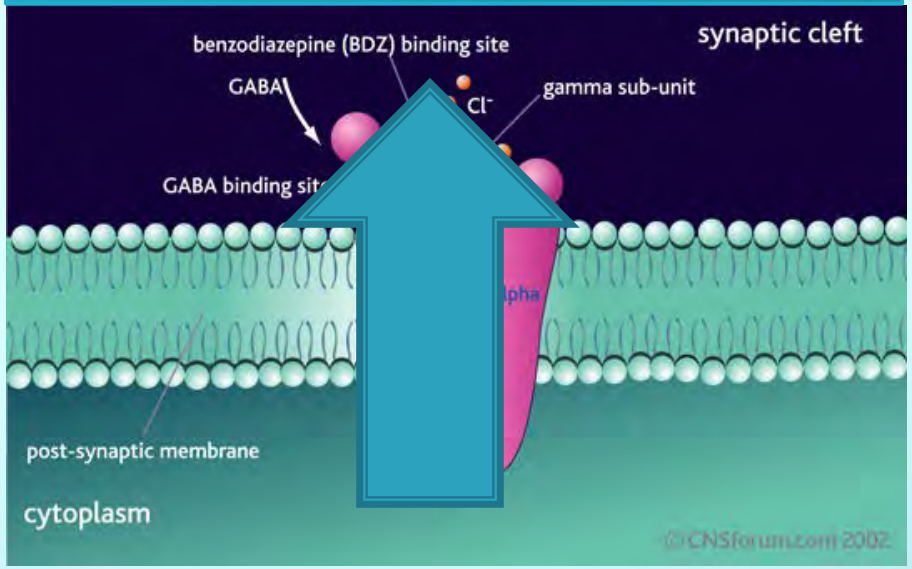

- amnesia, unconsciousness & immobility from a heterogeneity of agents which are potent modulators of neuronal activity throughout CNS
- emerging evidence that this may result in both positive and negative non-anesthetic effects

# Ligand-gated ion channels:
## molecular targets of anesthetic action

### NMDA (excitatory)




### $GABA_A$ (inhibitory)




*all anesthetics / sedatives either block NMDA &/or enhance $GABA_A$ to a degree* [1]

1 Campagna. *N Engl J Med* 348:2110;2003

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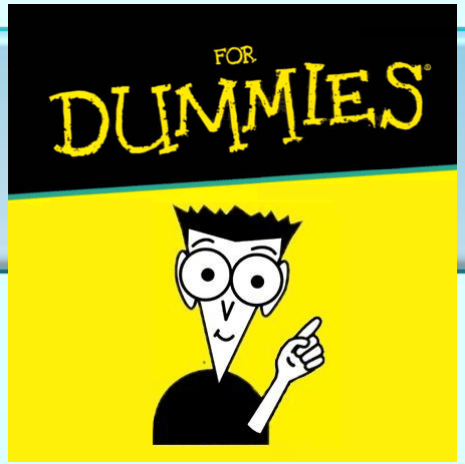
# Brain development

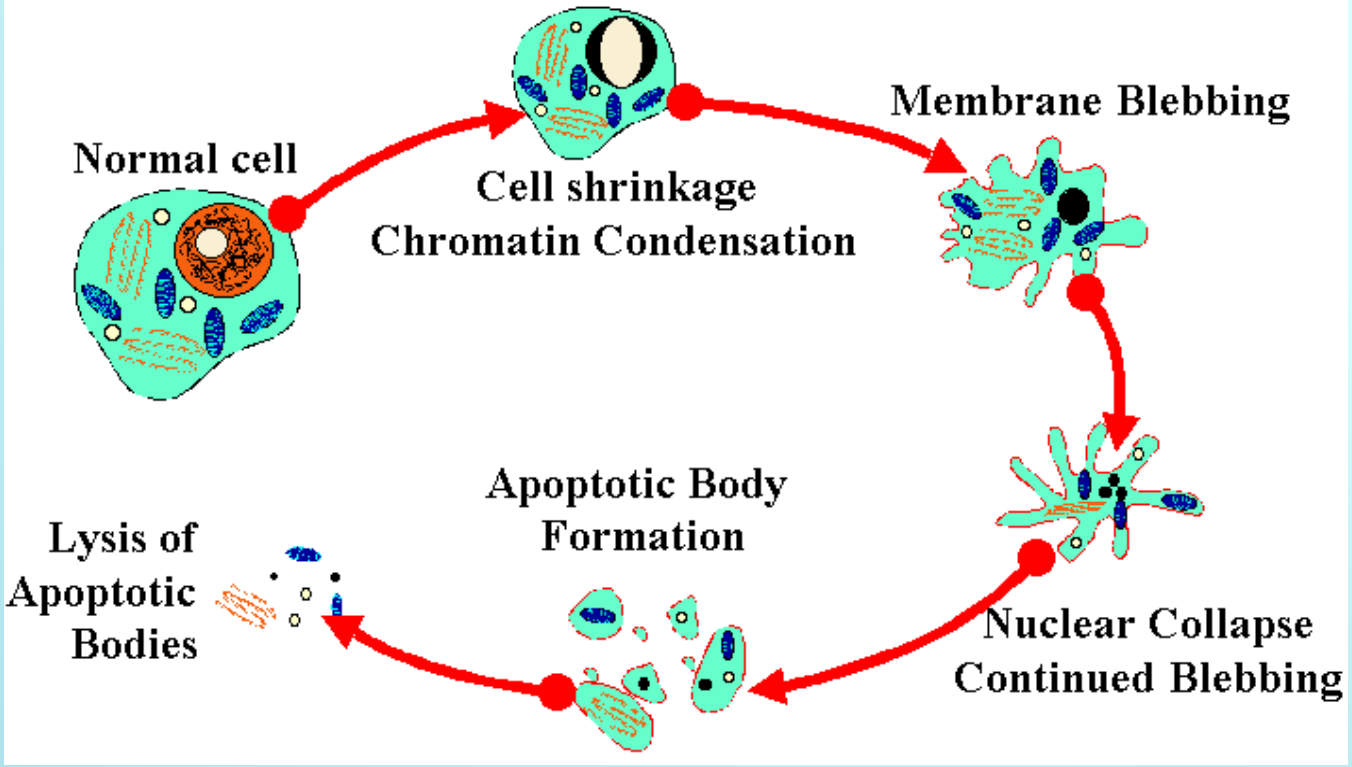



- CNS morphogenesis involves complex cellular processes (neurogenesis, differentiation, migration & synaptogenesis) – dependent on GABA and NMDA mediated neuronal activity
- in humans, rapid brain growth (RBG) or peak synaptogenesis (likely) 3rd trimester →2–3 yrs; ~ in small rodents to first 2 weeks

# Apoptosis: a key to normal development

- natural and ongoing pruning process for redundant cells (up to 50-70% of neurons)
- “programmed” through a variety of stimuli with both physiologic and pathologic roles
- extrinsic (death-receptor mediated) & intrinsic (mitochondrial) pathways exist

# Apoptosis
# (Programmed Cell Death)

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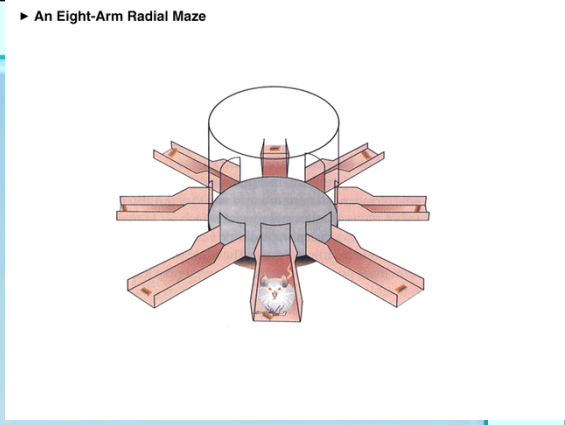
# Blockade NMDA receptors and apoptotic degeneration in the developing brain [1]




- NMDA antagonists, such as ketamine, trigger apoptosis in developing (P7 rat) brain
- similar response to $GABA_A$ agonists [2]
- anesthetic "cocktail" ↑ apoptosis & correlation w/ persistent behavioral changes in animals [3]


1 Ikonomidou et al. *Science* 283:70;1999
2 Olney et al. *Environ Health Perspect* 108:383;2000
3 Jevtovic-Todorovic et al. *J. Neurosci* 23:876;2003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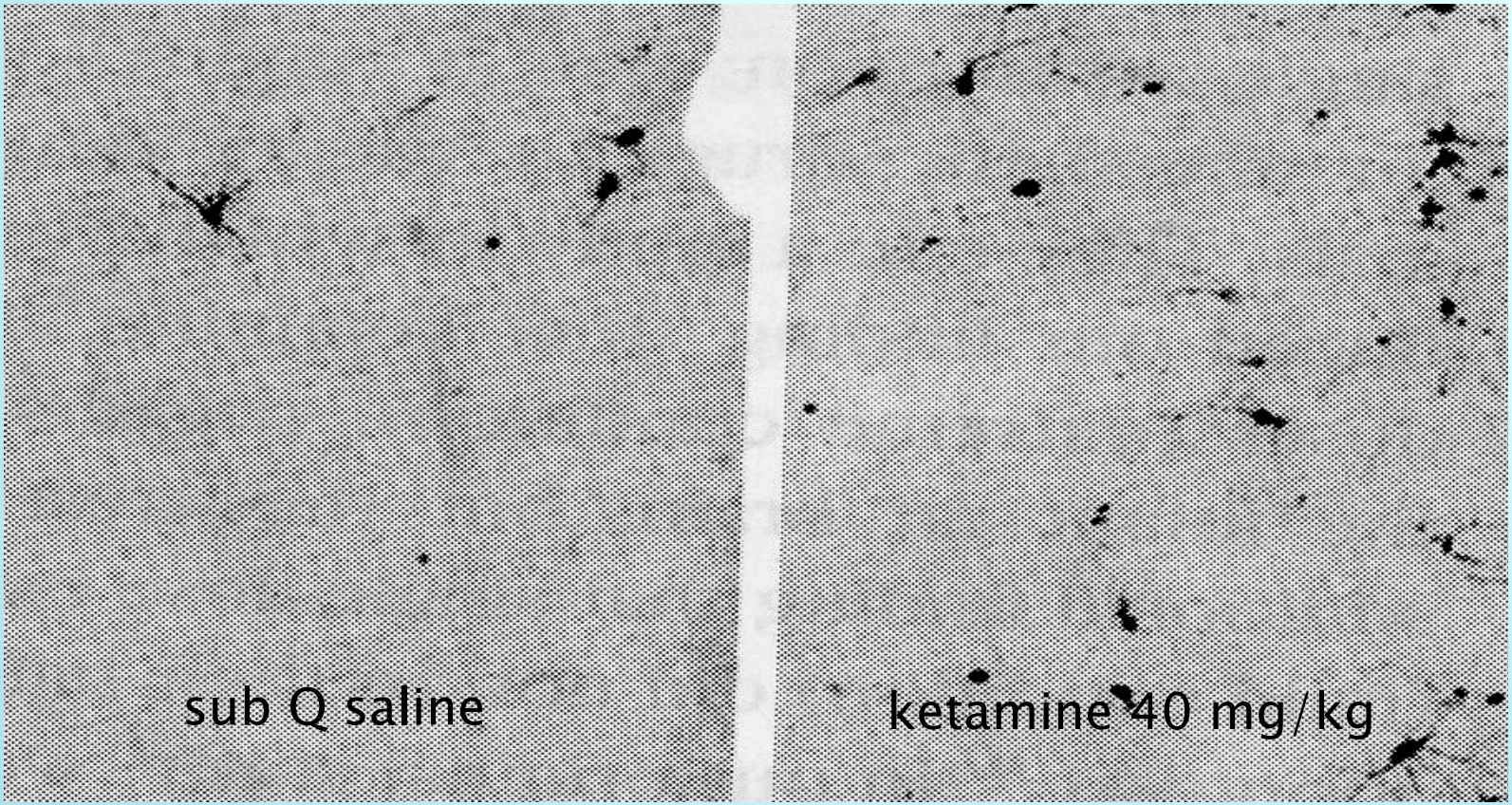
# Caspase-3 activation in caudate nuclei P7 mice 5° after exposure




Young C et al. *Br Journ Pharm 146:190;*2005

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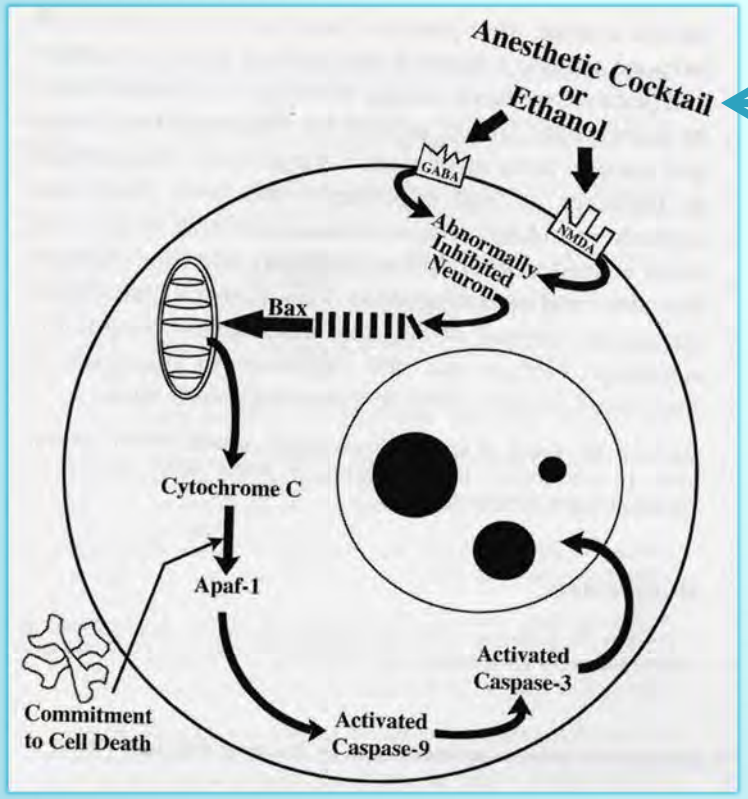
# Neuroapoptosis and AIDN




Young et al. *Cell Death and Differentiation* 2003

- mechanism unclear; untested hypothesis ↓ neural traffic → synaptic connection lost
  - but $GABA_A$ is excitatory, not inhibitory in immature neurons [1]
- ? ↑ NMDA receptor $Ca^{2+}$ influx [2]
- ? modulation of trophic factors such as BDNF±AKT [3]


1 Ben-Ari. *Physiol Rev* 87:1215;2007
2 Slikker. *J Appl Toxicol* 27:201;2007
3 Lu. *Apoptosis* 11:1603;2006

# Too much science!!

- apoptosis normal development of the CNS
- neuroapoptosis ↑ by a variety of exposures including NMDA antagonists / $GABA_A$ mimetics
- we assume (but aren't certain) this is bad (not just acceleration of normal process), although causality w/neurocognitive Δ's not established

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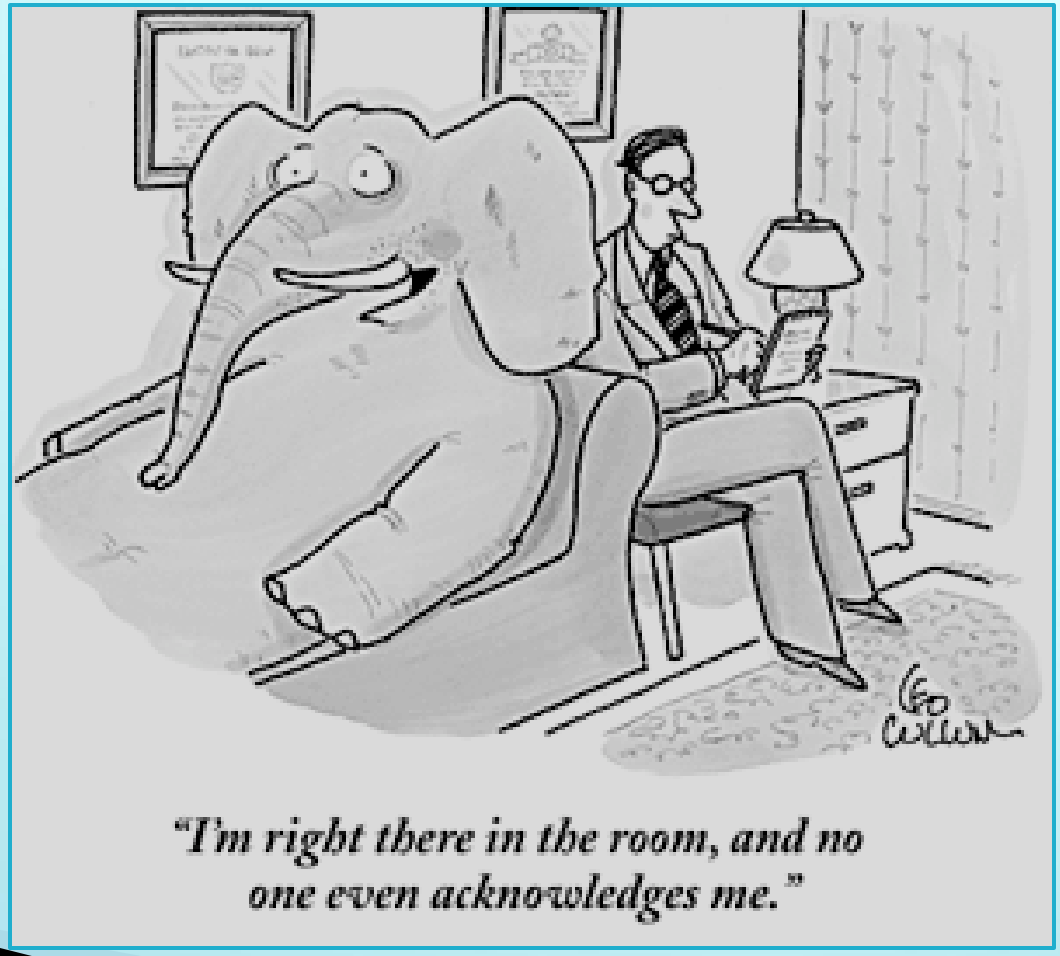
# Anesthetics used on children damage rat brains, study finds

*Researchers .. found ..common..drugs used in pediatric surgery could harm children exposed to anesthesia for long periods… brain damage in infant rats…children may be at risk for brain damage when exposed to anesthesia for long periods…elective surgeries for infants and toddlers …postponed long as possible…*

Tina Hesman. *St Louis Post-Dispatch*: Feb 1, 2003

# "Doctor, will the anesthesia make my child stupid?"



*"I'm right there in the room, and no one even acknowledges me."*

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# Difficulty extrapolating the animal data to humans (early criticisms) (I)

- morbidity lightly anesthetized neonates [1]
  - ketamine ↓ pain-related cell death in rats [2]
- humans are not rats! in terms of RBG→
  - much longer period relative to the exposure
  - ? different recovery profile & vulnerability
  - human equivalent to rat P7 really not well known; 32-36 wks vs. 17-20 wks PC [3]


1 Anand KJ. *Lancet* 1:62;1987
2 Anand KJ. *Pediatr Res* 62;2007
3 Clancy B. *Neurotoxicology* 28:931;2007

# Difficulty extrapolating the animal data to humans (early criticisms) (II)

- animal studies are otherwise flawed [1]
  - physiological monitoring lacking
  - malnutrition, glucose control
  - temperature homeostasis
  - dose/duration related effects
  - the neuronal excitation ass'd w/surgery or pain (which is lacking) is "protective"

1 Anand KJ, Soriano SG. *Anesthesiology* 101:527;2004

# FDA statement: March 2007

*..not adequate data to extrapolate the animal findings to humans…existing and well-understood risks of anesthesia continue to be the overwhelming considerations in designing an anesthetic, and the understood risks of delaying surgery are the primary reasons to determine the timing*

Anesthesia and Life Support Drugs Advisory Committee

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# Assessment of the effects of general anesthetics on developing brain function and neurocognitive function

*Primum non nocere*

"The evidence for anesthetic-induced neurodegeneration in animal models is compelling… anecdotal data point toward the possibility of neurological impairment after surgery & anesthesia"

Loepke & Soriano. *Anesth Analg* 106:1681;2008

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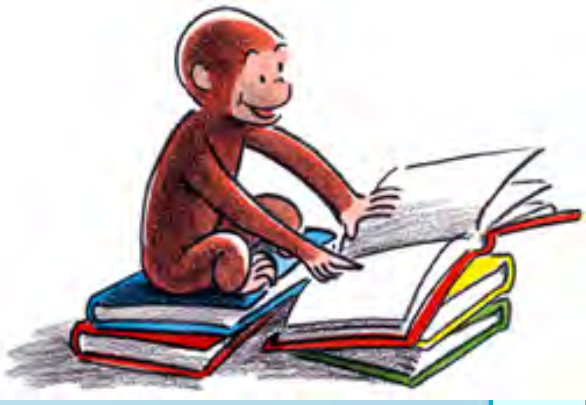
# The next step: study non-human primates (I)



## "LIGHT" KETAMINE ANESTHESIA*

- P5 or 3rd trimester rhesus monkeys: neuroapoptosis @ 9 & 24° but not @ 3°
- P35 monkeys: no neuroapoptosis

* plasma levels 5-10 X human for similar anesthesia

Slikker W. *Toxicol Sci* 98:145;2007

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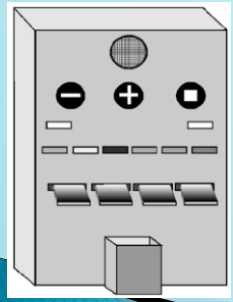
# The next step: study non-human primates (II)

## 24° "LIGHT" KETAMINE ANESTHESIA in P5-6

- OTB: persistent neurocognitive defects
- short-term memory, attention, color & position discrimination and time perception



Paule MG et al. *Neurotoxicol Teratol*; 2011

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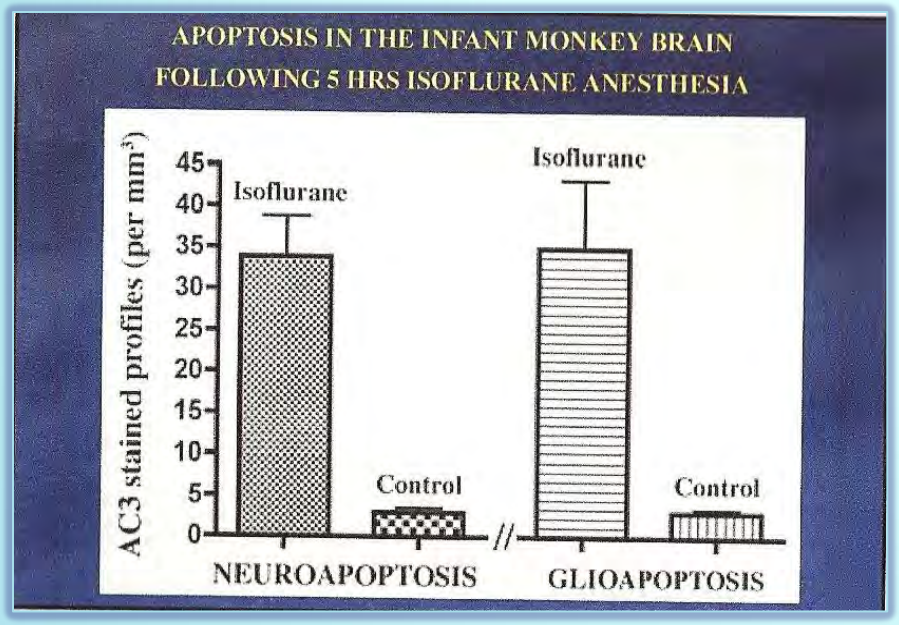
# A new finding from Wash U (Olney) and ONPRC (Brambrink)




P6 monkeys exposed to either "light" isoflurane or ketamine for $5^0$ w/control physiologic parameters

- neurons *and* oligodendrocytes affected with isoflurane 4x as potent as ketamine
- implications for growth & process formation

Brambrink AM et al. ISS:A10;2010

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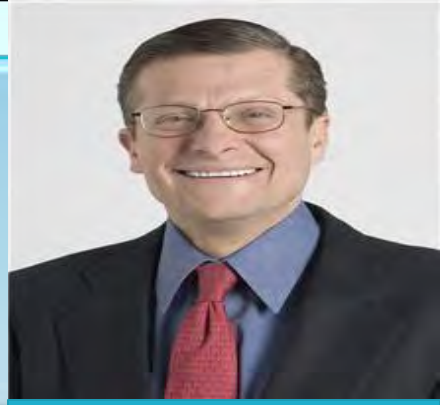
# 2010: IARS* and FDA (PPP) sign a formal memorandum of understanding



Michael Roizen

- **SmartTots** (Strategies for Mitigating Anesthesia-Related neuroToxicity in Tots)
- collaborative effort to ensure the safety of anesthetic drugs in children
- multiple stakeholders: professional societies, academic research institutions, patient advocacy groups, industry and non-profit

* International Anesthesia Research Society

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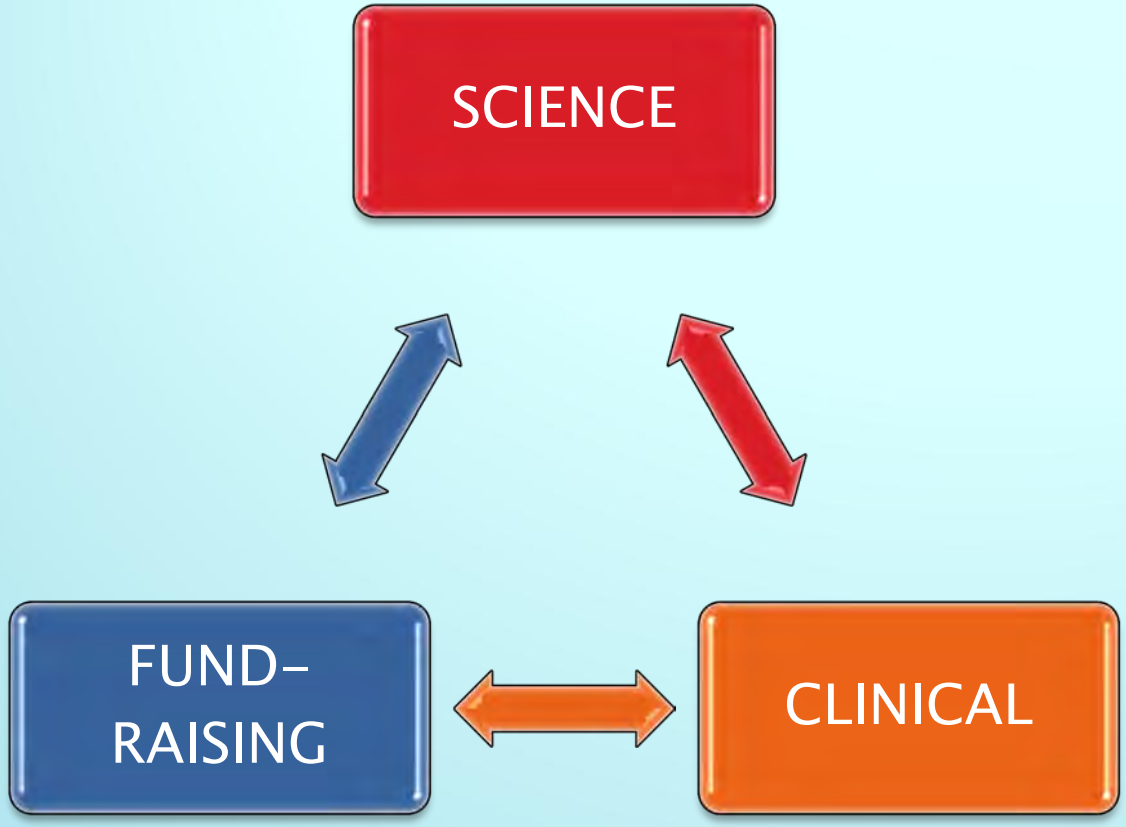
# SmartTots has mission to coordinate research and place outcomes and practice guidelines in public domain

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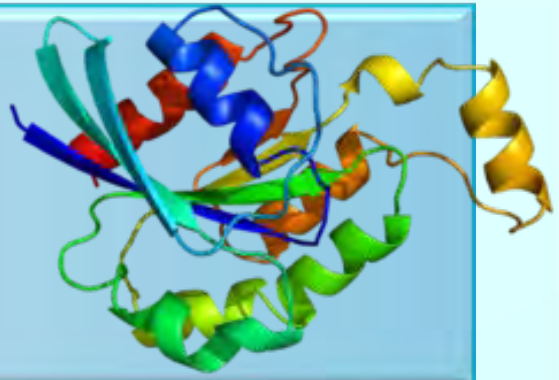
# AIDN research focus: the science



- precise elucidation of human synaptogenesis
- better understanding of AIDN mechanism [1]
- potential co-therapies that ↓ toxicity [2,3,4,5,6]


1 Lemkuil. *Anesthesiology* 114:49;2011 (RhoA ↑ w/actin depolymerization)
2 Creeley CE. *Anesth Analg* 110:442;2010 (dantrolene)
3 Inan. *Anesth Analg* 111:1400;2010 (lithium)
4 Sanders RD. *Anesthesiology* 110:1077;2009 (dexmedetomidine)
5 Yon JH. *Neurobiol Dis* 21:522; 2006 (melatonin)
6 Ma D. *Anesthesiology* 106:746;2007 (xenon)



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# The real question for SmartTots


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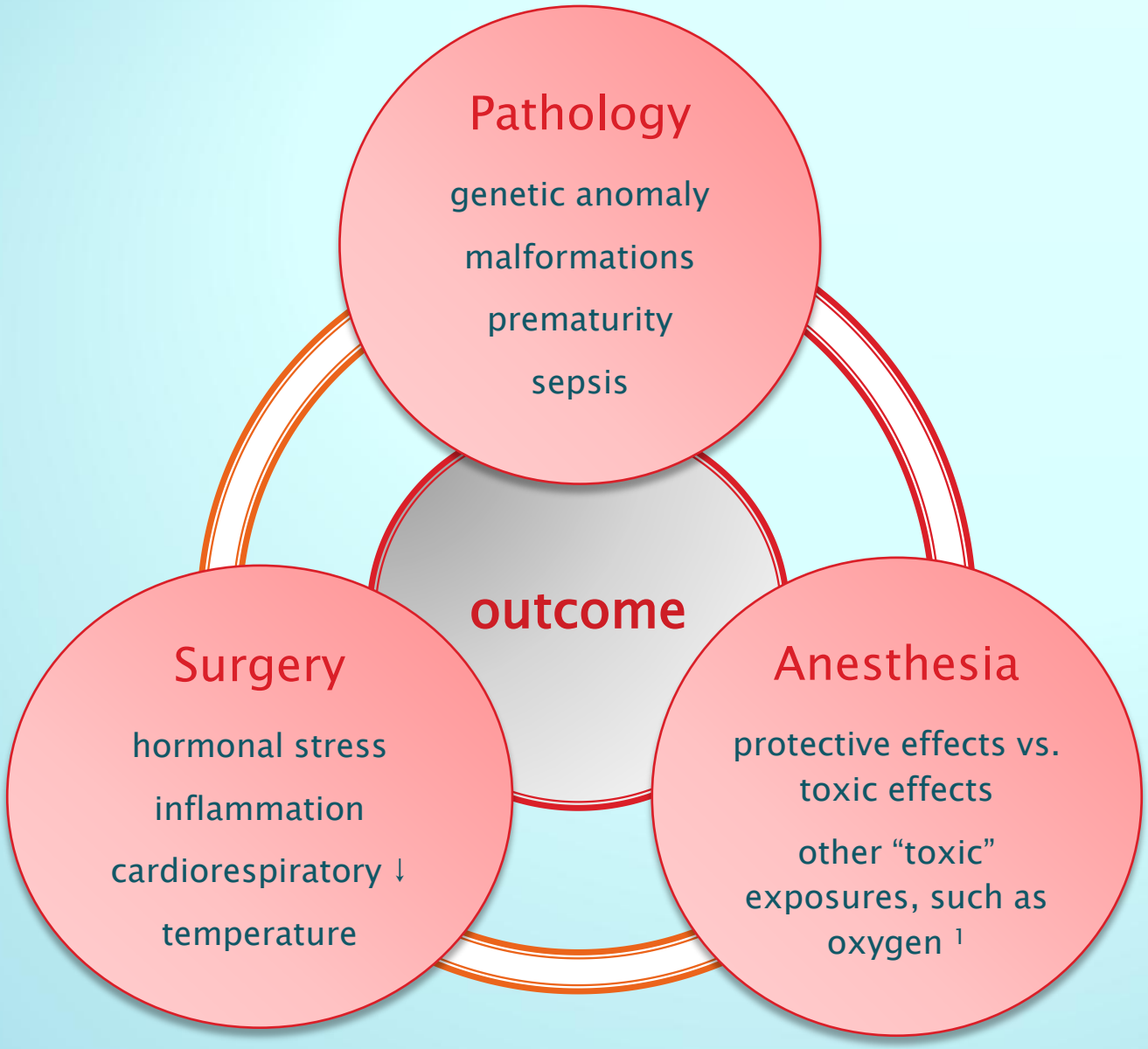
# Clinical studies of neurodevelopmental effects of anesthesia exposure during early childhood: evaluation of early "data"

- 5 retrospective studies published 2007-2010
- precise information about exposure (age, agent, duration and dose) often lacking
- outcome measures (learning disability, parent report of behavior) lack validation & specificity
  - unlike fetal alcohol syndrome, manifestations of AIDN subtle & nebulous, with multiple confounders




1 Hoehn et al. *Pediatr Res* 54:179;2003

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# AIDN: what do we "know" so far?

| STUDY | RESULTS |
|---|---|
| OLMSTEAD CTY BIRTH COHORT<br>1976–1982<br>"Learning Disability" as diagnosis | GA during delivery – ND [1]<br>*multiple* GA < 4 – ↑ LD [2] |
| NY STATE MEDICAID (retrospective)<br>383 IH repair < 3 vs.<br>5050 matched controls | ↑ diagnosis developmental or behavioral disorder (OR 2.3) [3] |
| NETHERLANDS TWIN REGISTRY<br>twins discordant surgery < age 3 | ND in teacher evaluations or educational achievement [4] |


1 Sprung et al. *Anesthesiology* 111:302;2009
2 Wilder et al. *Anesthesiology* 110:796;2009
3 DiMaggio et al. *J Neurosurg Anesthesiol* 21:286;2009
4 Bartels et al. *Twin Res Hum Genet* 12:246;2009

# Early childhood exposure to anesthesia & risk of developmental disorders: sibling birth cohort

- retrospective NYS Medicaid 10,450 sibs born 1999–2005; 304 exposed to surgery < 3
- ↑ likelihood behavioral disorder in those who had surgery BUT
  - if "only" 1 procedure, essentially the same risk
  - twins discordant for surgery showed no difference

DiMaggio.*Anesth Analg* 2011;113:1143

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# Long-term differences in cognitive and language ability after exposure to surgery and anesthesia in infancy

- prospective cohort (1989-92) 2868 children longitudinal neuropsychological testing (Raine)

| surgery < 3; testing at age 10 (CI >95%) | |
|---|---|
| **NO DIFFERENCE** | **IMPAIRMENT (odds ratio)** |
| cognitive function<br>perceptual reasoning<br>fine motor skills<br>gross motor skills<br>behavior<br>vocabulary<br>verbal ability | receptive language (2.3)<br>expressive language (1.7)<br>abstract reasoning (3.4) |

DiMaggio.IARS S336;May 2011

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where is this going??

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# AIDN: current prospective studies (I)

- GAS (GA – Apnea/Apoptosis – Spinal) *
  - international RCT (660) GA (sevo) vs. regional for IH
  - evals at 2 & 5 years standardized neuropsych, IQ

- PANDA (Ped Anesthesia NeuroDev Assessment) *
  - sibling-matched cohort study (500 pairs) ASA I-II with single exposure GA for IH repair < 36 months
  - extensive neuropsych testing between 8 & 15 years

* FDA/SmartTots funding

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# AIDN: current prospective studies (II)

- Danish Registry Study Group (Odense Univ)
  - nationwide epidemiologic study using educational achievement scores age 15-16
  - surgery < 1 vs. general population
  - retrospective data base (1986-1990): ND [1]

1 Hansen TG et al. *Anesthesiology* 114:1076;2011

# A dilemma for years to come

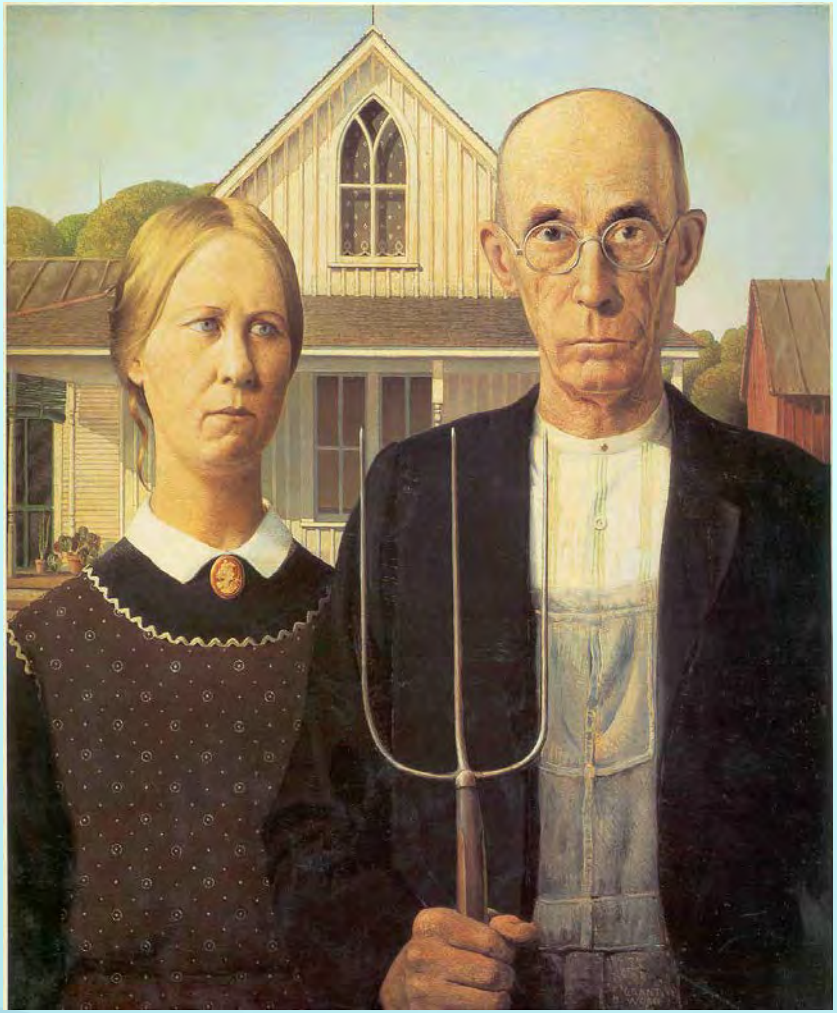
- isolation of potential neurotoxic effects related to anesthesia from other cofounders
- prospective studies underway but studies will take years and may be ultimately inconclusive
- single exposure (↓ power) vs. practical difficulty of prospective cohort w/↑ exposure

# FDA 2011: the challenge ahead

"generating definitive data about the effects of anesthetics on the developing brain will most likely take numerous animal and human studies spanning many years.. will pose enormous challenges to the medical and scientific community. It seems unlikely that any single individual or organization will be able to muster the resources to take on this project."

Rappaport B. *N Engl J Med* 2011;364:1387

# What do I tell the parents??



# www.smarttots.org information for parents (I)

- while investigations are underway, harm to children remains unproved; animal studies ..must not prompt changes with undue consequences .. such as postponing *necessary* surgery

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# www.smarttots.org information for parents (II)

- while there is no practical and safe alternative to general anesthesia for most procedures in children < 4, balanced techniques often allow for reduced exposure to those agents with potential harm

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OR DESK 444-6030

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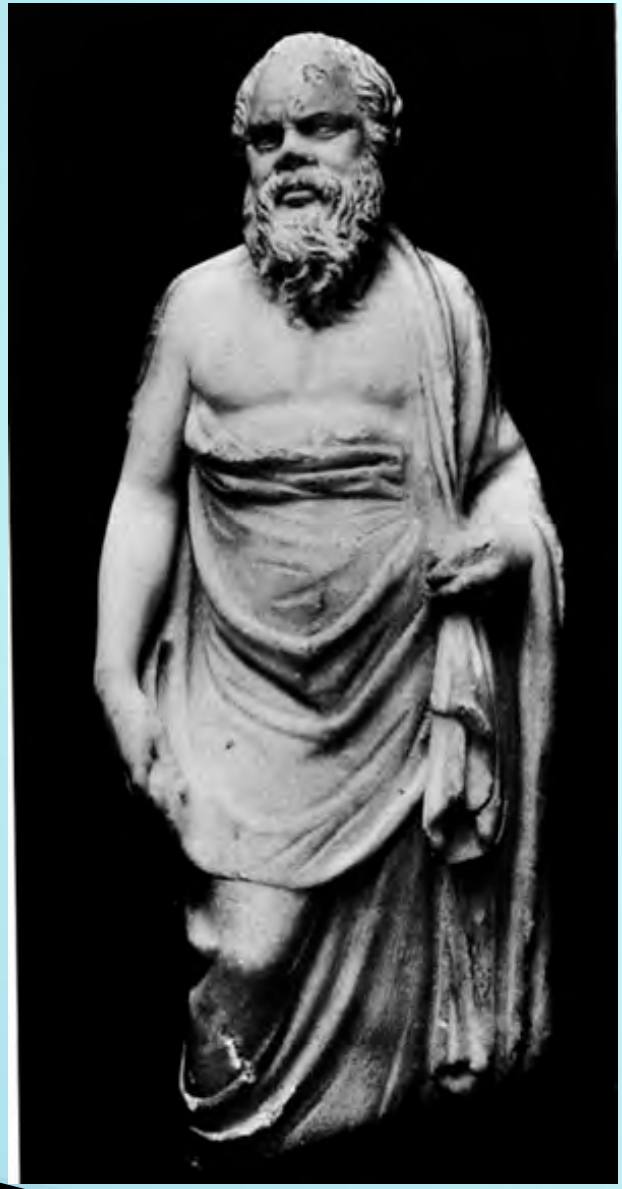

*I am the wisest man alive, for I know one thing, and that is that I know nothing.*

Socrates
469-399 BCE