Saul Bellow
Nobel Prize for Literature, 1976

"The work of the artist cannot be expected to comprehend the work of the scientist... [The work] sets up hypotheses and tests them in various ways, and it gives answers, but these are not definitive. However, they need not be definitive; they sing about the human situation."

Letter to Melvin Tumin, 1942, quoted in the New Yorker April 26,2010, p. 53

Advice for a Young Investigator Ramón y Cajal 1916

- I shall assume that the reader's general education and background are sufficient to understand that the major sources of knowledge include observation, experiment, and reasoning by induction and deduction.

Induction

- Generalizing from individual observations
  - **“When I had investigated my first two dozen cases of Parkinson, I was convinced that I knew where the cause of tremor and rigidity was located.” Lewy**
- **Can induction prove anything?**
  - **“When I had examined pathologically the seventh dozen of Parkinson brains, I was completely confused…"**

Deduction – using logic to go from the general to the particular

- Arthur is a dog
- All dogs have fleas
- Ergo, Arthur has fleas

Journal Club for April 13, 2012

The Parkinson Study Group NEJM 328:176-183 1993

- 1) Why were tocopherol and selegiline (deprenyl) chosen for the trial?
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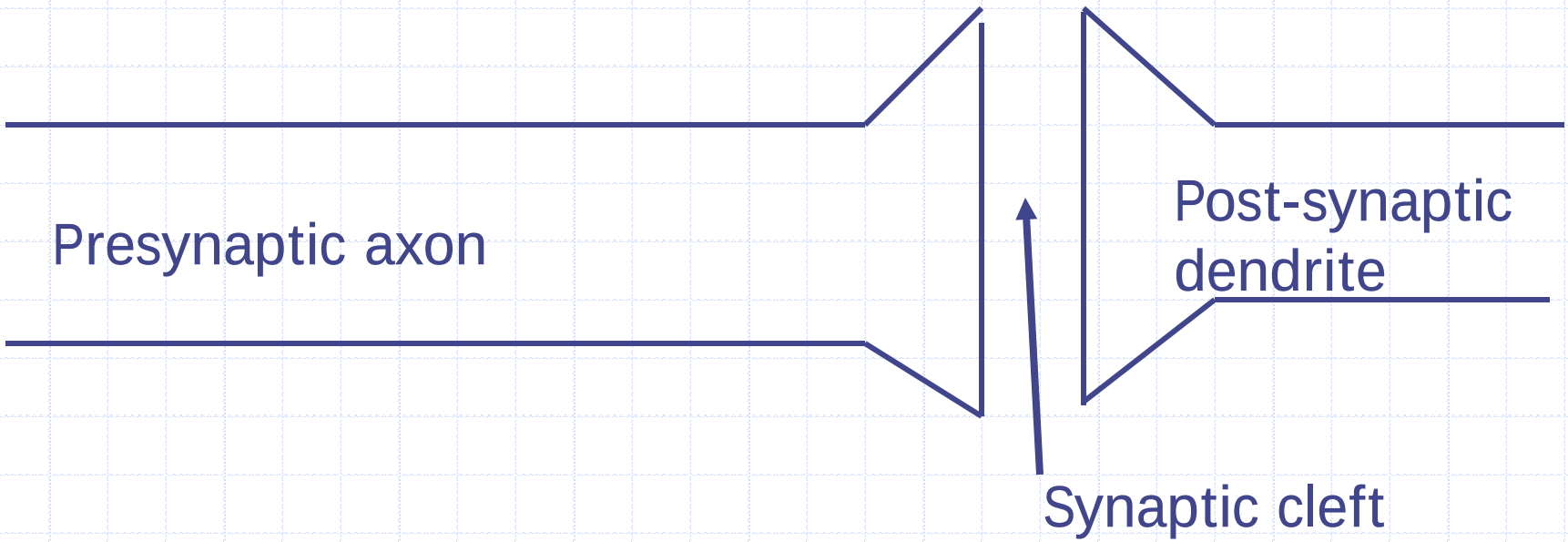
Journal Club contents

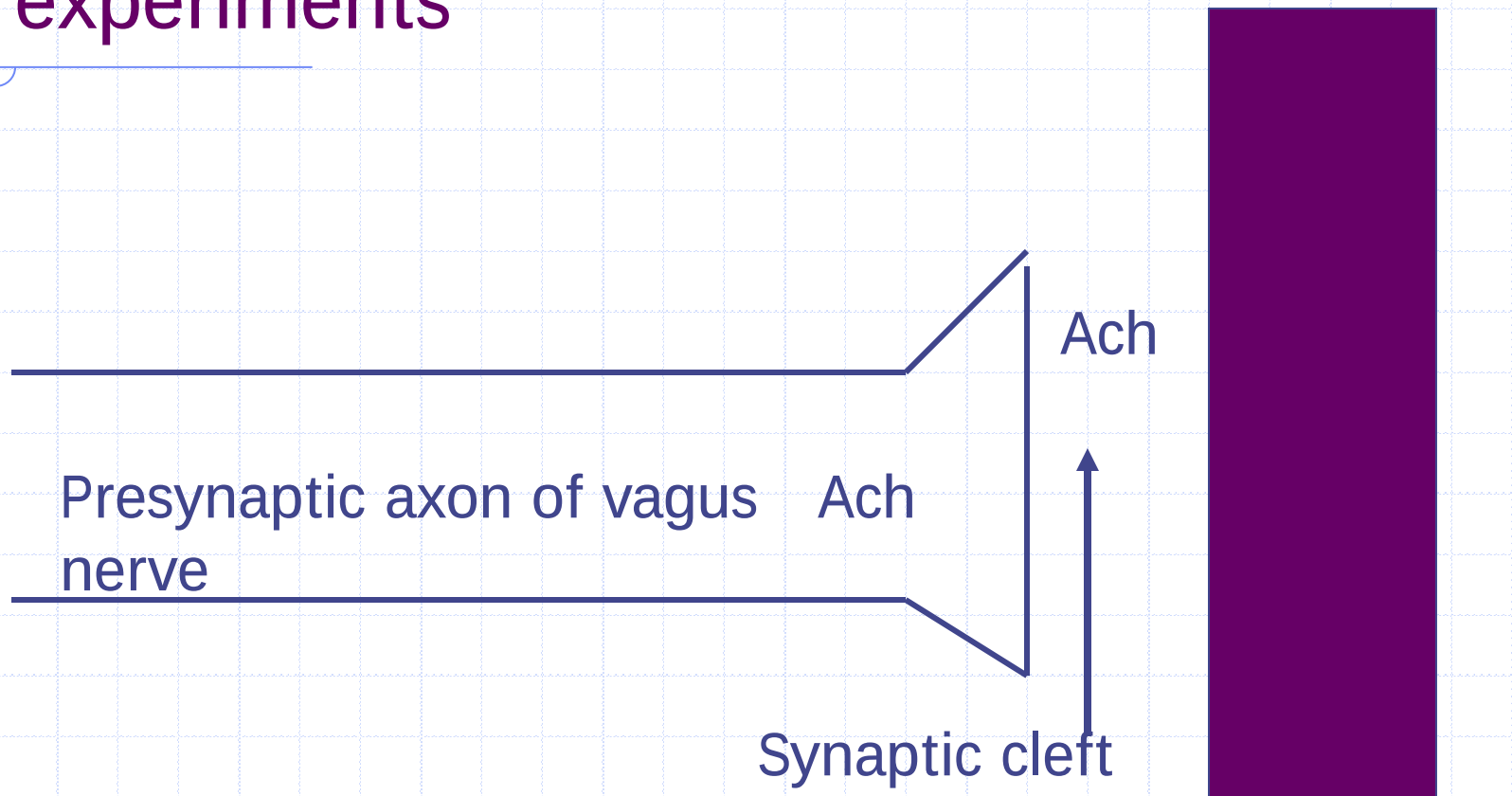
- Article citation
- Deep Background
- Methods
- Results
- Interpretation
- Critique

- Neurotransmitters explain movement of information across the synapse

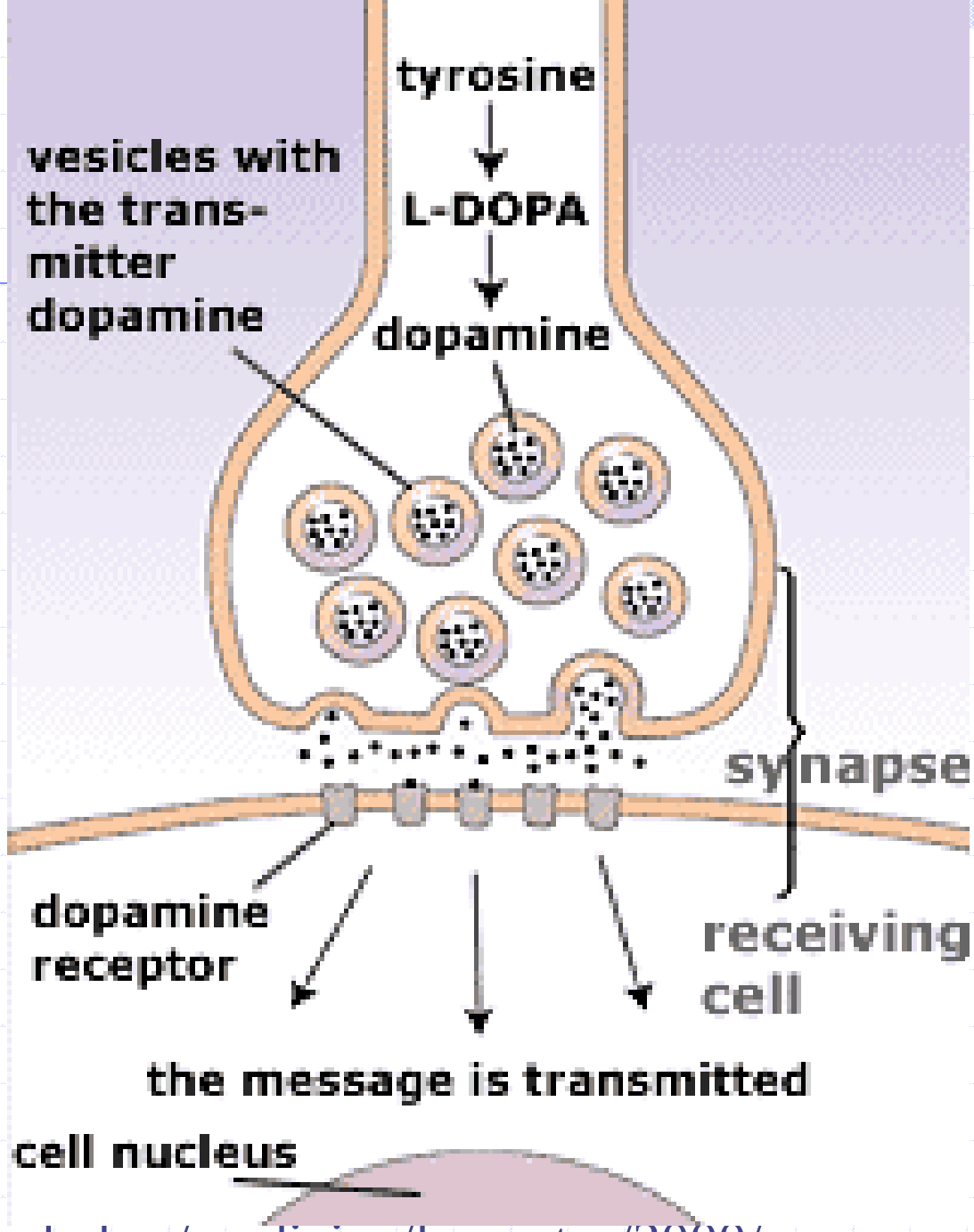
Simple model of a synapse



Model of a synapse between vagus nerve and heart muscle after Loewi's experiments



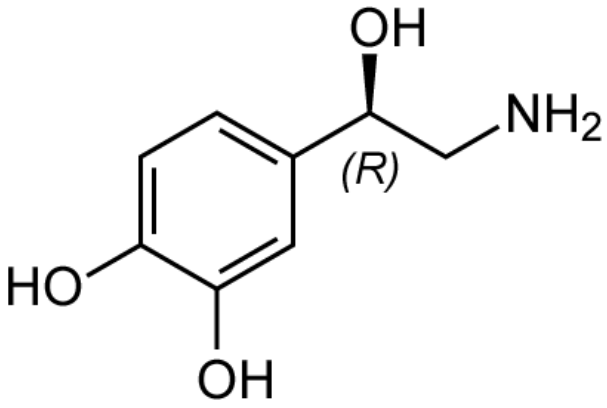
Ach = acetylcholine in vagus nerve and released into synaptic cleft to inhibit heart muscle beating



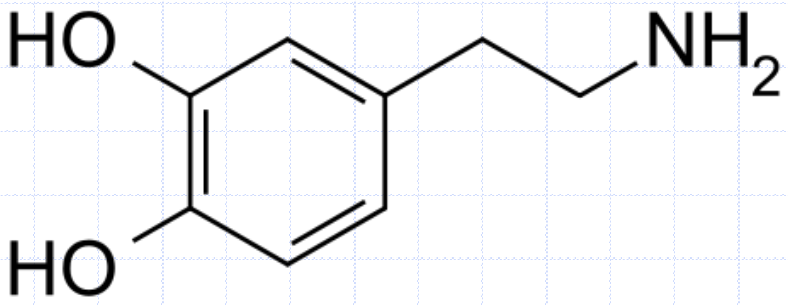
http://www.nobel.se/medicine/laureates/2000/

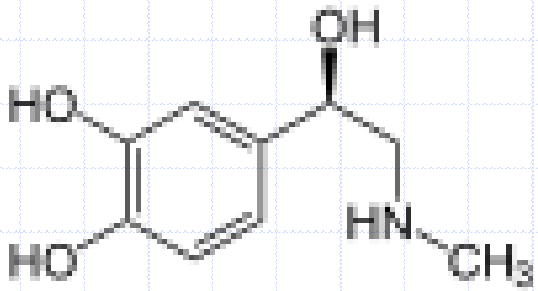
Monoamines

Norepinephrine

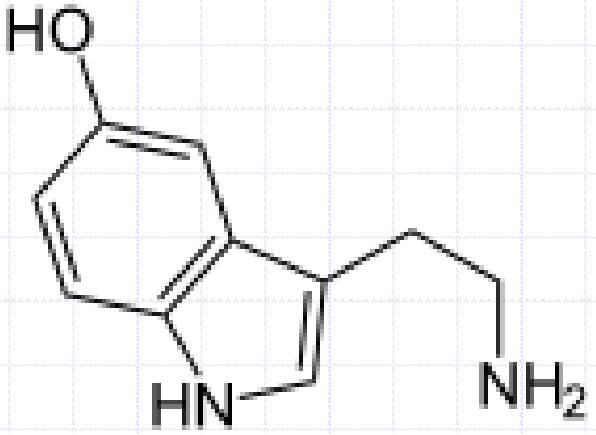


Dopamine





Epinephrine

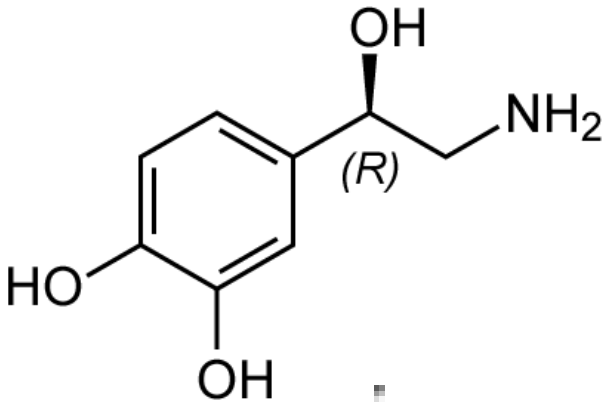


Serotonin

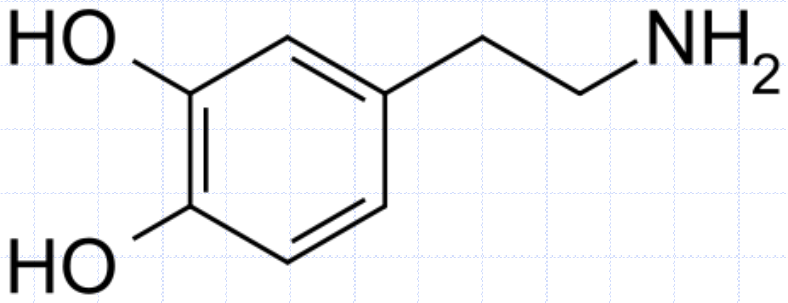
Wikipedia, Creative Commons

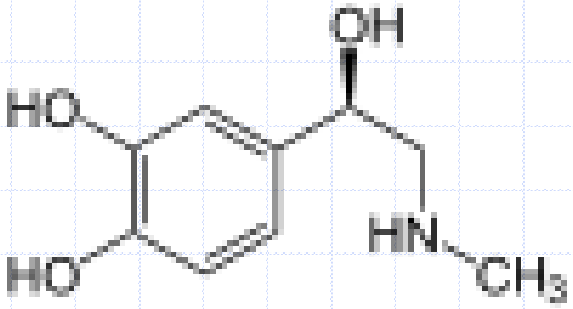
Cathecholamines

Norepinephrine



Dopamine

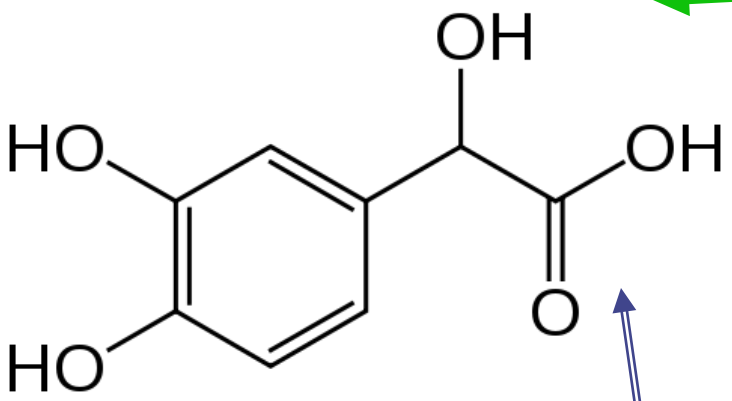




Epinephrine (Adrenaline)

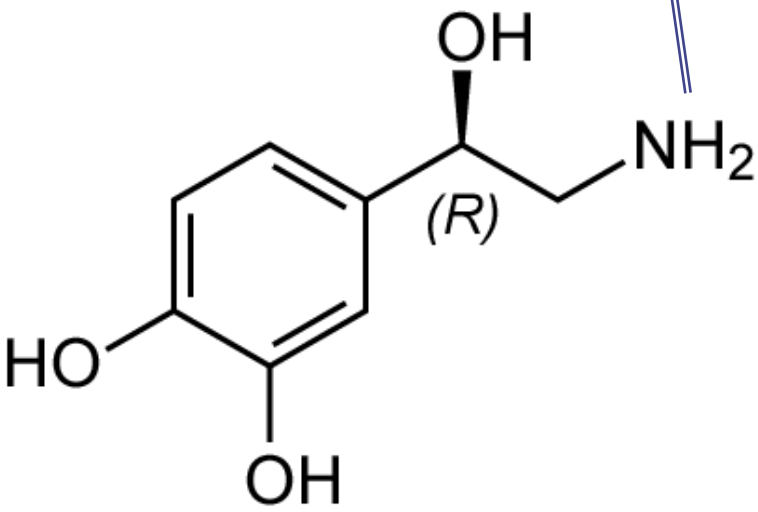
Wikipedia, Creative Commons

3,4-Dihydroxymandelic acid



Oxidized molecule

Reaction catalyzed by MAO, monoamine oxidase



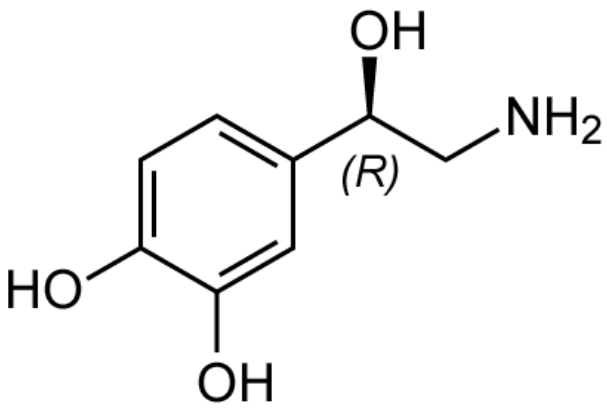
Norepinephrine

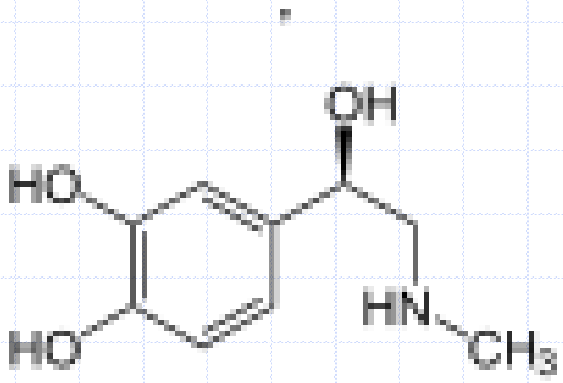
Monoamine

Wikipedia, Creative Commons

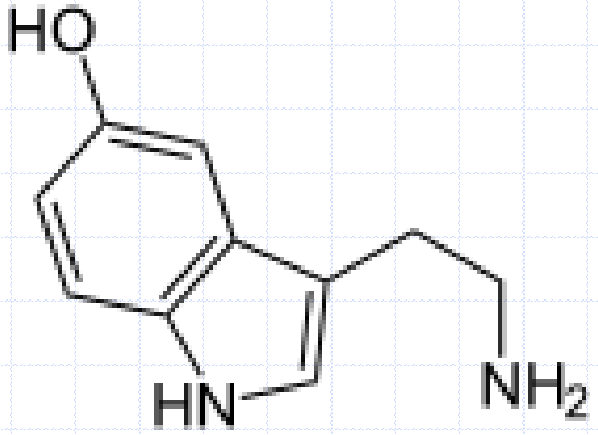
Monoamines Metabolized by MAO-A

Norepinephrine





Epinephrine

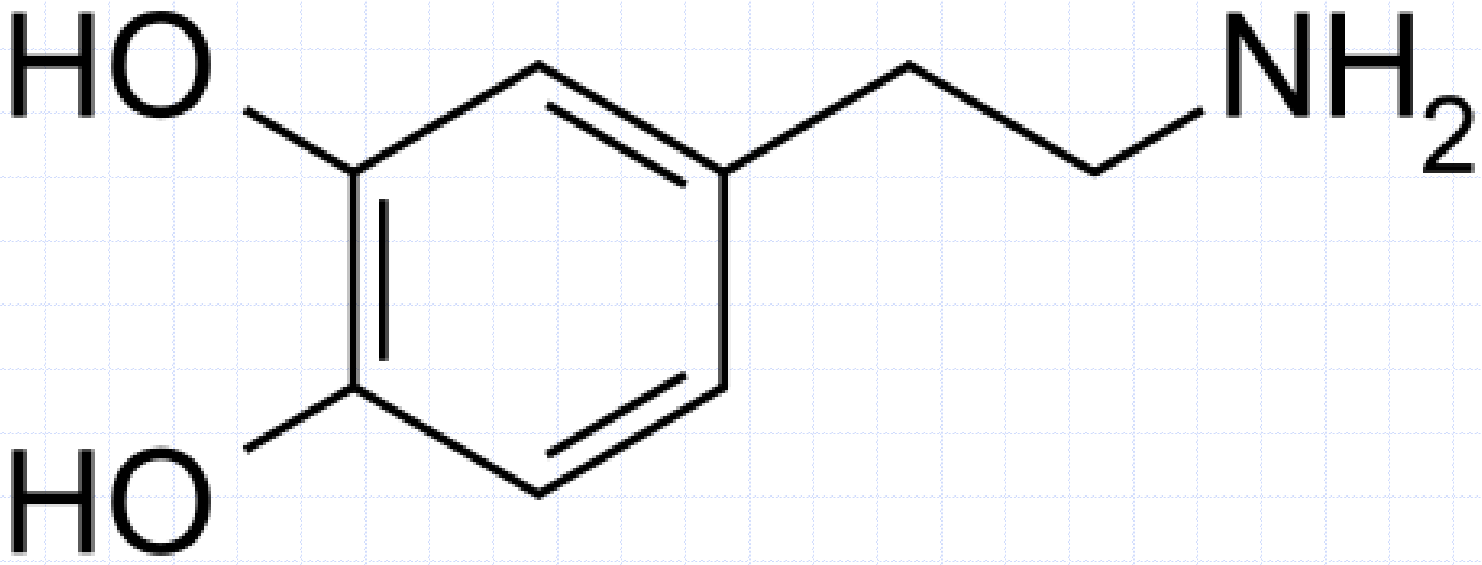


Serotonin

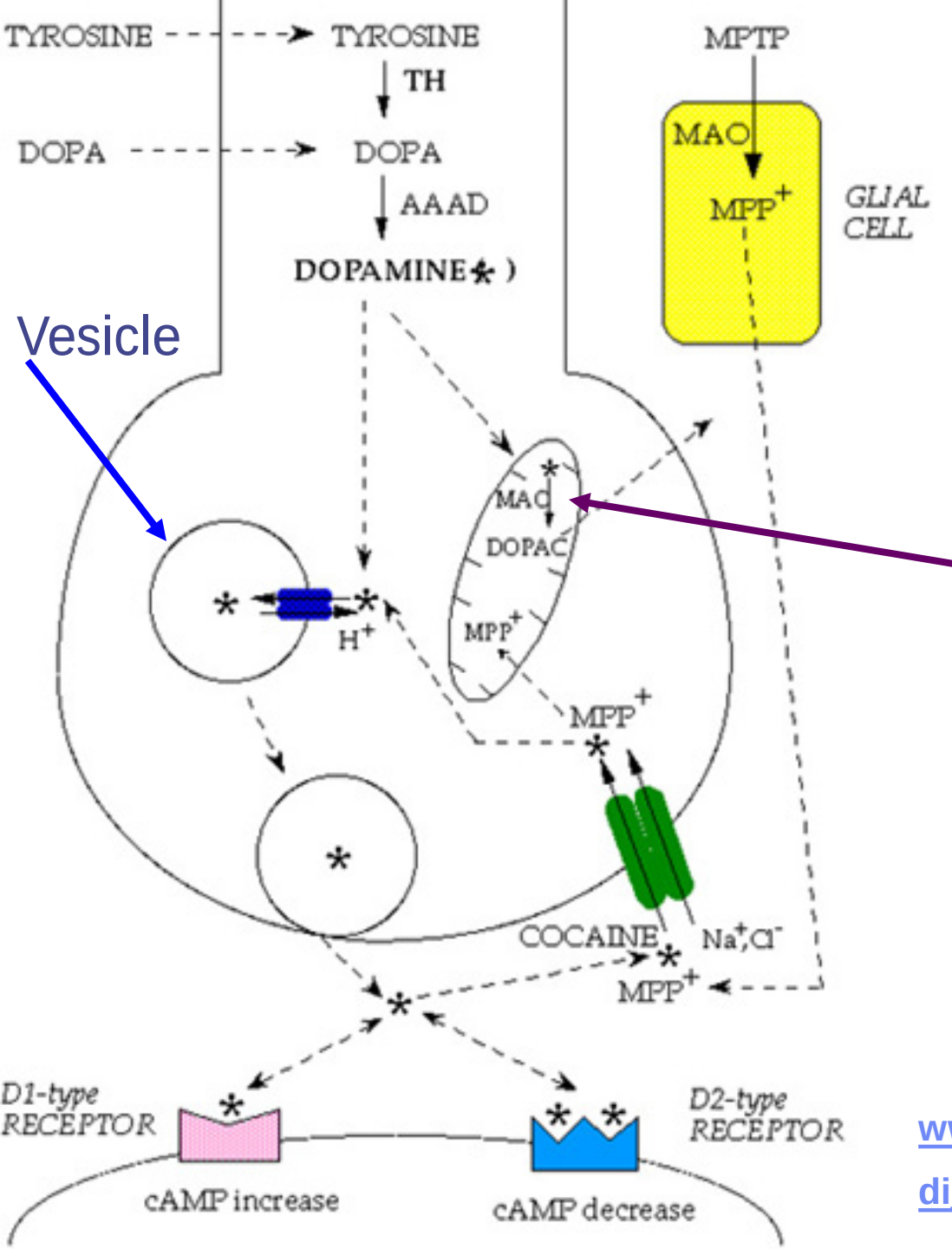
Wikipedia, Creative Commons

Monoamines Metabolized by MAO-B

Dopamine



Wikipedia, Creative Commons



After dopamine is released into the synapse, it is taken back into the neuron by the dopamine transporter (DAT). Once inside the cell, MAO helps to inactivate dopamine.

If MAO is blocked, more dopamine is available to go back into vesicles for reuse.

www.mcmaster.ca/inabis98/sadile/di_porzio0329/two.html

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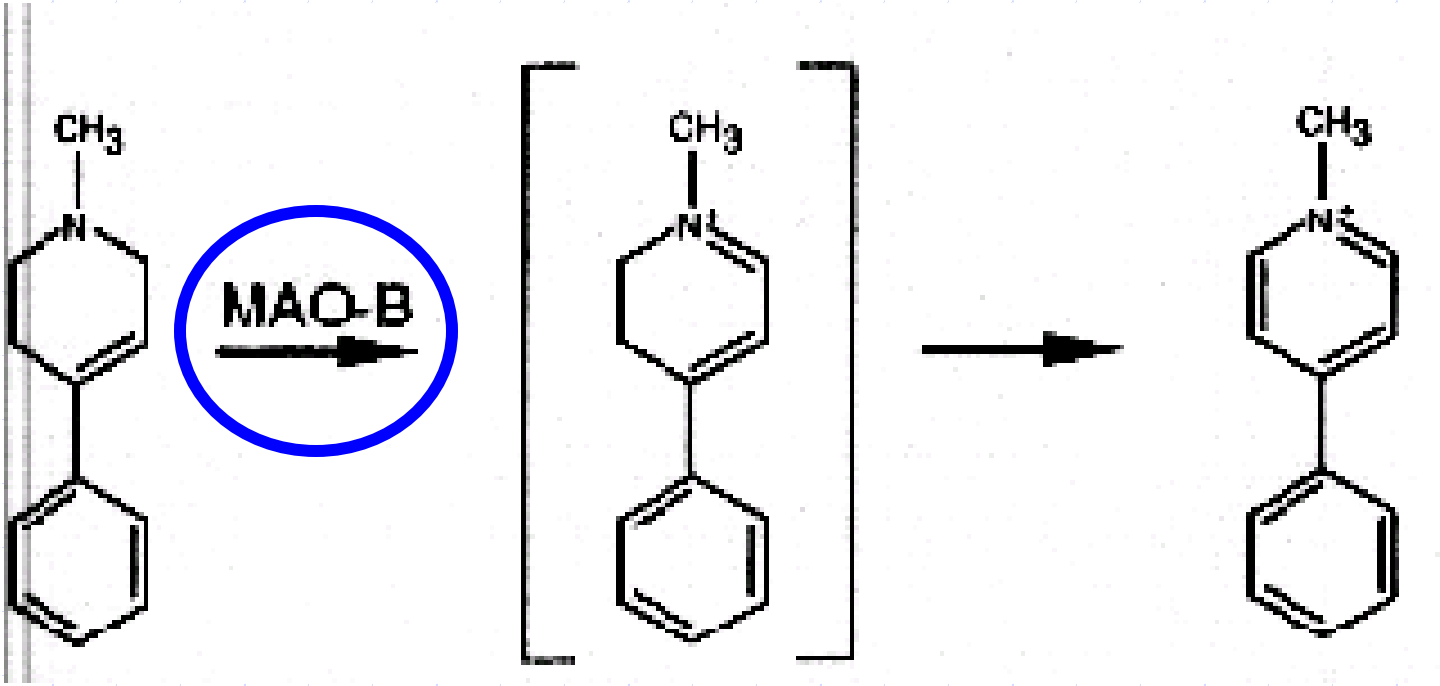
Metabolism of MPTP Methylphenyltetrahydropyridine



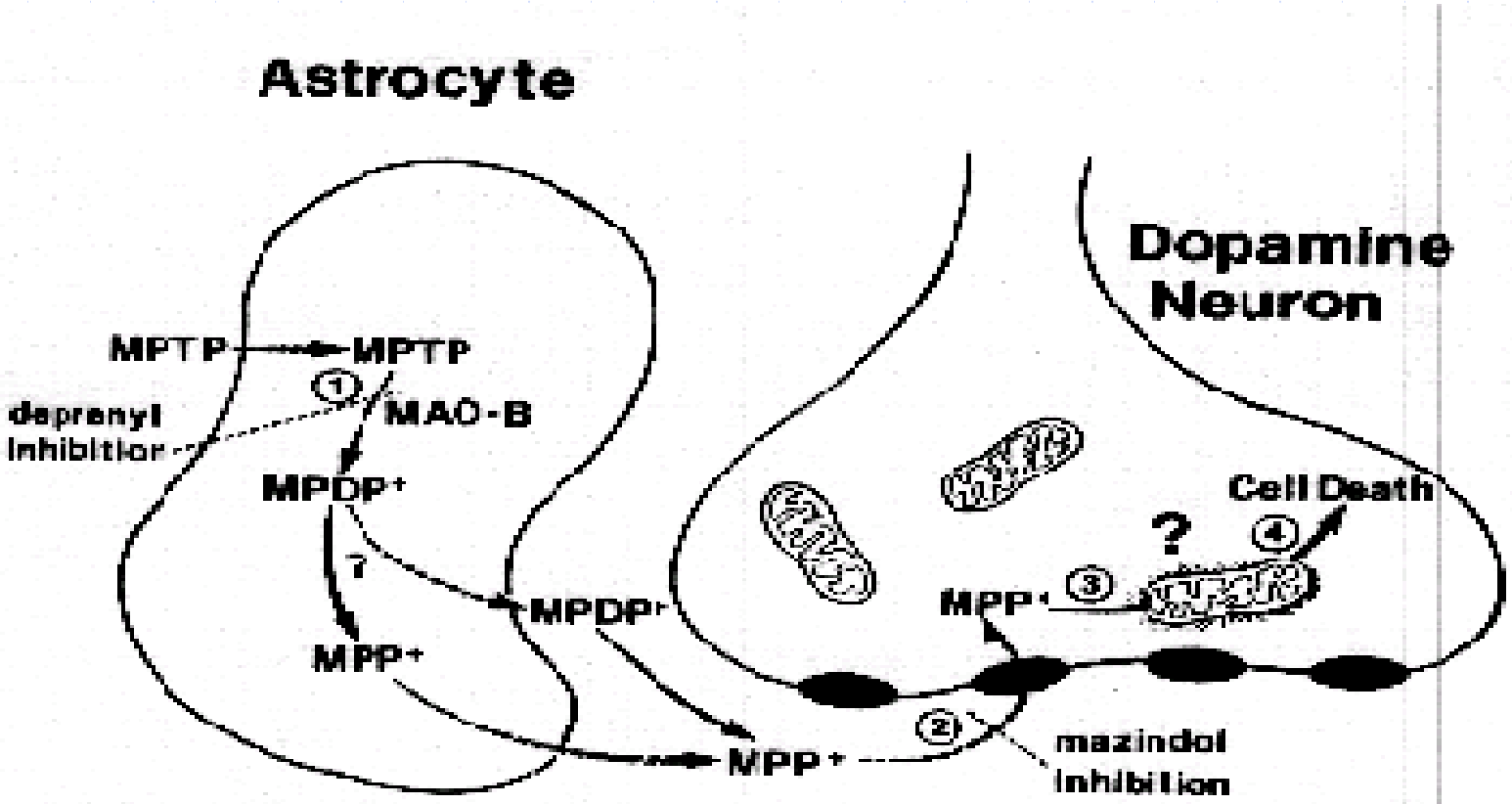
MPTP **MPDP+** **MPP+**

MAO = monoamine oxidase

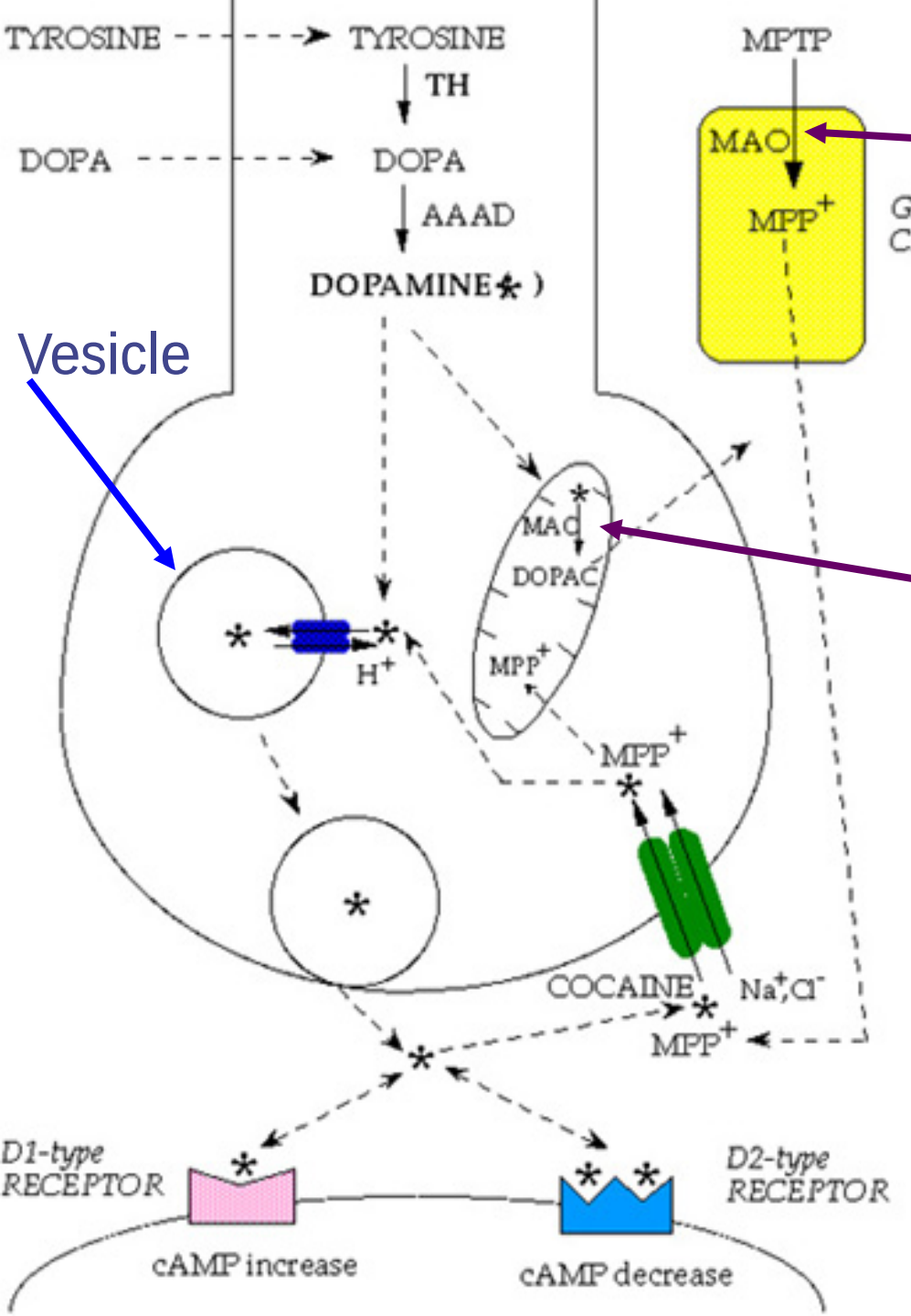
MPTP and Animal Models of Parkinson's Disease

MPTP = Protoxin

MPP + = Toxin



Sonsalla PK, Golbe LI **Deprenyl as prophylaxis against Parkinson's disease?** Clin Neuropharmacol. 1988;11:500-11.



MAO in astrocyte

MAO in neuron

www.mcmaster.ca/inabis98/sadile/di_porzio0329/two.html

Experiments in animals suggest selegiline might be neuroprotective

- Animals given MPTP develop parkinsonism
- Selegiline blocks the activity of MAO
- Animals given selegiline before being given MPTP do not develop parkinsonism
- Hypothesis: If Parkinson's disease is caused by environmental or endogenous protoxins activated by MAO, then selegiline might prevent development and progression of Parkinson's disease

Clinical trials

- Phase I – dose finding
- Phase II – therapeutic value and adverse effects
- Phase III – randomized controlled double blind

Clinical trials

- Phase I – dose finding
- Phase II – therapeutic value and adverse effects
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Selegiline Phase 2 results

- Patients treated with selegiline + L-DOPA did better than those treated with L-DOPA alone
- Uncontrolled 9 year series: those treated with selegiline lived longer

Journal Club for April 13, 2012

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Reasons for trying Vitamin E

- Anti-oxidant effect
- Phase I and II trials

DATATOP Methods?

DATATOP Methods
800 patients

	Vitamin E 1000 IU Twice daily	control E
Selegiline	Both drugs	Selegiline + control E
control S	Vitamin E + control S	Both controls

NEJM 1993;328:176

Journal Club for April 13, 2012

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Clinical Trial Vocabulary

- Controlled
- Randomized
- Double-blind
- Statistical significance
- Clinical significance
- Null ***hypothesis***
- Primary outcome measure

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- Controlled
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Deduction – using logic to go from the general to the particular

- Arthur is a dog
- All dogs have fleas
- Ergo, Arthur has fleas

Proving a Hypothesis

All dogs have fleas.

Deduction plus Observation can Disprove an Hypothesis

- Arthur is a dog
- All dogs have fleas
- Ergo, Arthur has fleas

- Arthur does not have fleas
  - This is an inductive step.
  - How accurate is the observation?
- Some dogs are flealess.
- The hypothesis must be wrong if Arthur is really a dog.

Deduction plus Observation can Disprove an Hypothesis

- Arthur is a dog
- All dogs have fleas
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- Arthur does not have fleas
  - This is an inductive step.
  - How accurate is the observation?
- Some dogs are flealess.
- The hypothesis must be wrong if Arthur is really a dog.
  - "All dogs have fleas" was the null hypothesis for this experiment.

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- The null hypothesis is the opposite of what we really want to prove. We prove our hypothesis by disproving the null hypothesis.

Hypothesis testing

- *Null hypothesis*:

There is no therapeutic difference between control S and selegiline

- *Alternative hypothesis*:

Selegiline is more effective than control S.

Hypothesis testing

- *Null hypothesis*:

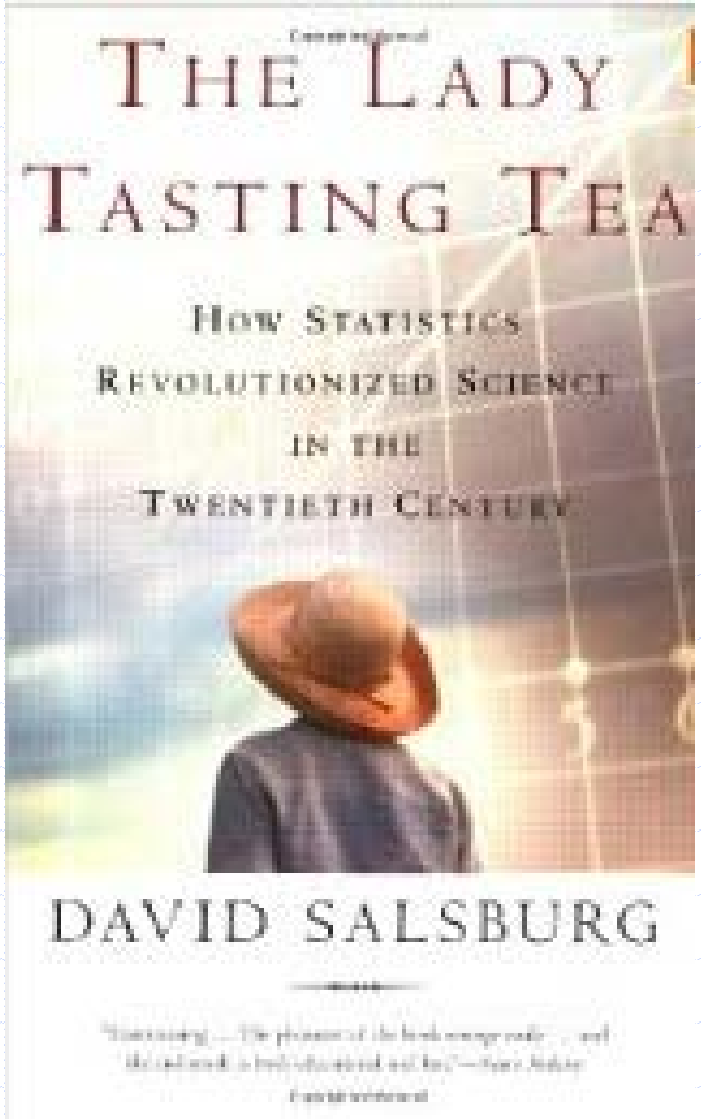
There is no therapeutic difference between control E and vitamin E

- *Alternative hypothesis*:

Vitamin E is more effective than control E.

What are the chances of getting 5 heads if you flip a coin 5 times?

- At a tea party in Cambridge in the 1920s a lady insisted that tea poured into milk tastes different than milk poured into tea.
- RA Fisher proposed to test her hypothesis scientifically.



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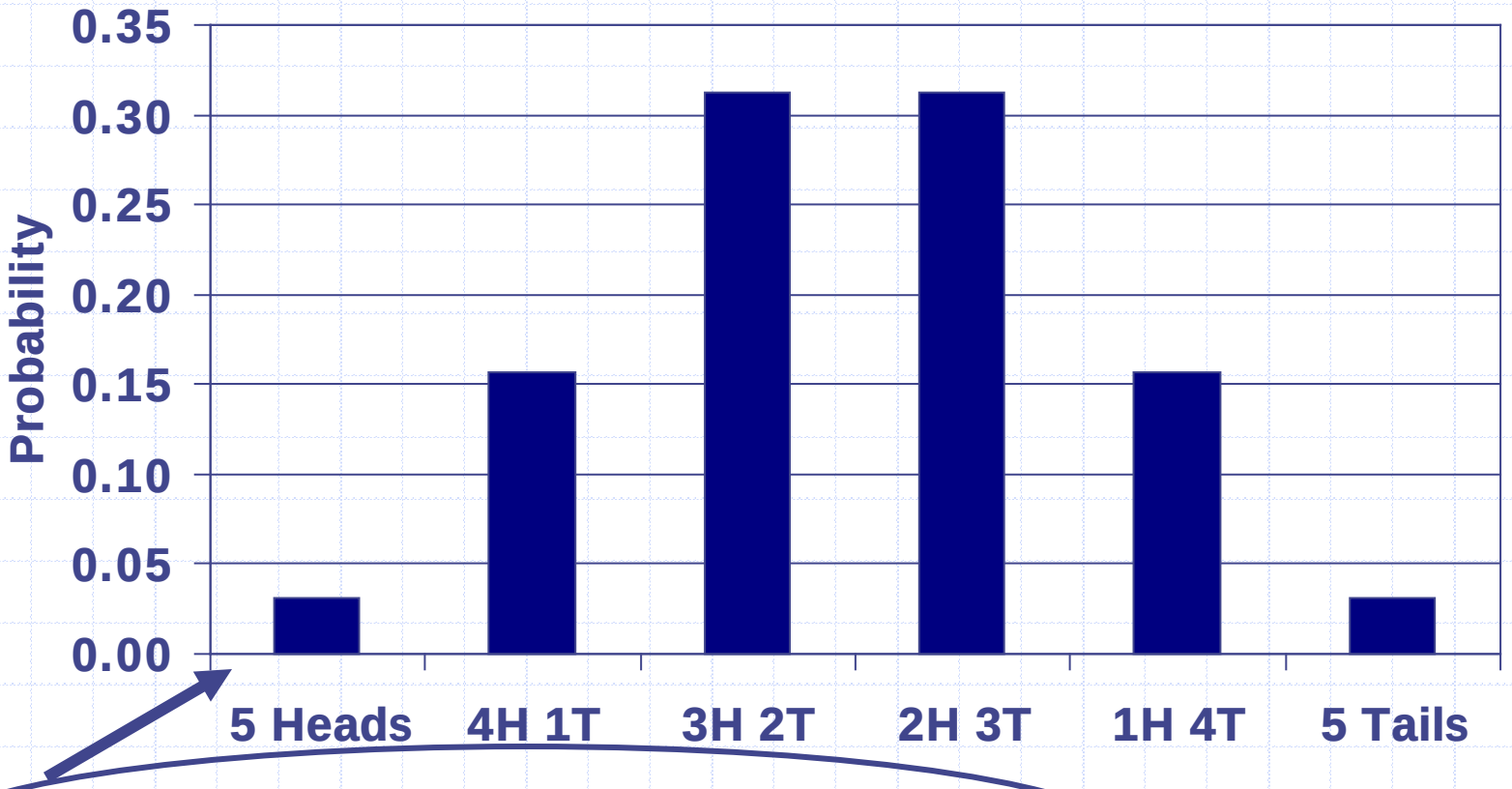

1/32 = ½ x ½ x ½ x ½ x ½ = 0.03125

Hypothesis: This coin comes up heads more than tails

- Null hypothesis: this coin comes up head and tails equally.
- Experiment: Flip the coin 5 times
  - If we get 5 heads, null hypothesis is disproved. $P < 0.05$

This coin is imbalanced
Null hypothesis is disproved.

	Study Results	
	True	False
Really true	True Positive	False Negative
Really false	False Positive $P < 0.05$	True Negative

Hypothesis: This coin comes up heads more than tails

- Null hypothesis: this coin comes up head and tails equally.
- Experiment: Flip the coin 5 times
  - If we get 5 heads, null hypothesis is disproved. $P < 0.05$
  - If we get any other result, null hypothesis is not disproved. We do not know whether the too sides are balanced or unbalanced.

What are the chances of getting 5 heads if you flip a coin 5 times?

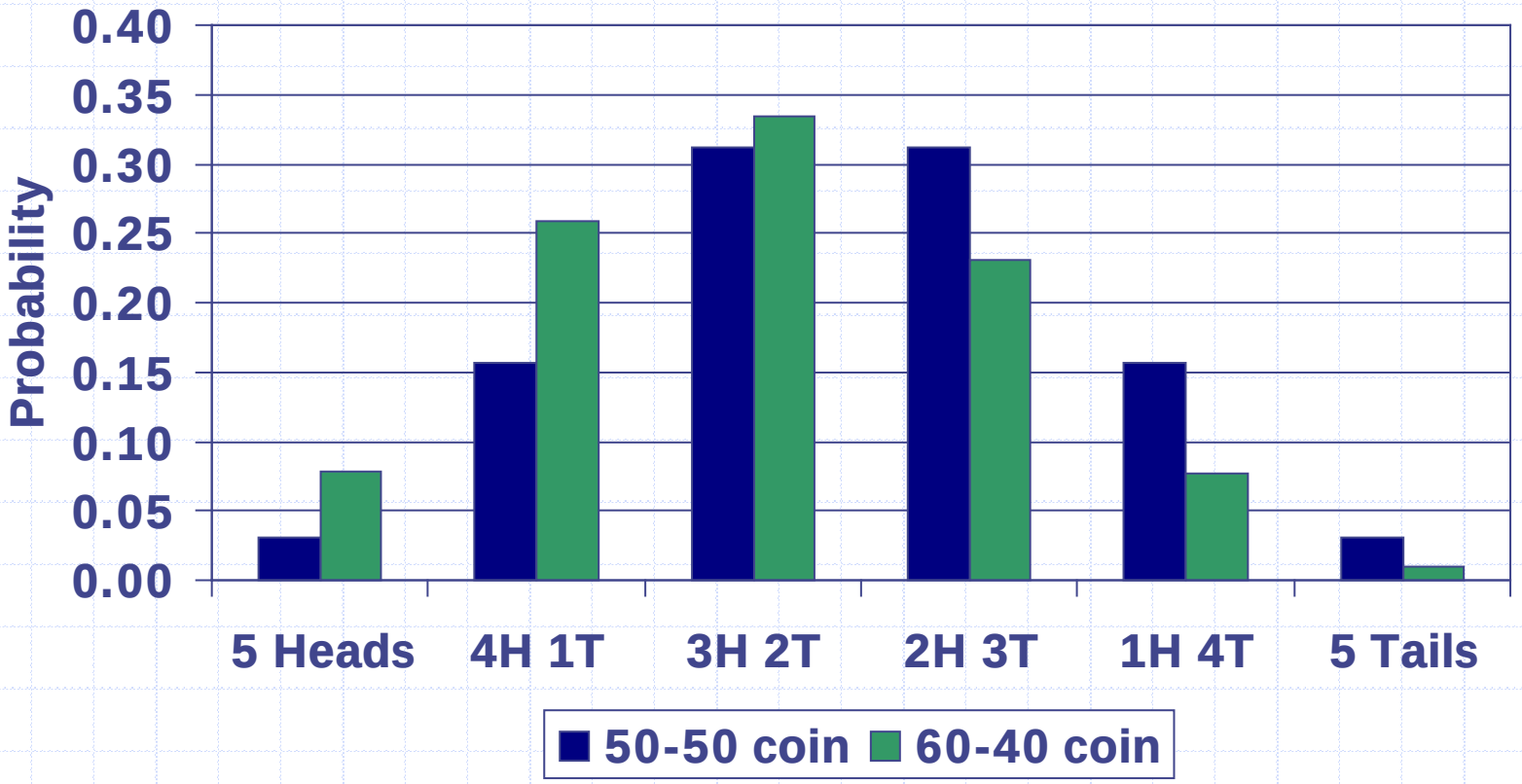

Table 1. Baseline Comparisons at the Second DATATOP Randomization[a]

Ann. Neurol. 2002;51:604

	Placebo Subjects (withdrawn from Deprenyl)	Deprenyl Subjects (continued Deprenyl)
n	177	191
Age (yr) at original DATATOP randomization	61.5 (9.4)	61.8 (8.7)
Age (yr) at second DATATOP randomization	66.8 (9.3)	67.1 (8.7)
Original active deprenyl assignment in DATATOP	92 (52.0%)	109 (57.1%)
Original active tocopherol assignment in DATATOP	98 (55.4%)	91 (47.6%)
Women	55 (31.1%)	66 (34.6%)
Minorities	3 (1.7%)	4 (2.1%)
Wearing off	94 (53.1%)	101 (52.9%)
Dyskinesia	65 (36.7%)	77 (40.3%)
On–off ($p = 0.028$)	15 (8.5%)	6 (3.1%)
Wearing off, dyskinesia, or on–off	111 (62.7%)	122 (63.9%)
Freezing of gait ($p = 0.063$)	54 (30.5%)	42 (22.0%)
Dementia	8 (4.5%)	7 (3.7%)
Confusion	10 (5.7%)	9 (4.7%)
Hoehn–Yahr stage		
At original randomization	1.63 (0.52)	1.59 (0.53)
At second randomization	2.11 (0.56)	2.10 (0.53)
Schwab–England Activities of Daily Living (ADL)		
At original randomization	91.5 (6.1)	92.0 (5.9)
At second randomization	86.0 (9.5)	86.8 (8.9)
Total UPDRS		
At original randomization	25.6 (11.8)	24.1 (11.3)
At second randomization	30.2 (16.8)	29.4 (14.6)
Motor UPDRS		
At original randomization	17.3 (9.0)	16.3 (8.4)
At second randomization	20.1 (11.5)	19.6 (10.6)
Mental UPDRS		
At original randomization	1.1 (1.3)	0.8 (1.1)
At second randomization	1.3 (1.7)	1.3 (1.6)
ADL UPDRS		
At original randomization	7.2 (3.5)	6.9 (3.8)
At second randomization	8.8 (5.8)	8.6 (5.0)

Table 1 checks randomization.

Journal Club for April 13, 2012

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Primary Outcome Variable

- What should we measure to decide if vitamin E or selegiline works?
- The time to prescription of L-DOPA therapy by the blinded treating physician.

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DATATOP – Vitamin E results

- There is no statistically significant difference between vitamin E and control
- The null hypothesis is not rejected
  - There is no therapeutic difference between control E and vitamin E
- *This does not mean that the null hypothesis is proven*

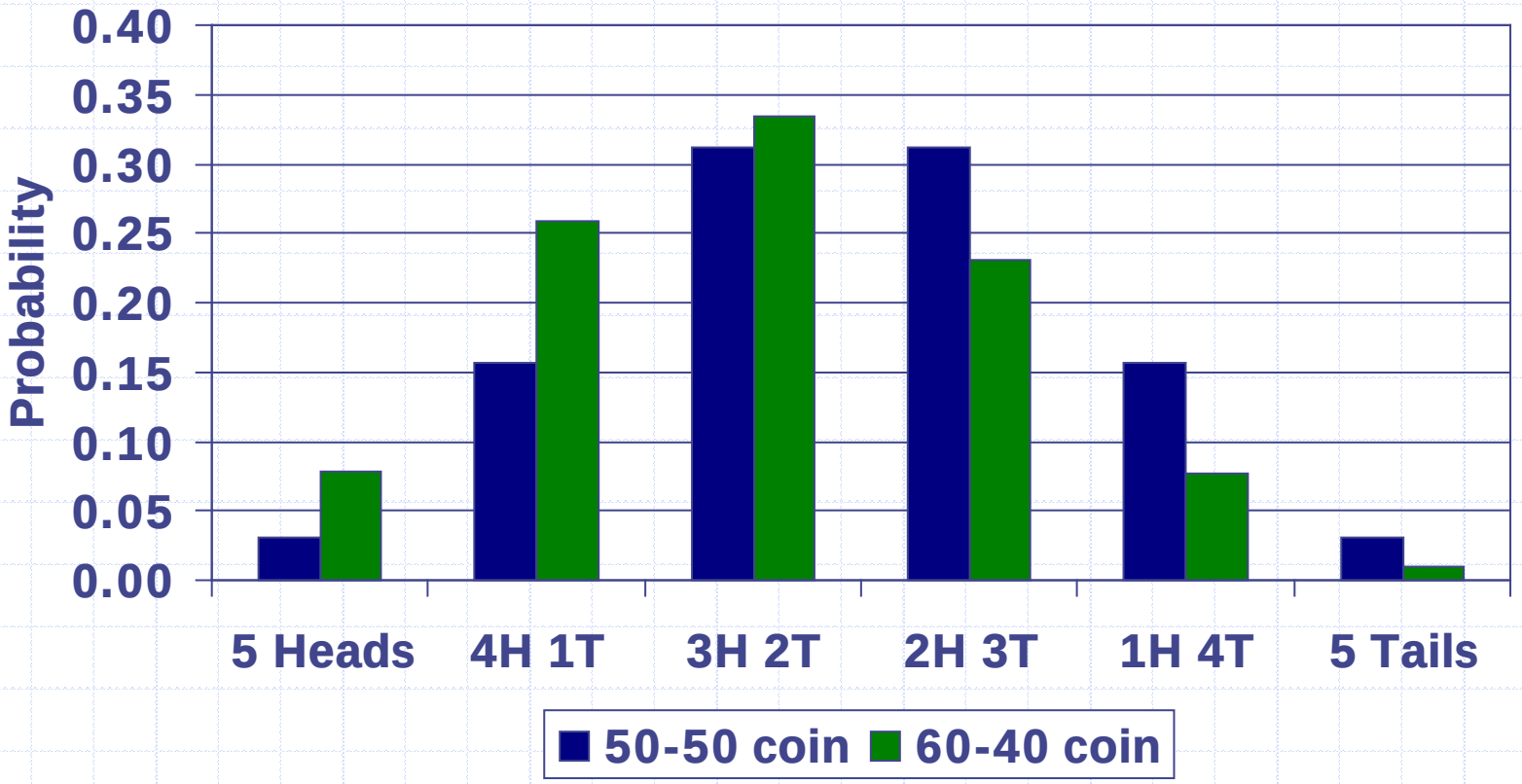
Truth of Hypothesis

	Vitamin E is better than placebo	
	True	False
Really true	True Positive	False Negative?
Really false	False Positive	True Negative?

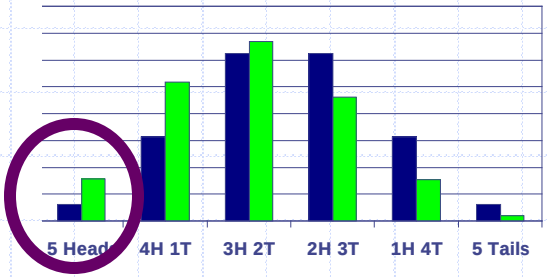
Why was the null hypothesis not rejected?

- True Negative
  - Vitamin E does not work.
- False Negative
  - The wrong dose of vitamin E was used.
  - Too few patients were tested; the study was underpowered.

What are the chances of getting 5 heads if you flip a coin 5 times?



For a 60-40 Coin, A Study of 5 Flips is Underpowered



	Study Results: True	Study Results: False
Really true	True Positive 8%	False Negative 92%
Really false	False Positive	True Negative

Why was the null hypothesis not rejected?

- True Negative
  - Vitamin E does not work.
- False Negative
  - The wrong dose of vitamin E was used.
  - Too few patients were tested; the study was underpowered.
  - The outcome measure was wrong.
  - The patient population was wrong.
  - The control patients were also taking vitamin E.
  - Bad luck, etc., etc., etc.

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DATATOP – Primary endpoint: Time until institution of L-DOPA

control S	454 days
Selegiline	719 days

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Significance

- **Clinically** significant?
- **Statistically** significant?

Significance

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- **Statistically** significant: having a high likelihood of being true (often 95%, $p < 0.05$). In the DATATOP trial, selegiline outcome was different from control ($p<0.001$),

Truth of Hypothesis

	Selegiline is better than placebo	
	True	False
Really true	True Positive	False Negative
Really false	False Positive P < 0.001	True Negative

Significance

- **Clinically** significant: having a meaningful or important effect of a patient's quality of life. In the DATATOP trial, selegiline delayed start of L-DOPA treatment by about 9 months.
- **Statistically** significant: having a high likelihood of being true (often 95%, $p < 0.05$). In the DATATOP trial, selegiline outcome was different from control ($p<0.001$),

DATATOP – Selegiline results

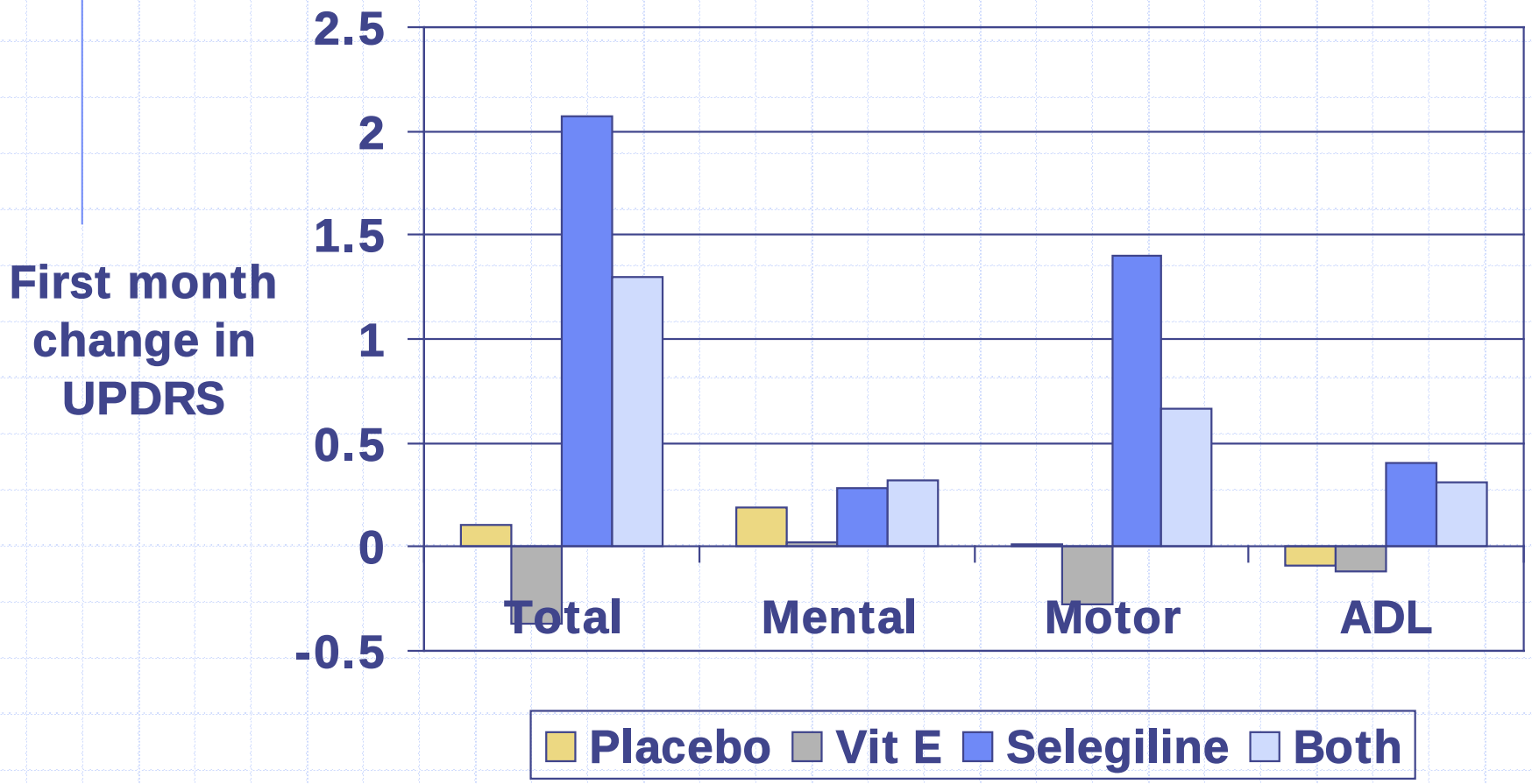
- The null hypothesis is rejected (disproved), therefore:
- The alternative hypothesis is proven
- Selegiline is effective treatment for Parkinson's disease
  - *My father began taking selegiline. It cost > $100 / month. He could not tell if it was helping*

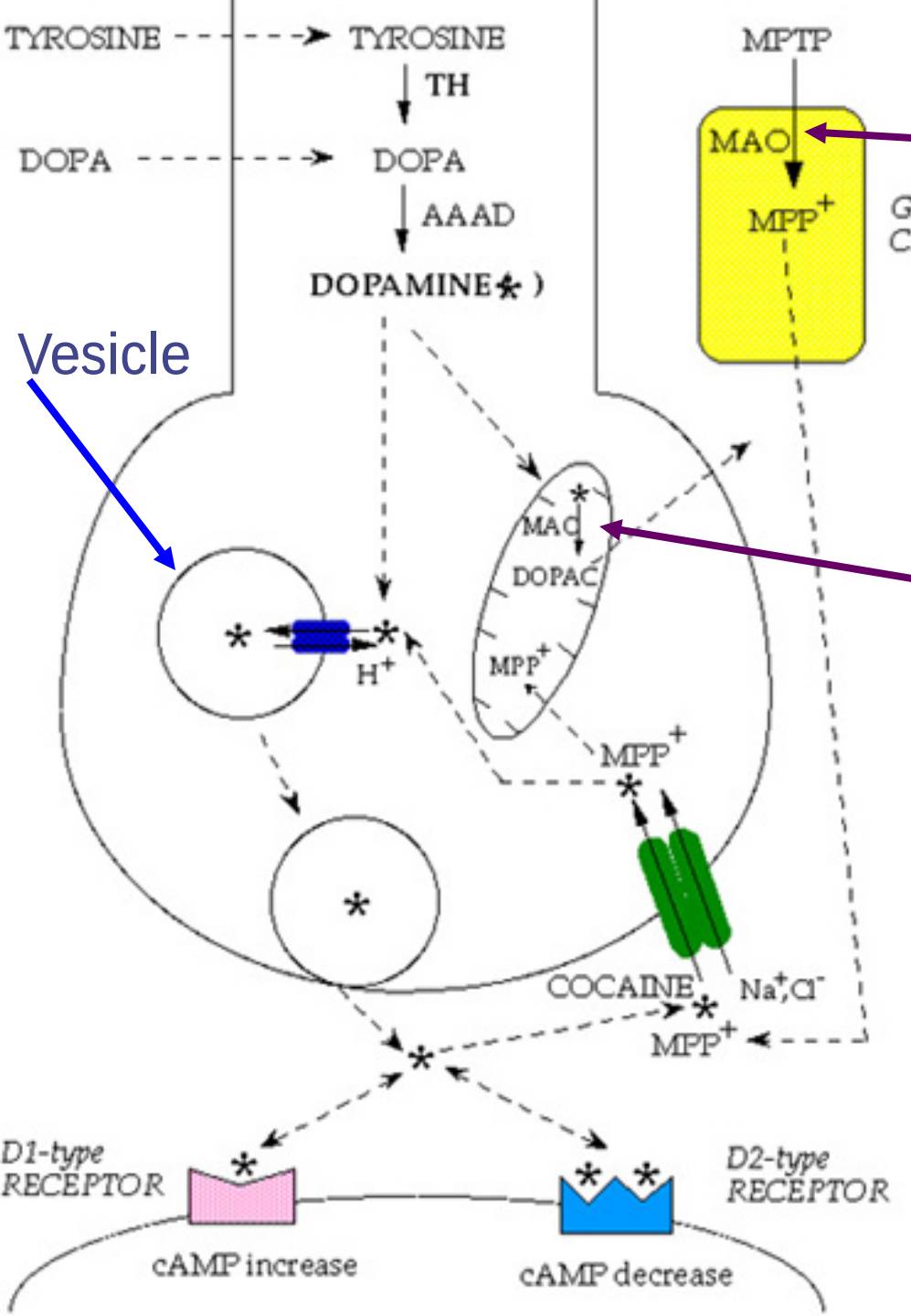
DATATOP – Selegiline results

- The null hypothesis is rejected (disproved), therefore:
- The alternative hypothesis is proven
- Selegiline is effective treatment for Parkinson's disease
  - *Is this effect due to neuroprotection or to symptomatic improvement?*

DATATOP Trial
NEJM 1993; 328:176

Selegiline does improve symptoms and signs of Parkinson's disease, at least a little.





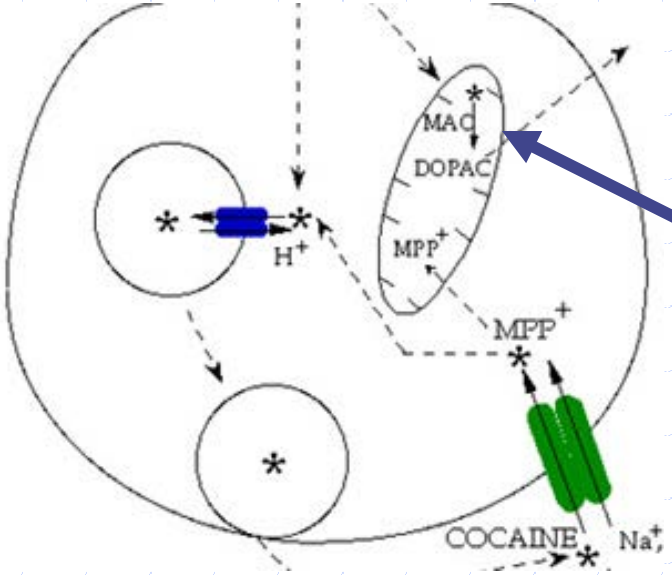
MAO in astrocyte

MAO in neuron

www.mcmaster.ca/inabis98/sadile/di_porzio0329/two.html

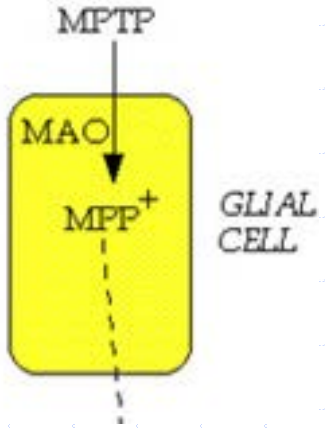
Selegiline – MAO B inhibitor

- Symptomatic therapy – prevent breakdown of dopamine?
- Neuroprotective therapy – prevent formation of toxins?



MAO

Neuronal Astrocytic



DATATOP – Selegiline results

- #1 (Original Hypothesis) A) if Parkinson's disease is caused by environmental or endogenous protoxins activated by MAO, then B) selegiline might prevent development and progression of Parkinson's disease
- Null Hypothesis: Selegiline is not effective treatment for Parkinson's Disease
- #2 (Proven) Selegiline is effective treatment for Parkinson's disease

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- *#2* Selegiline is effective treatment for Parkinson's disease
- *does not prove*
- *#1B* selegiline might prevent development and progression of Parkinson's disease
- *because selegiline might be symptomatic rather than neuroprotective therapy.*

DATATOP – Selegiline results

- #1 (Original Hypothesis) A) if Parkinson's disease is caused by environmental or endogenous protoxins activated by MAO, then B) selegiline might prevent development and progression of Parkinson's disease
- Null Hypothesis: Selegiline is not effective treatment for Parkinson's Disease
- #2 (Proven) Selegiline is effective treatment for Parkinson's disease

- *#2 does not prove #1B because selegiline might be symptomatic rather than neuroprotective therapy*
- *Even if #1B were true,*
  - selegiline prevents development and progression of Parkinson's disease
- *#1A is unproven*
  - Parkinson's disease is caused by environmental or endogenous protoxins activated by MAO
- *because the converse is not necessarily true.*

"All dogs have fleas" does not mean that "everyone with fleas is a dog."

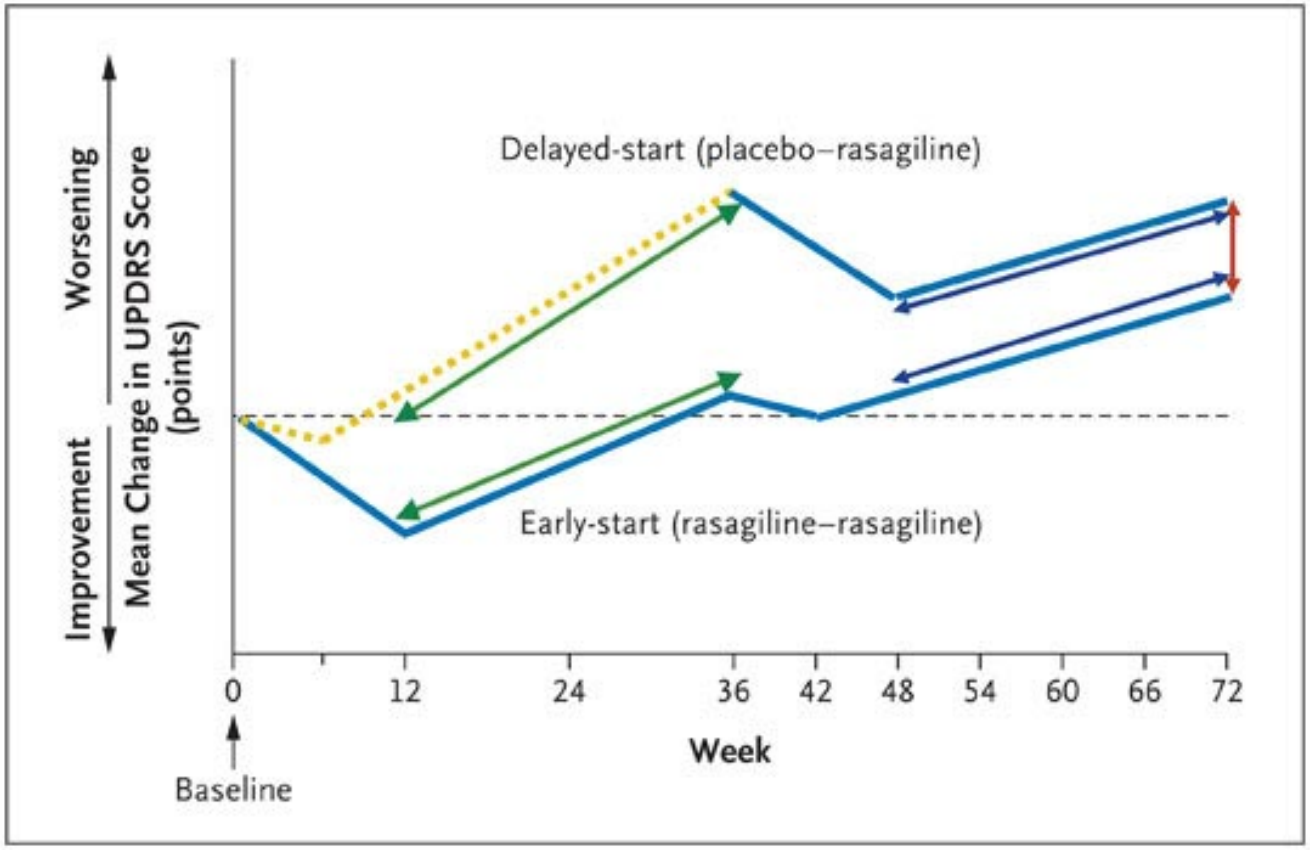
Post DATATOP experience

- Randomized trial: Selegiline + L-DOPA v. L-DOPA alone: no selegiline benefit
- Possible increased mortality of selegiline treated patients
- Reanalysis of DATATOP: results explicable by symptomatic effect
  - *My father stopped taking selegiline because he felt no improvement of his symptoms.*

Post DATATOP experience

- Randomized trial: Selegiline + L-DOPA v. L-DOPA alone: no selegiline benefit
- Possible increased mortality of selegiline treated patients
- Reanalysis of DATATOP: results explicable by symptomatic effect
- Rerandomization and follow-up of DATATOP patients: selegiline increases dyskinesias, delays development of freezing and motor on-off
- Rasagiline (another MAO-B inhibitor) looks neuroprotective in a delayed-start trial

A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease



Olanow et al N Engl J Med. 2009 Sep 24;361(13):1268-78.

The NEW ENGLAND JOURNAL of MEDICINE

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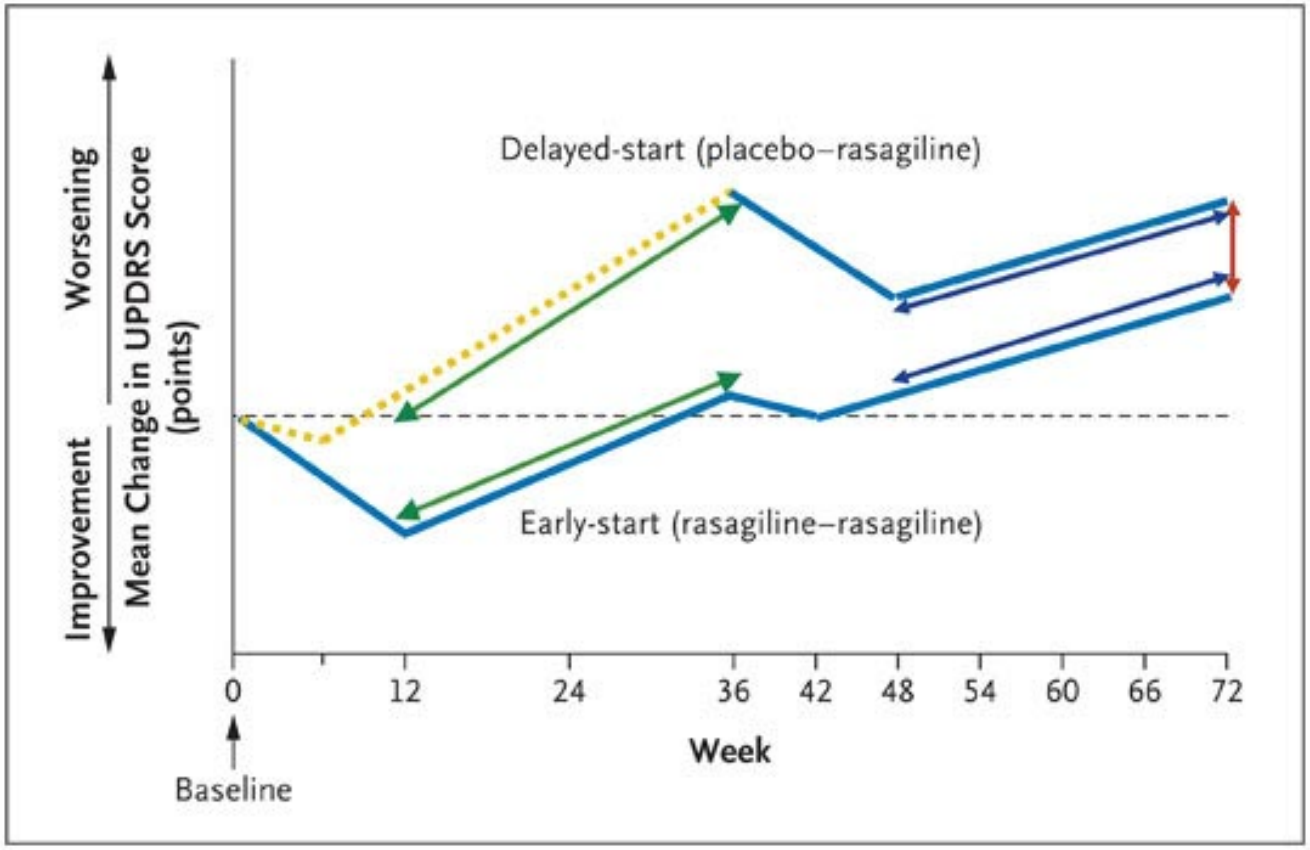

Green arrow: rasagiline better than placebo for rate of change from baseline

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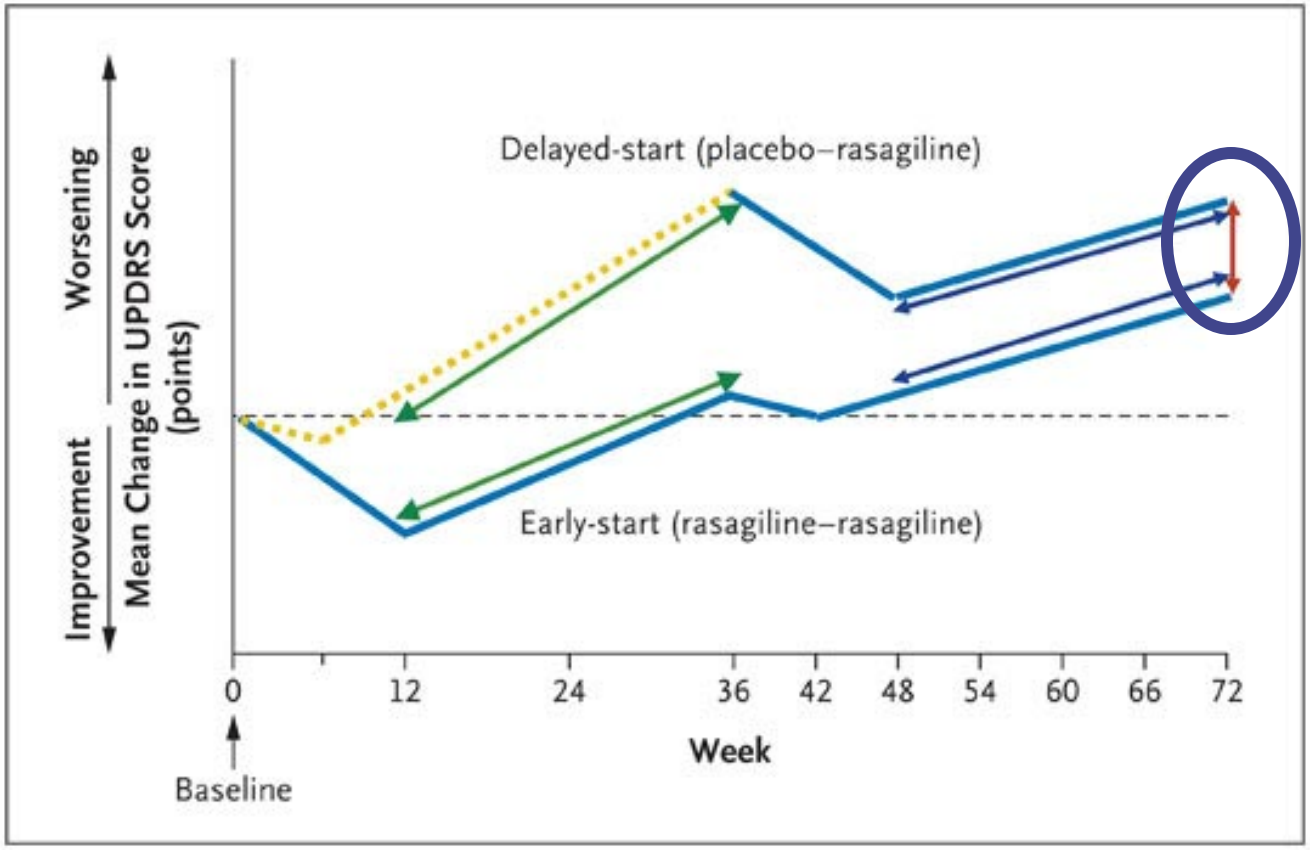

Red arrow: early-start better than late-start at 72 weeks

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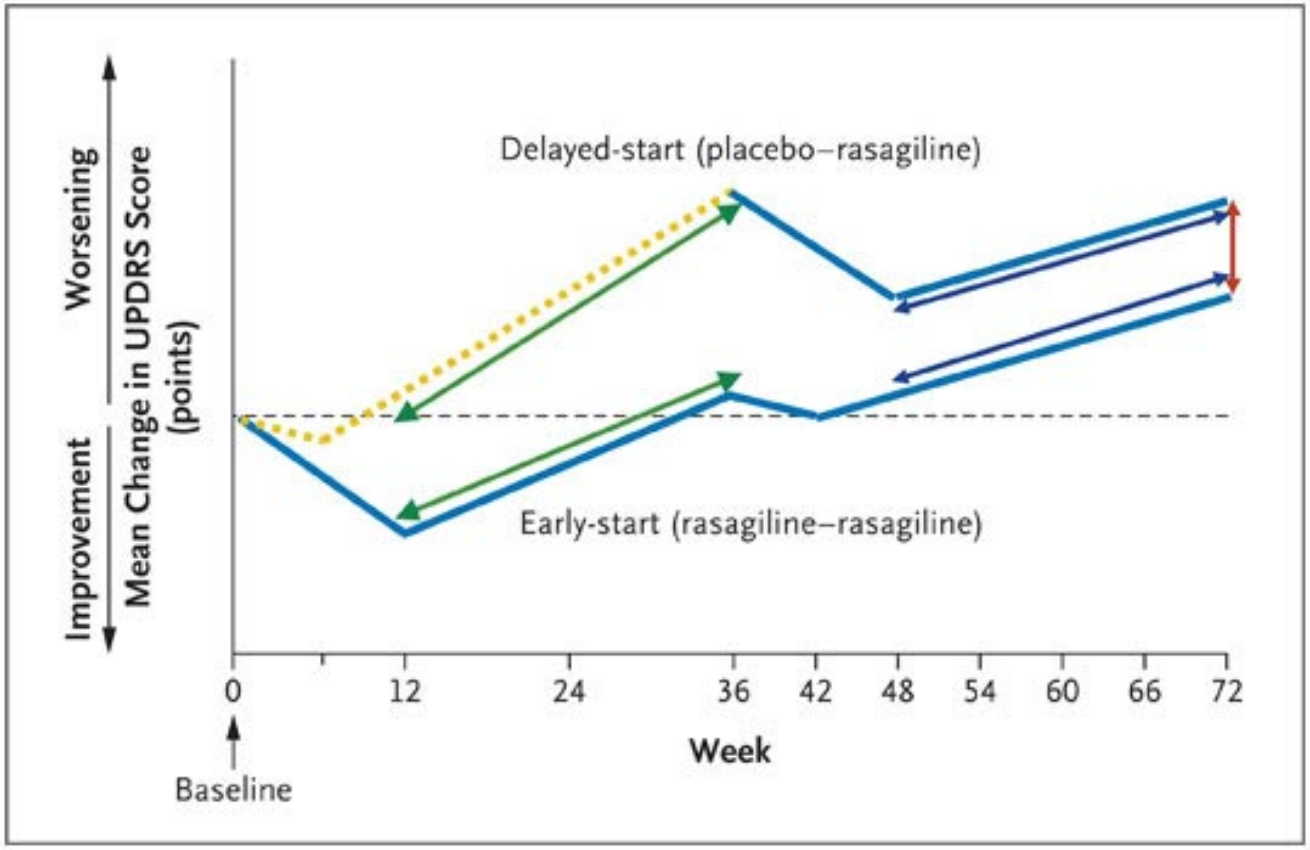
A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease



Blue arrow: early-start no worse than late-start for rate of change between weeks 48 and 72.

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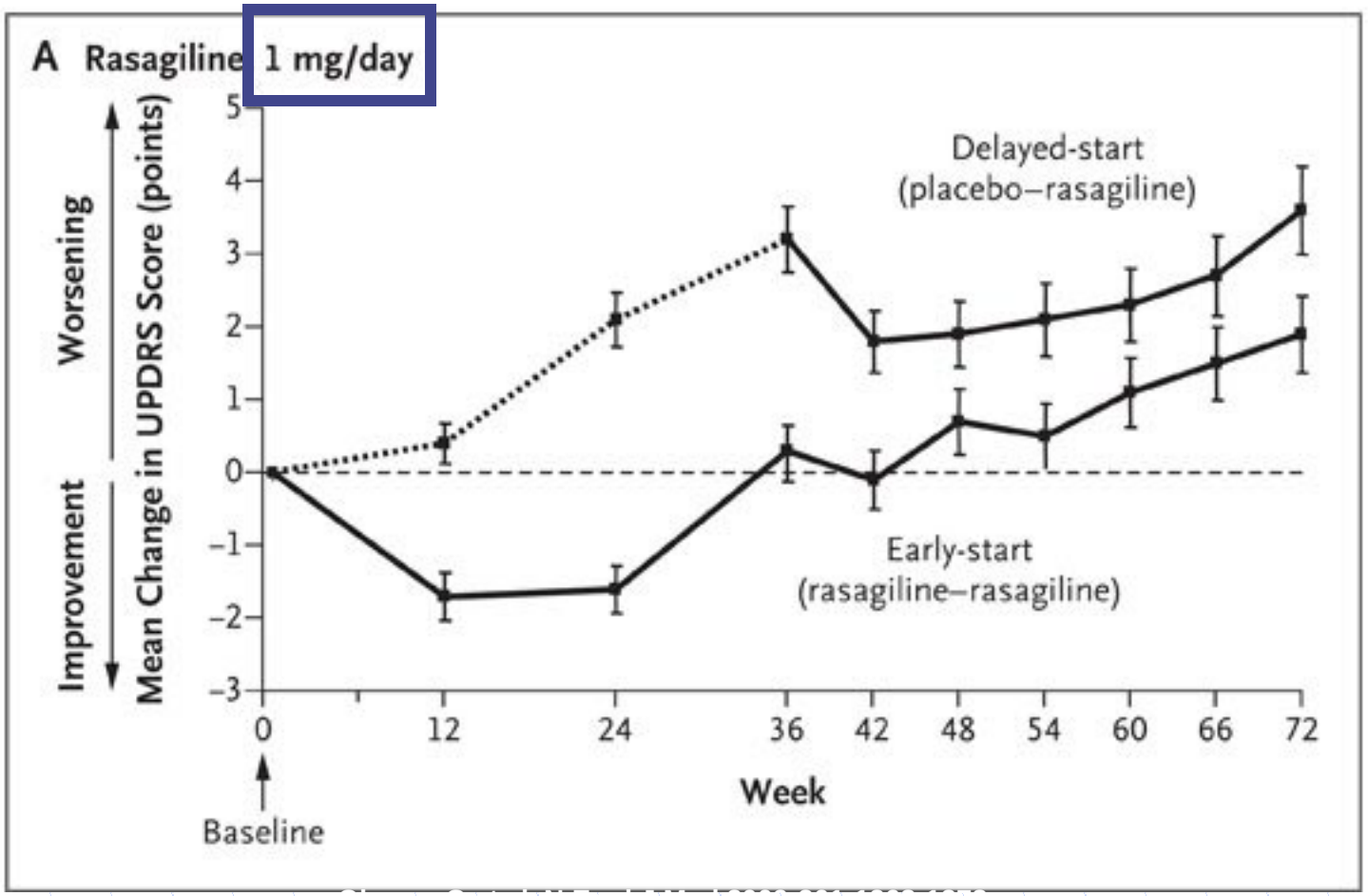

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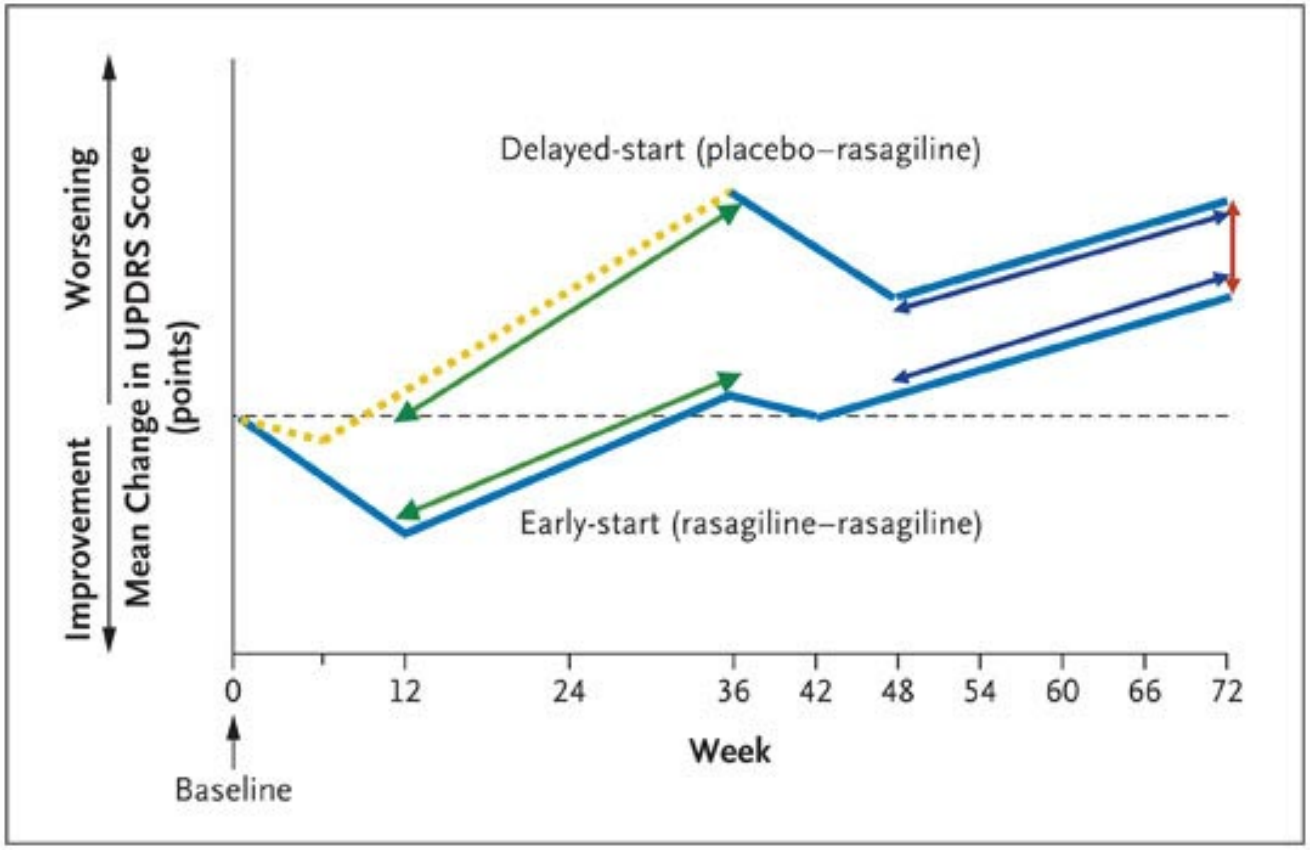

Green p=0.02; Red p=0.01; Blue p < 0.001

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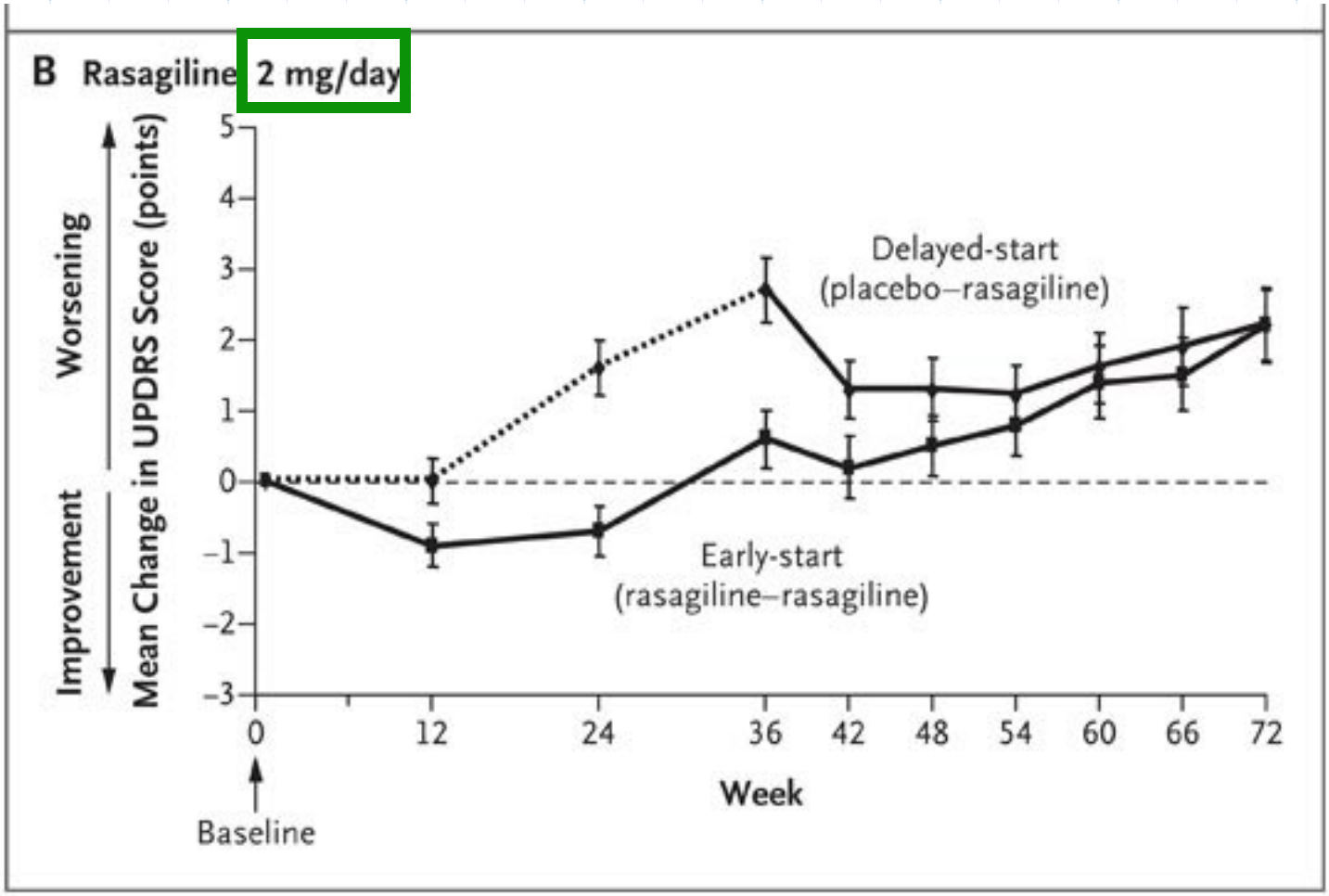
Disclosure

- I was a site principal investigator for the ANDANTE study of rasagiline sponsored by TEVA.

Critique of ADAGIO Study

- 2 mg dose of rasagiline did not meet all endpoints

A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease



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Critique of ADAGIO Study

- 2 mg dose of rasagiline did not meet all endpoints
- Rasagiline benefit may not be clinically significant
- We do not know if rasagiline effect persists for a longer time
- We do not know if rasagiline has any benefit in more advance Parkinson's disease
- Perhaps any successful drug therapy has some neuroprotective effect
- We do not know if rasagiline results can be extrapolated to selegiline

Strengths	Weaknesses
Randomized, controlled trial	
Study groups very similar before treatment	Costly, cumbersome
Conducted by well-established methodologic rules	Involve limited number of participants
Considered gold standard for assessing efficacy	Often underrepresent key patient groups
Can be registered to prevent selective reporting	Short duration
	Comparator (or placebo) often irrelevant
	May measure surrogate end points rather than clinical outcomes
	Protocol may not reflect typical care

Avorn **In Defense of Pharmacoepidemiology — Embracing the Yin and Yang of Drug Research** N Engl J Med. 2007 Nov 29;357(22):2219-21

The NEW ENGLAND JOURNAL of MEDICINE

Randomized Controlled Trials Weaknesses

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The Debate Continues

- Rasagiline, Parkinson neuroprotection, and delayed-start trials. Still no satisfaction?
  - Ahlskog and Utti

  Neurology 2010; 74: 1143-1148
- The delayed-start study in Parkinson disease. Can't satisfy everyone.
  - Olanow and Rascol

  Neurology 2010; 74: 1149-1151

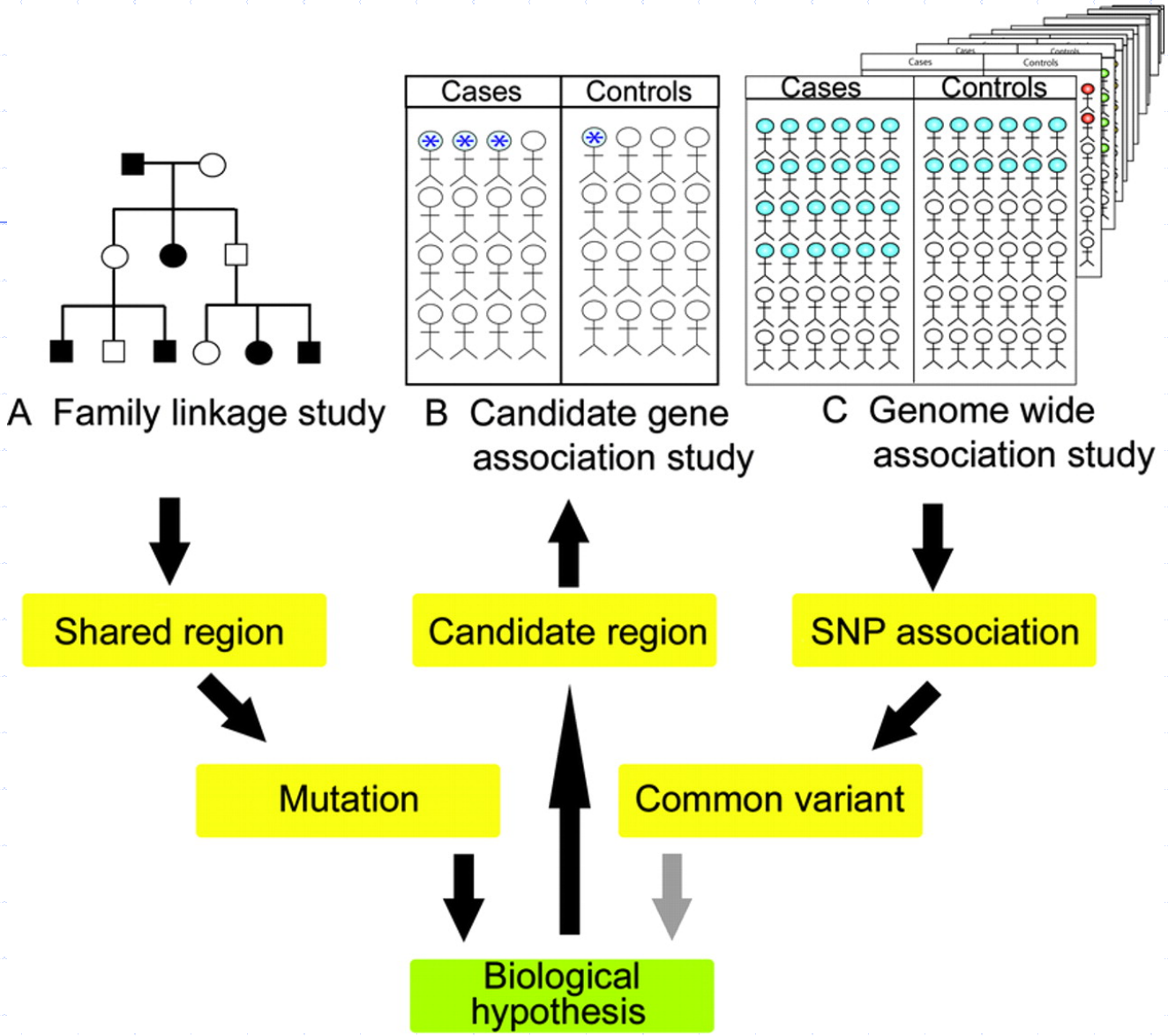
Someone in our class can predict results of coin flips!

Someone in our class can predict results of coin flips.

- Is this hypothesis testing or hypothesis generating?
- Now we need a hypothesis testing experiment.

Using DNA Microarrays to Study Parkinson's Disease

- Looking for candidate genes
- Looking at gene expression



Mullen, S. A. et al. Neurology 2009;72:558-565

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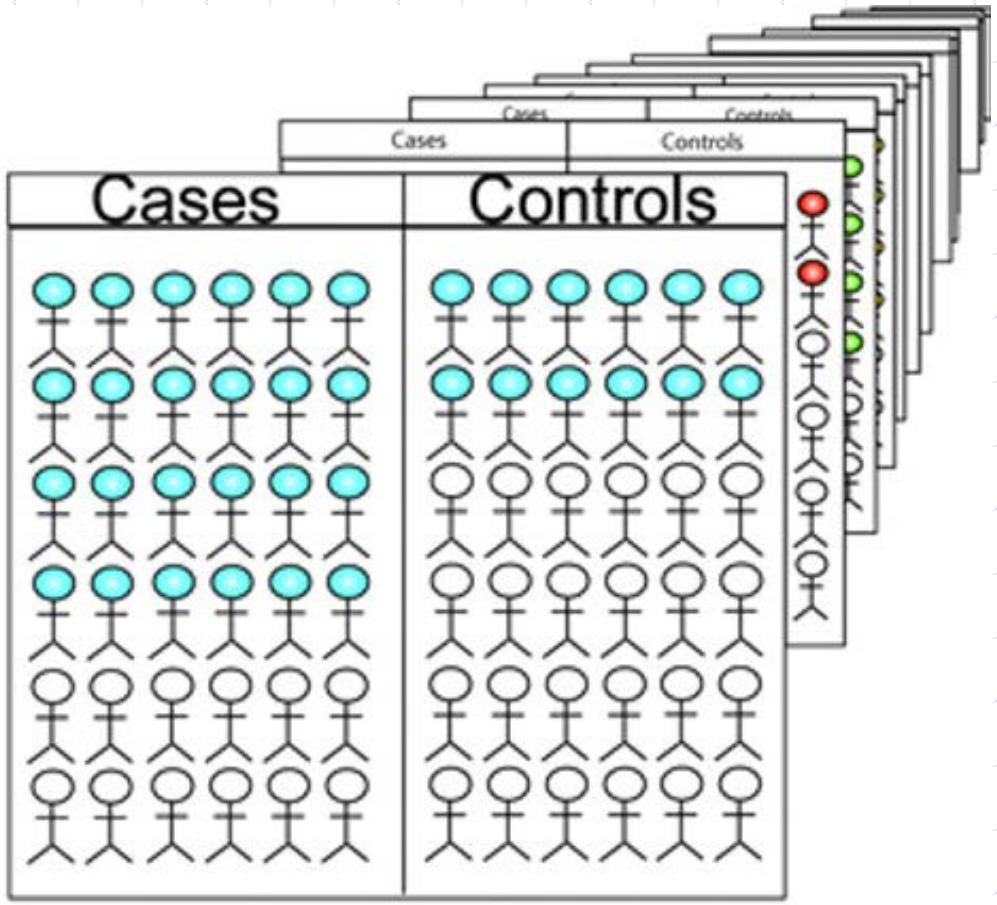

C Genome wide association study

Mullen, S. A. et al. Neurology 2009;72:558-565

High-Resolution Whole-Genome Association Study of Parkinson Disease

- "The genotyping platform employed high-density oligonucleotide,photolithographic microarrays (DNA chips), such that one hybridization yielded genotypes for 85,000 SNPs in a single individual."
- SNP = single nucleotide polymorphism

Am. J. Hum. Genet. 77:685–693, 2005

High-Resolution Whole-Genome Association Study of Parkinson Disease

- Tier 1 -- 443 sib pairs discordant for Parkinson's disease
  - Genotype 198,345 SNPs
  - Found 1793 associated with Parkinson's disease ($P<0.01$)
  - 1793/198345 = 0.009

Am. J. Hum. Genet. 77:685–693, 2005

High-Resolution Whole-Genome Association Study of Parkinson Disease

- Tier 2 – 332 unrelated pairs discordant for Parkinson's disease
  - Genotype 1793 Parkinson's disease-associated SNPs
  - Found 11 associated with Parkinson's disease ($P<0.01$)
  - 11/1793 = 0.006

Am. J. Hum. Genet. 77:685–693, 2005

Test yourself: explain these terms to your parents.

- Control
- Randomized
- Double-blind
- Null hypothesis
- Primary outcome measure
- Statistical significance
- Clinical significance