# Current and Future Research: Schizophrenia

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# Disclosures

- Consulting/Advisory Boards:
  - Amgen, Takeda, Medavante, Teva, Sofinnova
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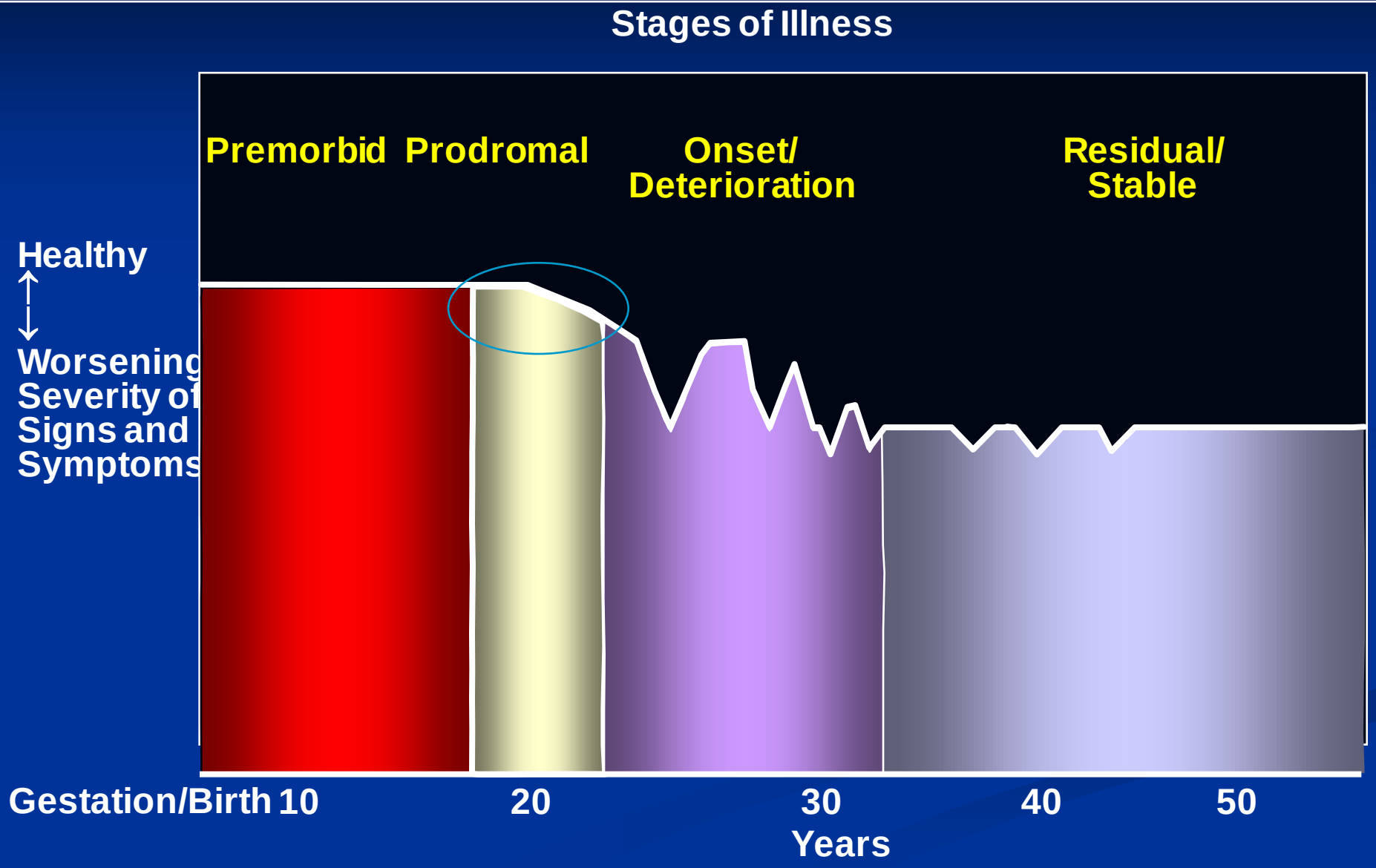
  - None
- Stock/Equity Holdings:
  - None

# Natural History of Schizophrenia




adapted from *Breier 1991; Lieberman 2005*

# The Case for Early Intervention

*Early intervention results in:*

- Decreased inpatient admissions and ER visits (Krstev 2004)
- Reduced duration of untreated psychosis (Perkins 2005)
- Fewer relapses (Mihalopoulos 2009)
- Lower levels of positive and negative symptoms and improved functioning long term (Addington 2004; Krstev 2004)
- Reduced health care costs (Yung 2007)
  - 66% cost reduction compared to usual treatment (Mihalopoulos 2009)
  - $7,500 per person per year cost savings (Orygen Research Center 2008)

# Goals of Current Clinical Trials in Prodromal and First-Episode Schizophrenia

- Improve the long term illness trajectory through early intervention
  - E.g., Recovery After an Initial Schizophrenia Episode (RAISE) - NIMH, multi-site assessment of currently available "optimal" therapy
  - Enroll symptomatic patients – late prodromal or 1st episode
- Delay the onset of schizophrenia through early intervention
  - E.g., McGlashan et al, McGrory et al
  - Enroll prodromal patients, symptomatic Dx (e.g., SIPS)

# Challenges for Current Trials

- Improve case selection, decrease non-conversion rates
- Current conversion rate from prodrome to schizophrenia is approximately 30%
- Conversion rate improves (>65%) by sample enrichment with risk factors (Cannon et al 2008)
- Substantial research assessing biomarkers that predict conversion is currently ongoing (e.g., MRI, MRS, ERPs, genetics, etc) but not yet ready for registration trials
- Recruitment/retention is particularly challenging for prodromal/1st episode patients

# Prediction of Psychosis in Youth at High Clinical Risk

- Genetic risk for schizophrenia with recent deterioration
- Unusual thought content
- Suspicion/paranoia
- Social impairment
- Substance abuse

2 or 3 of these variables predict psychosis **68%-80%** of the time

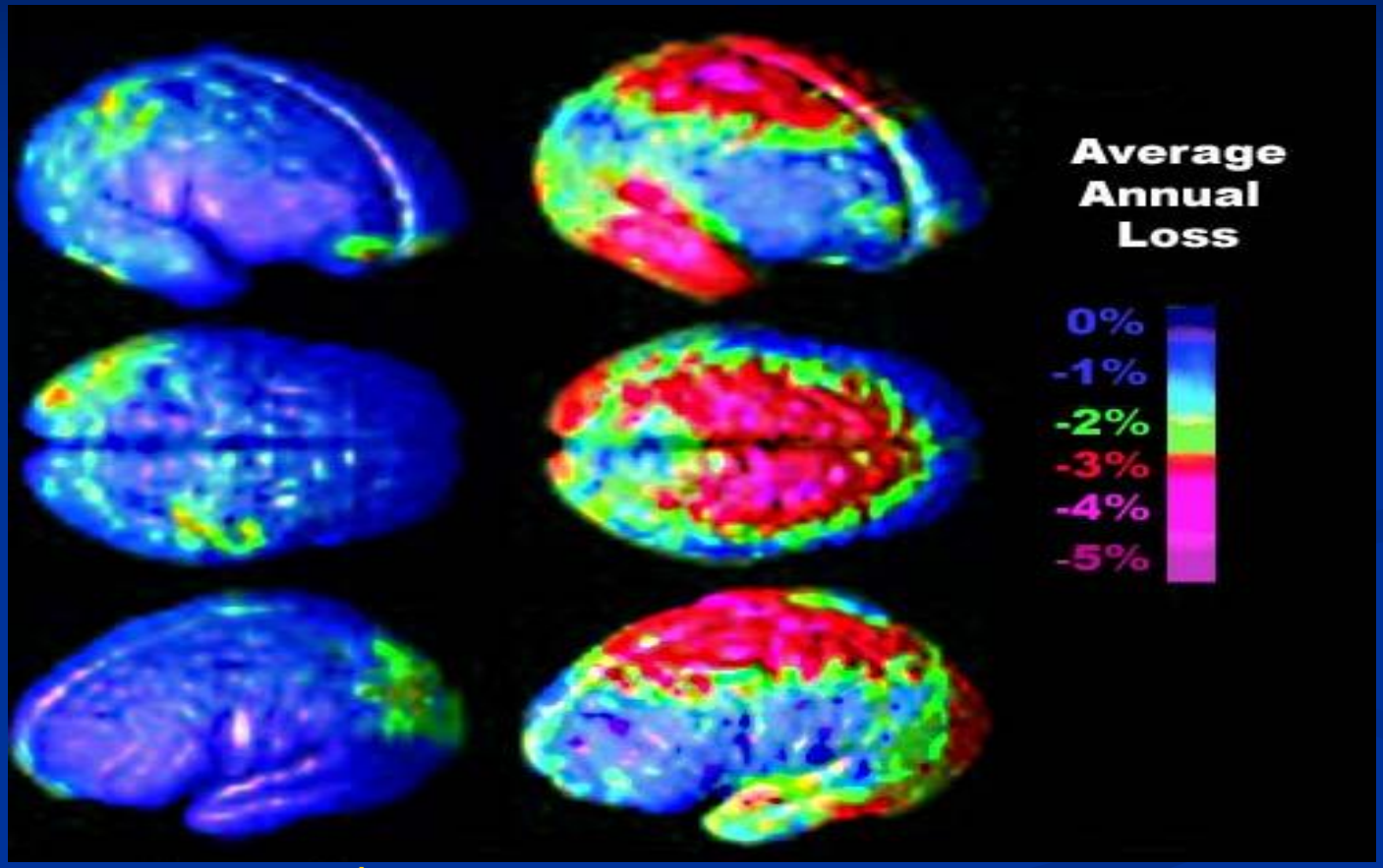
Cannon et al, *Arch Gen Psychiatry* 65(1):28-37, 2008

# Challenges for Future Research in Prodromal and First Episode Schizophrenia

- Validate diagnostic biomarkers
  - Proposal: Initiate an ADNI-like program for the schiz prodrome
- Establish intermediate/surrogate endpoints for illness onset
- Address recruitment/retention issues
  - Proposal: Establish academic clinical trial site networks
- Assess novel agents and targets
  - E.g., Neuroprotection, Disease modification, Cortical gray matter loss

# Gray Matter Loss in Early-Onset Schizophrenia:

## *A target for novel therapeutics?*




Normal Adolescents

Schizophrenia Subjects

Thompson, et al. *PNAS*. 2001.

# Progressive Brain Changes in 1st-Episode Children and Adolescents

- **Methods**
  - Age: 15.5 years, minimal prior APD exposure
  - 2 year follow up, 6 sites
- **Results**
  - Frontal gray decreases/CSF increases in schiz (not in BP) compared to controls
  - Brian changes related to weeks hospitalized, negative symptoms
  - APDs did not appear to account for brain changes

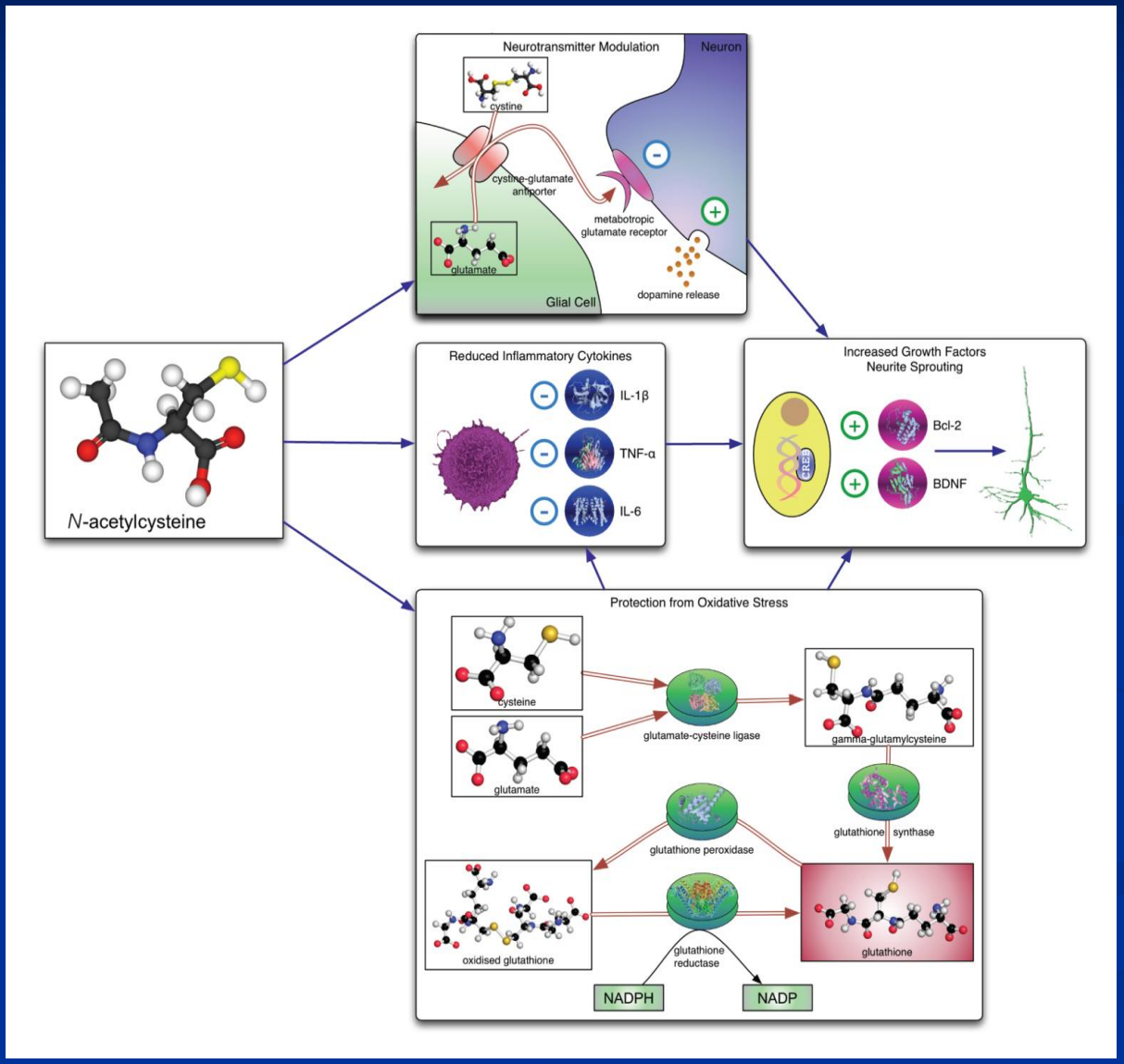
Arango et al Arch Gen Psych 2012

# Hypotheses for Progressive Cortical loss

- Glutamatergic excitotxicity
- Oxidative stress
- Inflammation
- Excessive pruning
- Possible contributory effects of (some)antipsychotic drug exposure

Coyle 1996; Ho et al 2011; Lewis 2011

# N-acetyl Cysteine (NAC): Mechanisms of Action




- Increases glutathione levels by delivering cysteine to brain – the rate limiting precursor for glutathione synthesis (Gysin 2007)
- Regulates intra- and extra-neuronal glutamate through the cystine-glutamate antiporter (Dringen 2000)
- Reduces inflammatory cytokines (Chen 2008)

Dean et al 2011

# N-acetyl Cysteine Treatment in Psychiatric Disorders

**Psychosis**

- Schizophrenia — Berk 2008, Lavoie 2006, Bulut 2009
- Bipolar — Berk 2008

**Addictions**

- Cocaine — Mardikian 2007, LaRowe 2006, 2007
- Cannabis — Gray 2010
- Nicotine — Knackstedt 2009, VanSchooten 2002
- Gambling — Grant 2007

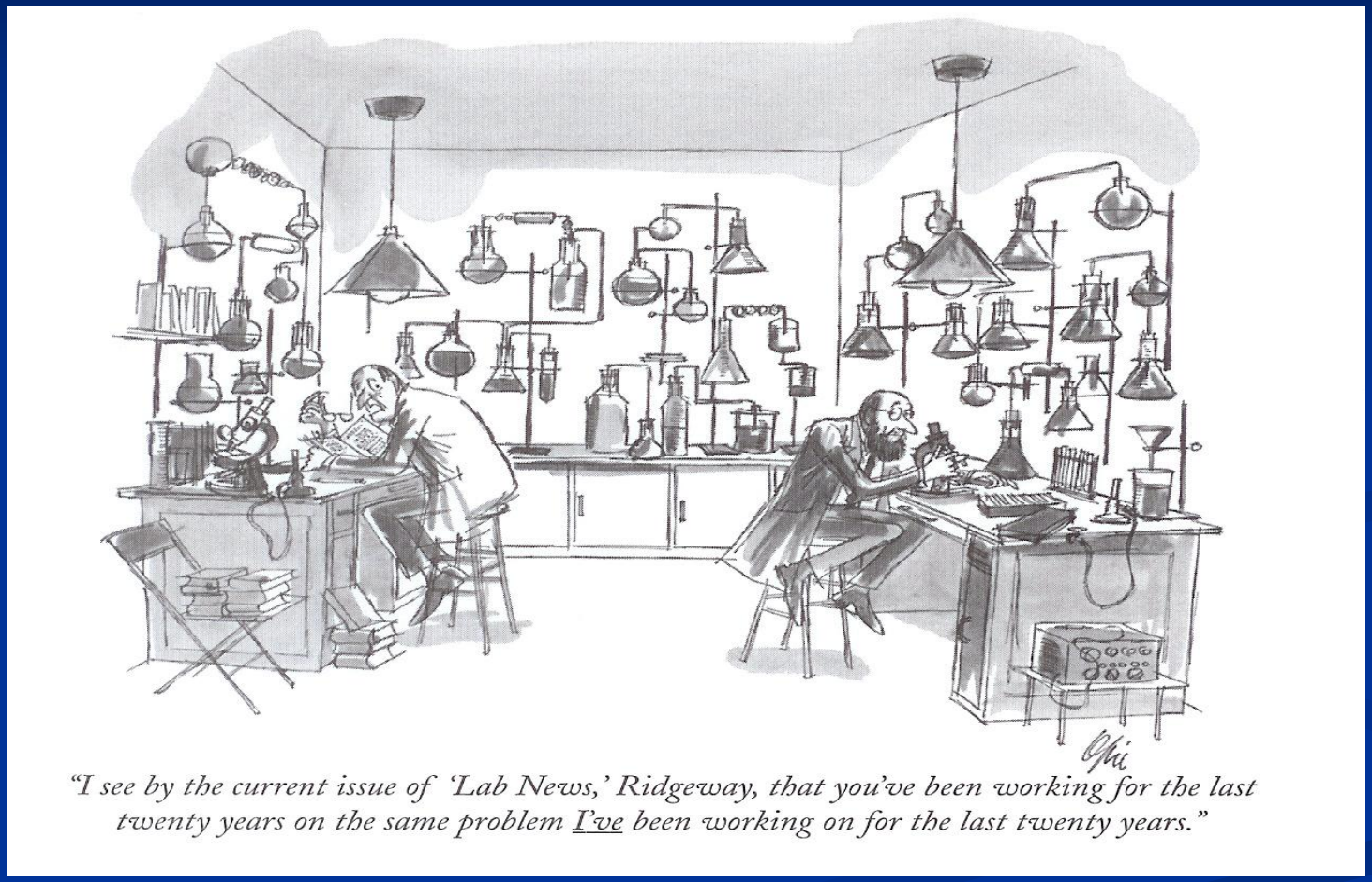
**Compulsive Behaviors**

- OCD — Lafleur 2006
- Trichotillomania — Grant 2009, Odlaug 2007
- Nail Biting, skin picking — Berk 2009 , Odlaug 2007

# Prevention of Cortical Erosion by Treatment with N-Acetyl Cysteine

- Primary aim: determine if NAC prevents cortical erosion in early stage psychosis
- N=60 early stage psychosis patients from IU/PARC
- 12 month, double blind NAC vs. Placebo
- Outcome measures: serial MRI/MRS, cognition, ERP, symptoms, functioning
- Funding agency: Stanley Foundation
- Results pending

# Importance of Collaboration



*"I see by the current issue of 'Lab News,' Ridgeway, that you've been working for the last twenty years on the same problem I've been working on for the last twenty years."*

***"Why can't we all just get along?"***

**- Rodney King**

# Thank you for your attention!

Questions

Comments

Discussion