

Meet the
Scientist
A Virtual Q&A Discussion

 **BRAIN &
BEHAVIOR**
RESEARCH FOUNDATION
Awarding **NARSAD** Grants

LOSING TOUCH WITH REALITY ***SEARCHING FOR THE SEEDS OF PSYCHOSIS***

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as of Sep 1, 2017:

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Symptoms of Psychosis

Disorganized speech or behavior

- Illogical or incomprehensible speech

Hallucinations

- Hearing voices or other senses

Delusions

- Fixed false beliefs, commonly paranoid or grandiose
- Searching for meaning in irrelevant stimuli

Who has psychosis?

Schizophrenia and Schizoaffective disorder

Common with bipolar disorder (one in four)

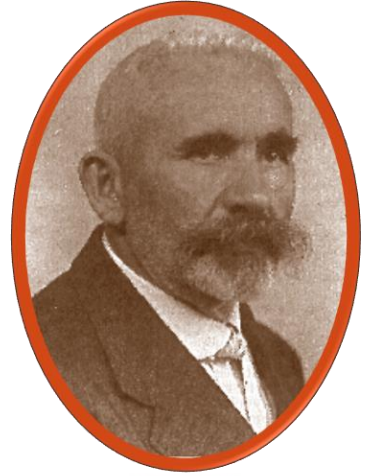
Many with Depression, Drug use, PTSD, Autism

A third of those with Dementia



Emil Kraepelin

Founder of modern scientific psychiatry



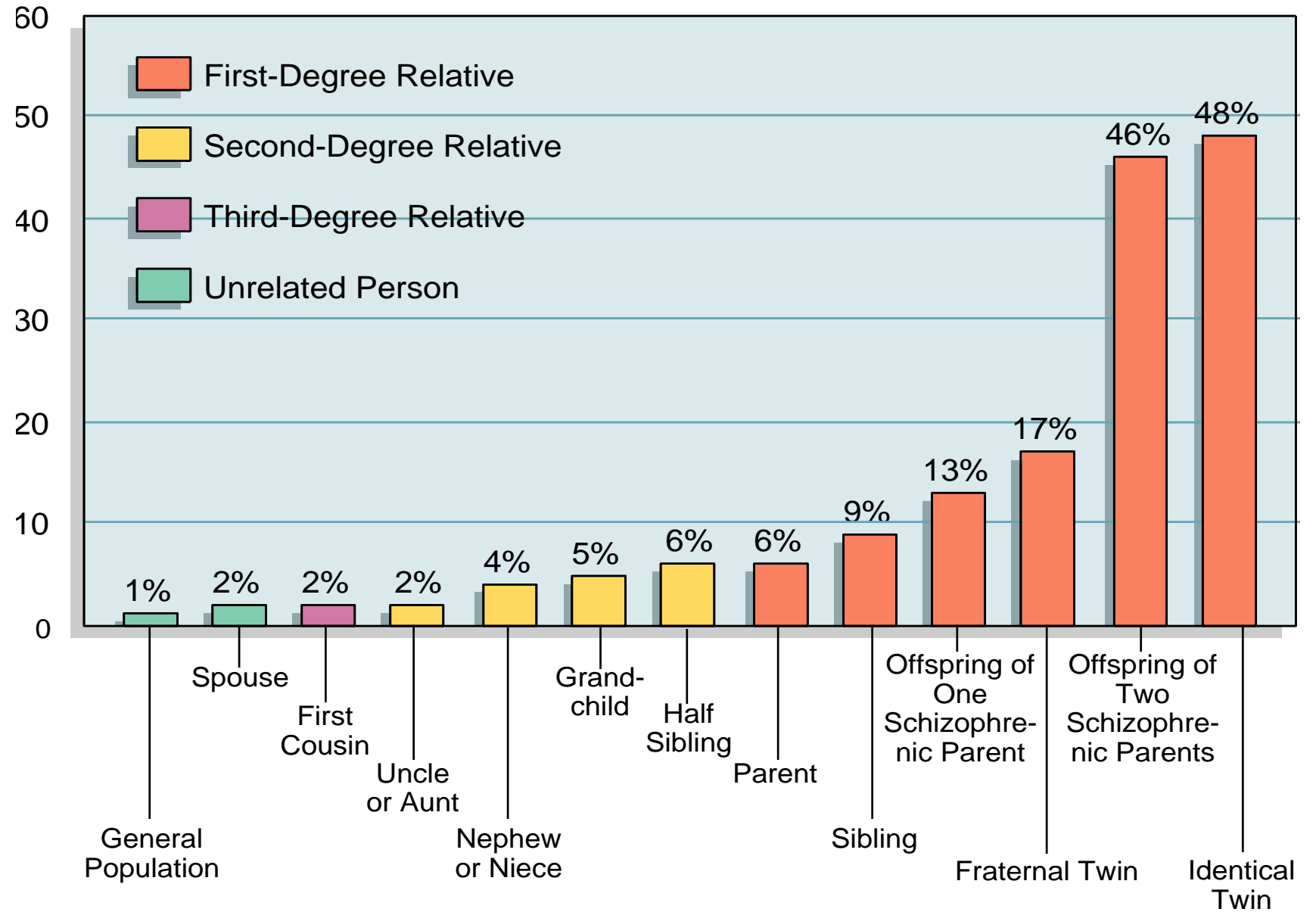
Described “dementia praecox” as an early onset dementia that includes psychosis.

*“attacks the frontal area of the brain, central convolutions, and the temporal lobe”
(1896).*

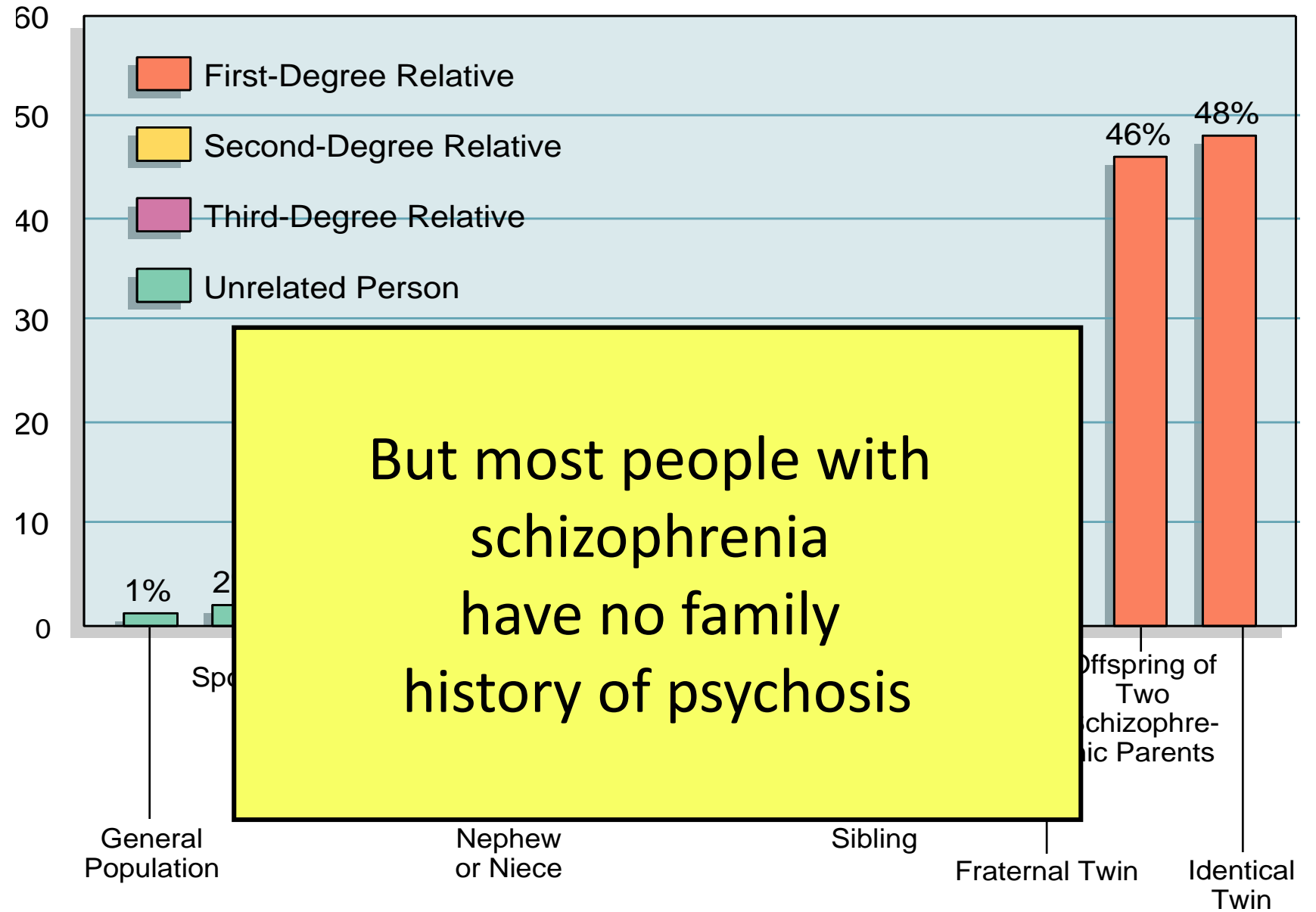
Kraepelin observed that some relatives had a taint of the disorder.

Rudin (1916) conducted the first scientifically sound study of schizophrenia, finding association but no simple pattern. Twin studies by Luxenburger (1926) confirmed the risk was increased by shared genes. They launched psychiatric genetics.

Family history



Family history



Schizophrenia as a SOCIAL DISORDER

1940s – 1970s

PSYCHOSIS WAS ATTRIBUTED TO BAD PARENTING!

Schizophrenogenic mother

- Causes the illness in her child.

Parental rejection

- An aggressive, rejecting, domineering, or mother; passive or indifferent or threatening father.

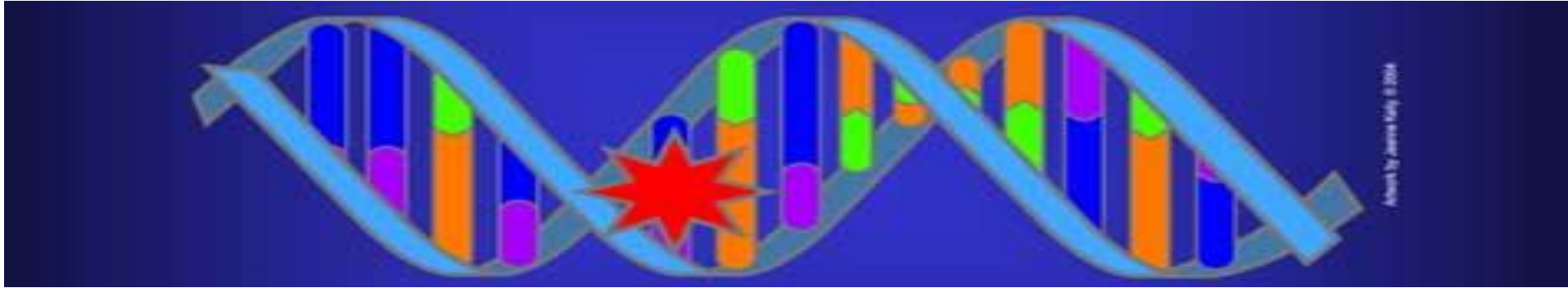
Double bind communication

- Called schisms and skews. Mothers communicate with conflicting messages.

Finally discredited by brain imaging studies and cognitive tests showing deficits even in highly intelligent patients.

But stigma and guilt and shame remains....

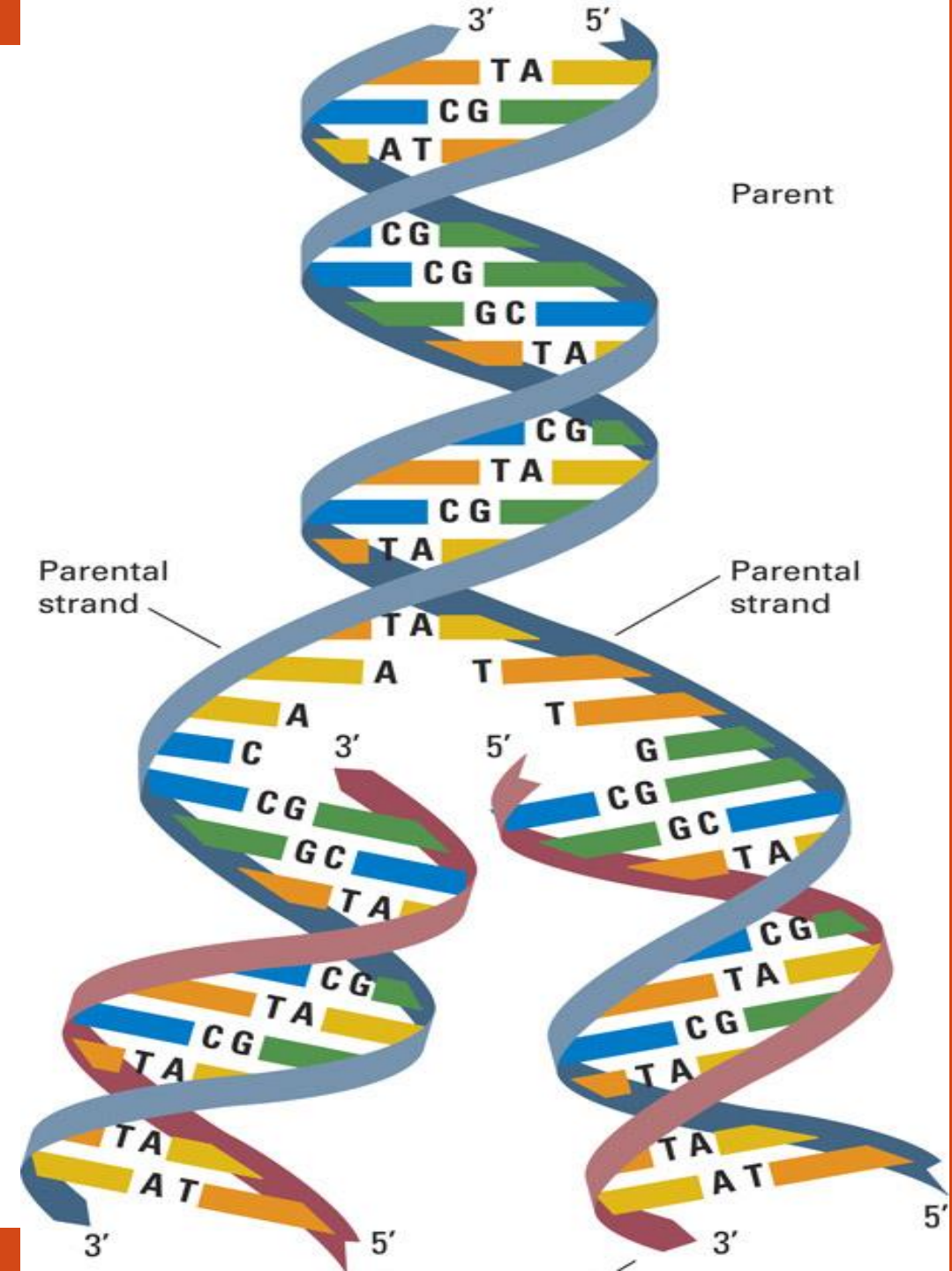
What causes non-familial cases?



New mutations in genes affecting brain function were proposed to explain the origin of psychosis a half century ago.

But the idea was discounted.

A mutation is a changes in
DNA sequence that can
disrupt function of the gene



Where do mutations come from in humans?

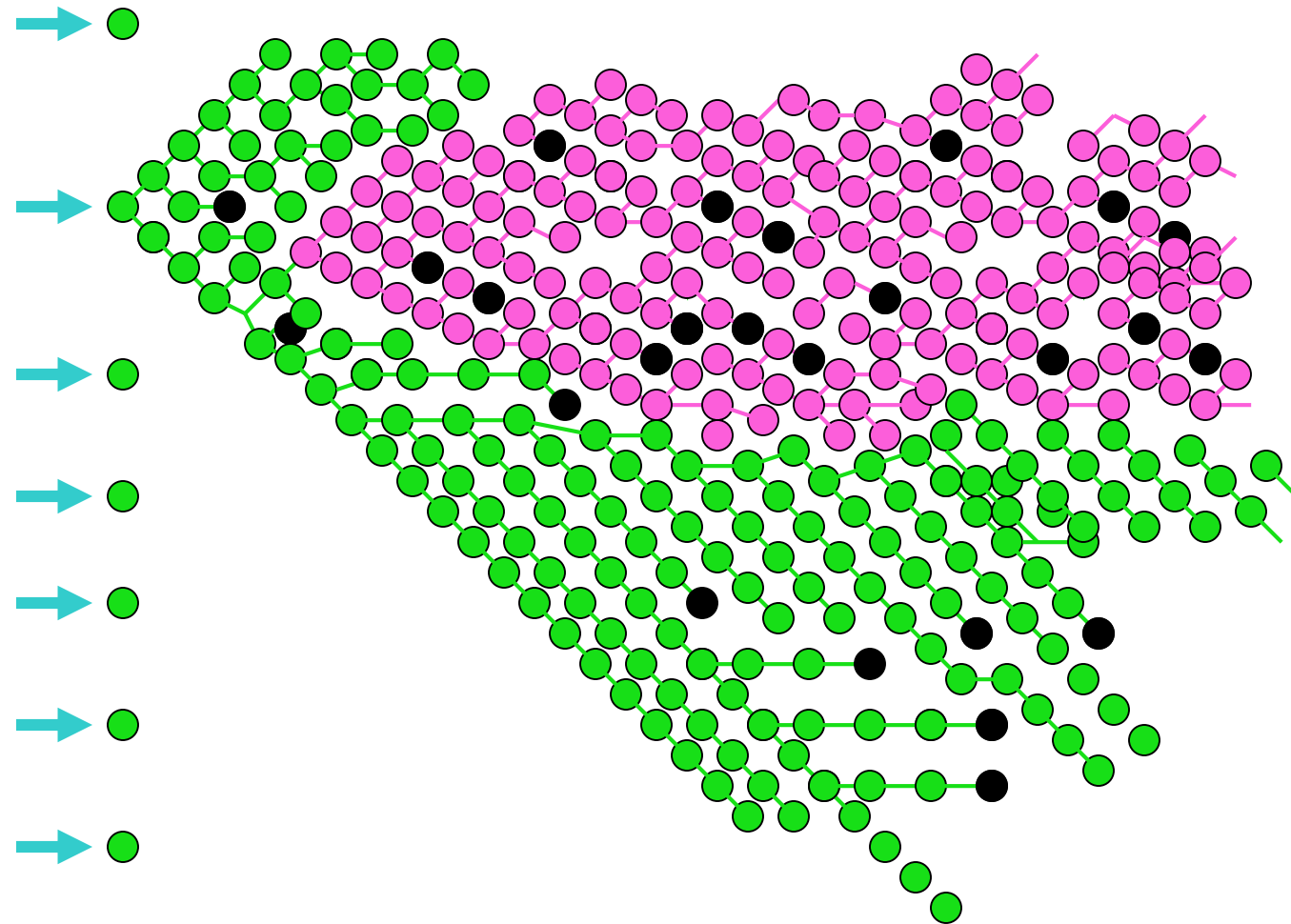
In women, future egg cells are formed before birth. All but the last occurs during fetal life.

New mutations in humans arise in the male parent in proportion to his age!
Sperm are produced continually over a man's life.
Future sperm cells divide every 16 days.



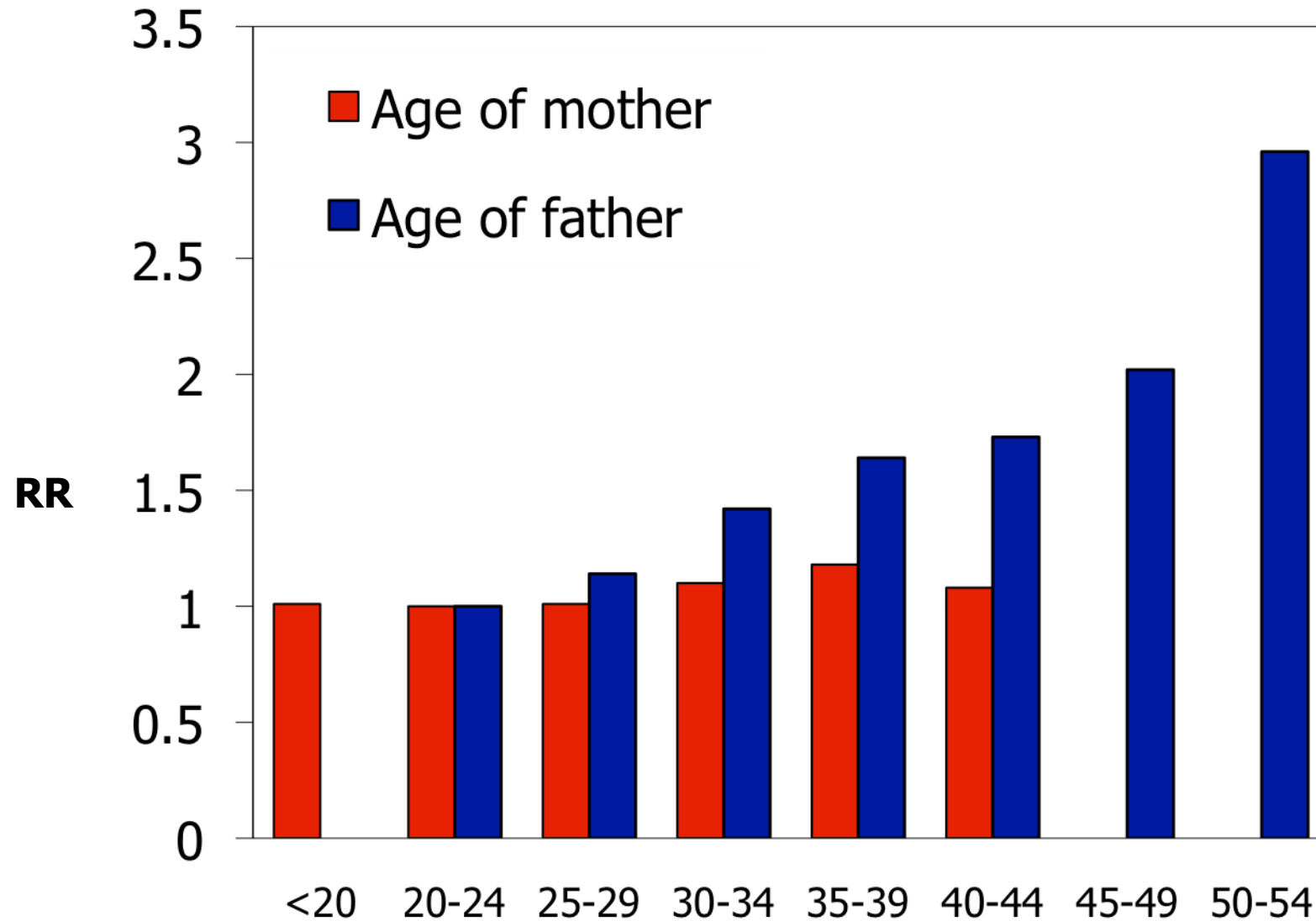
- 200 times by age 20
- 660 by age 40

Sperm precursor cells with mutations that make them divide more quickly will increase in proportion as men age



Fathers' age predicts diseases with no family history

Age of fathers explained a 1/4th of cases in the Jerusalem population



Malaspina et al 2001

Replicated world wide in many, many studies.

Finding influential genes for different versions of psychosis



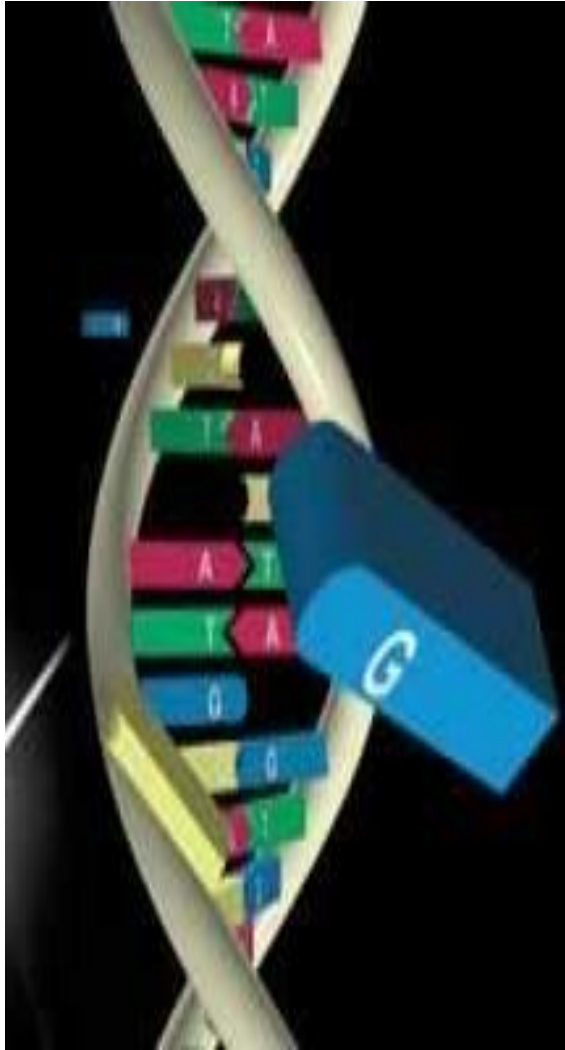
Study psychosis risk in an entire population (**epidemiology**).

Compare DNA sequences of healthy parents to ill offspring (**genetics**).



Find mutations that disrupt brain genes in psychosis (**clinical care**).

Genes prone to mutations can highlight some influential pathways for psychosis



Highlighting roles for:

- Zinc
- Proteins involved in bowel inflammation
- Tumor suppressor genes
- Brain growth factors

For a portion of cases we will soon find person-specific treatments

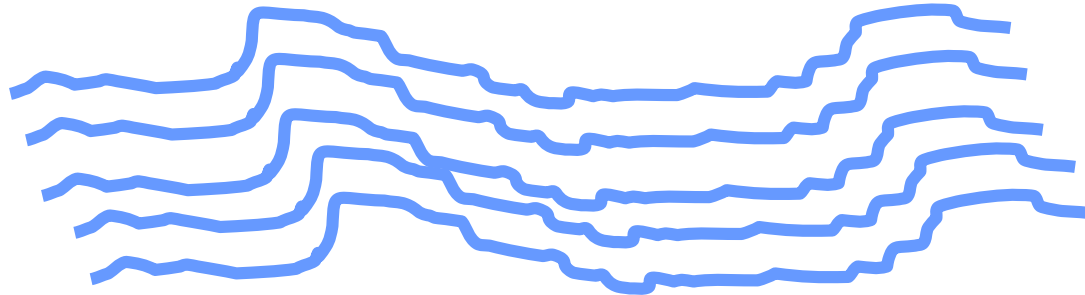
Kranz et al 2016: Phenotypically distinct subtypes of psychosis accompany novel or rare variants in four different signaling genes. EBioMedicine.

Epigenetics: Exposures can alter gene expression

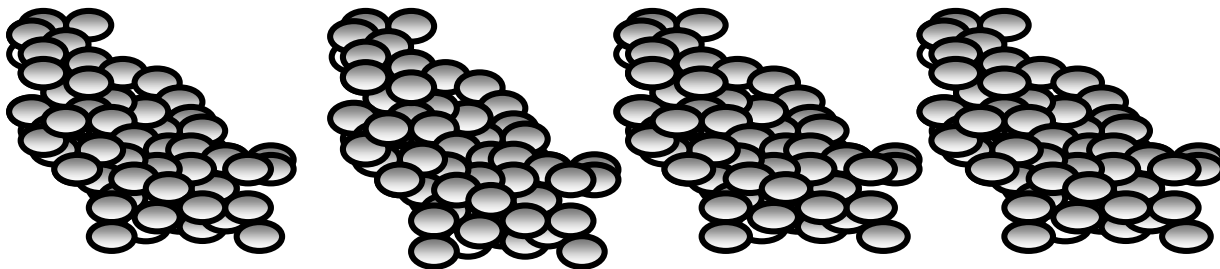
Scenario 'A'



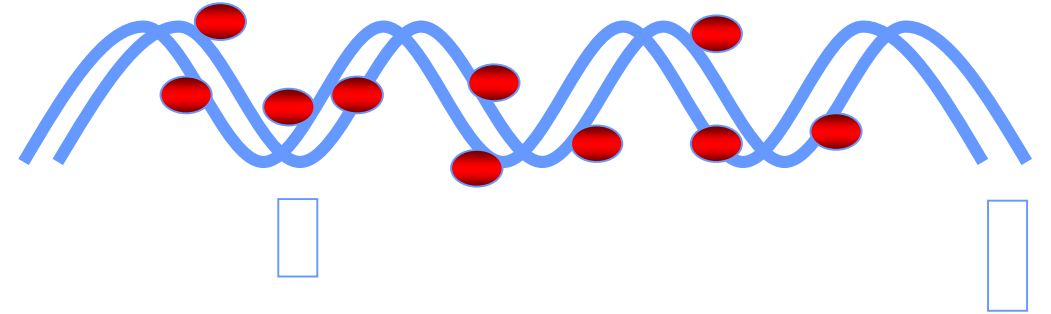
significant expression



large amounts of protein



Scenario 'B'

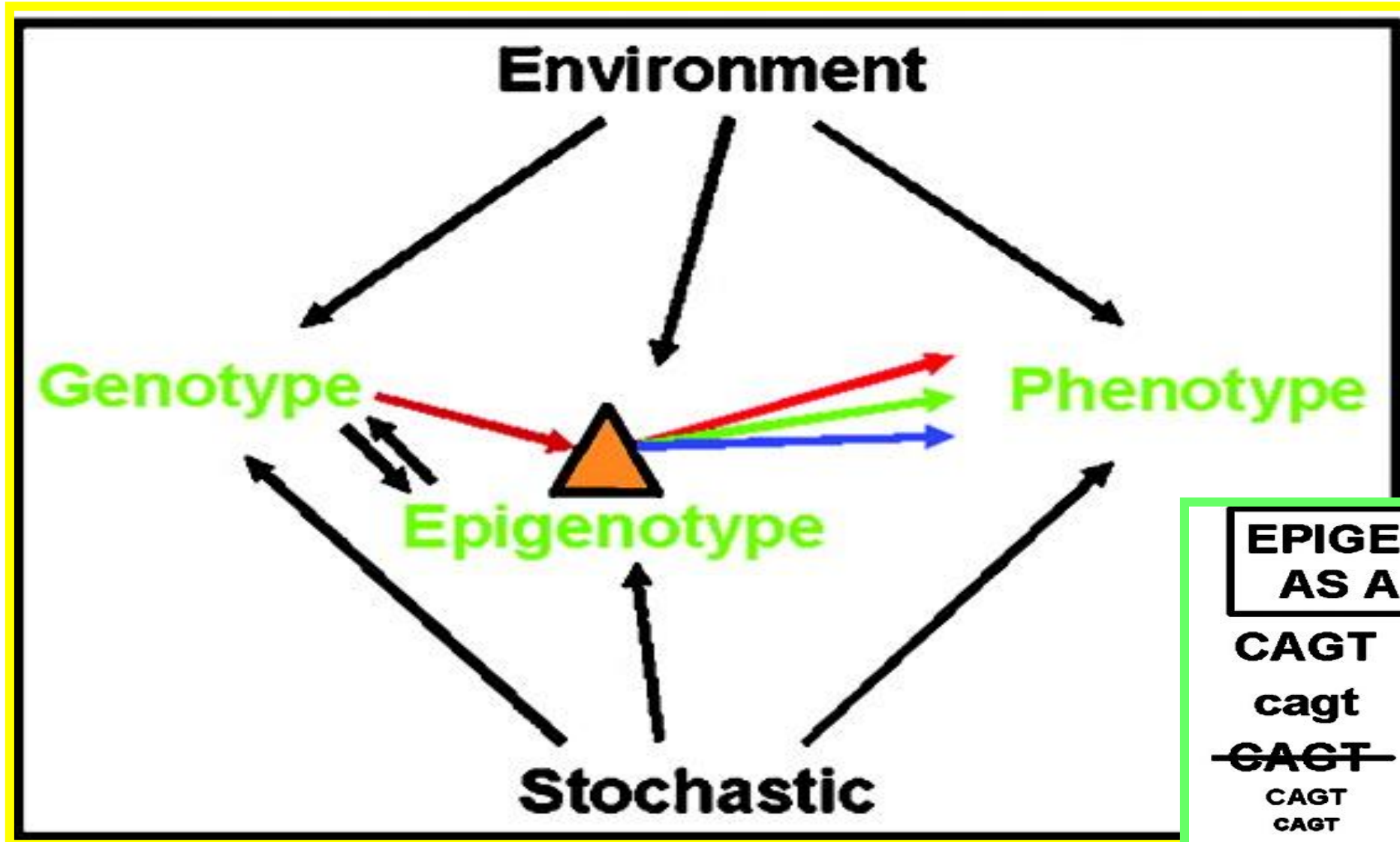


*no
expression*

*no
protein*

See Milekic et al 2015, Age-related sperm DNA methylation changes. Molecular Psychiatry

Nature and nurture can both influence genetics



EPIGENETICS AS A FONT

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Where does the pendulum swing now?

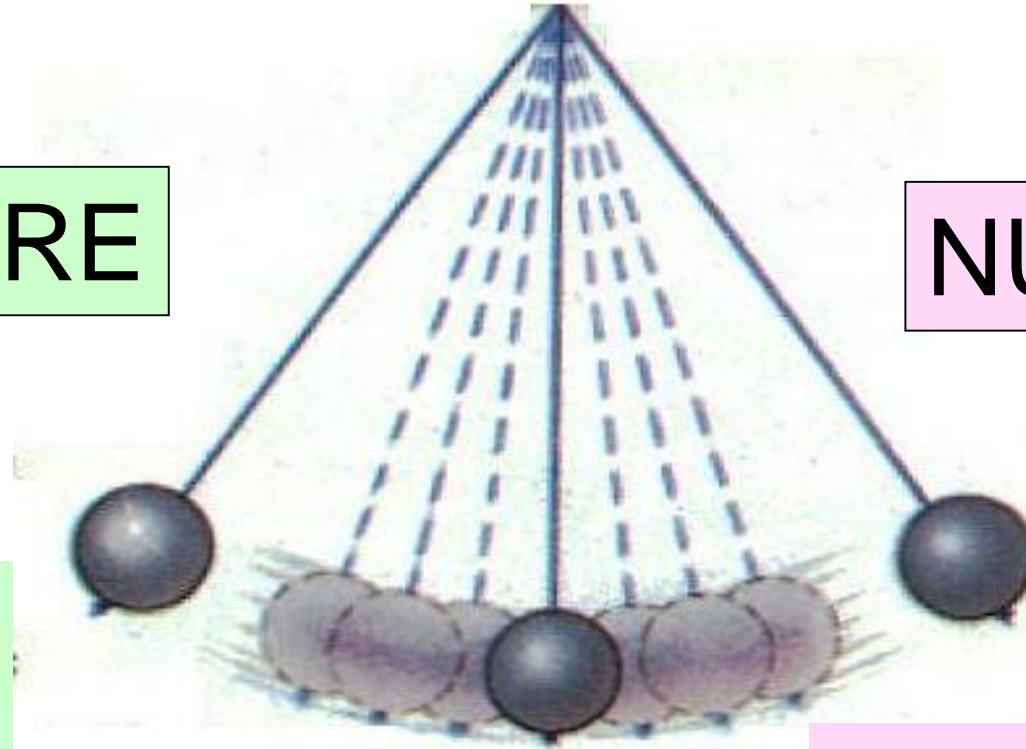
NATURE

Family history
Later paternal age
Many risk genes

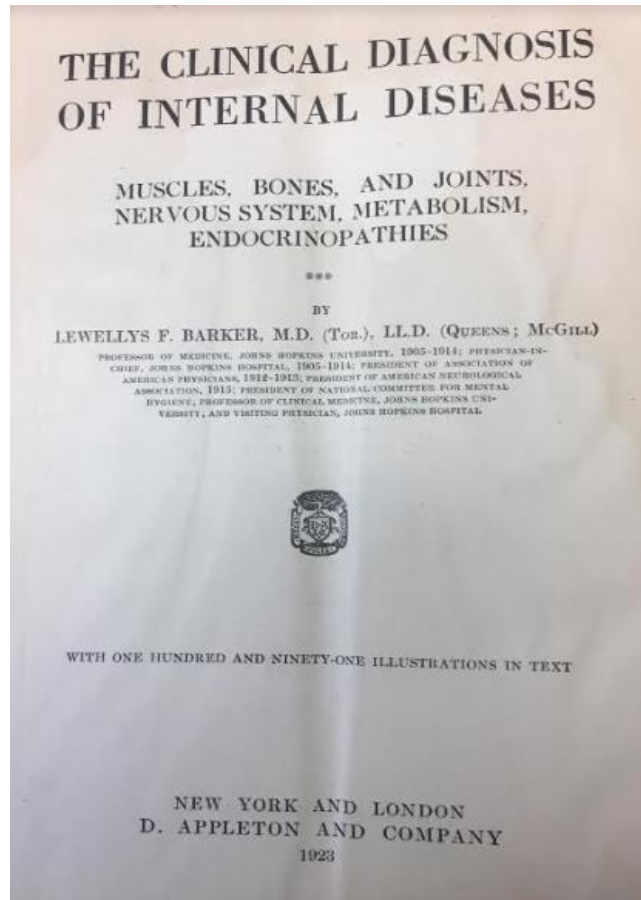
Autoimmune conditions,
inflammation,
immune activation

NURTURE

Cannabis abuse, prenatal
adversity, stress and
trauma, brain injury,
infection, urban birth,
season of birth, migration



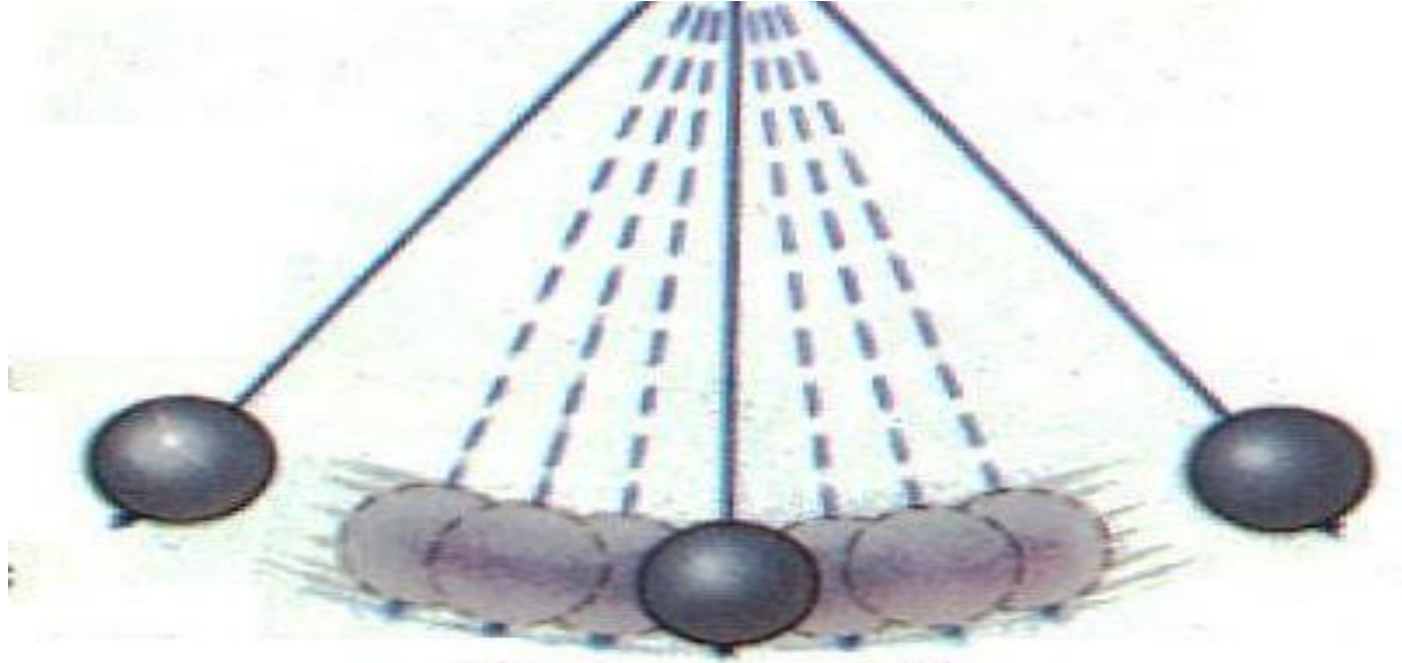
Genes and environment circa 1928!



“Most people who go insane are victims of bad heredity... unable to bear the strain of the struggle of existence (psychic shocks), or of infection or intoxication...”

“...there can be little doubt that the latter depend on (brain) structural alterations too fine for recognition by our current methods”.

Historical pendulum on origins of



Renaissance:
Demons
Sinners
Witchcraft
Punishment from god

Imbalance of 4 body humors;
Diet, environment, activity, age
Hippocrates, More ancient Greek/Roman/Egypt,
Ayurveda-until 19th c
Now relevant to the microbiome

A relatively recent expansion of psychosis

St Mary's of Bedlam:

Mental patients were first admitted in 1403.

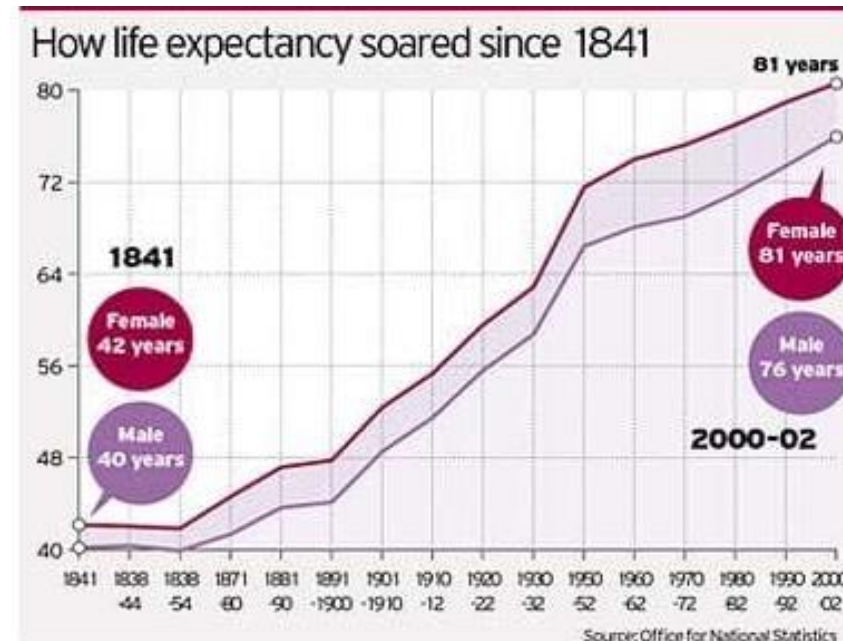
By 1547 it was totally devoted to care of insane.

In the middle ages the community was responsible for the insane



Urban life? Breakdown of the family? Infections?

Current rates of psychosis may date only to the 1790's





The notion that psychosis was caused by the psychology of mothers was readily accepted in the 1940's and became entrenched in medical and public opinion, despite rich ideas to the contrary, many of which are now evident again.



A notion that the genetic seeds of psychosis arise in fathers across the generations remains a difficult concept, even for most scientists.

CONCLUSIONS

1

Gene variants for psychiatric illnesses are common, but they are not generally specific for different conditions.

2

Those with psychosis carry more rare genes and new mutations, introduced into the population with paternal age.

3

Genes for psychosis commonly interact with environmental exposures, particularly stress and other inflammatory ones.

4

The severe chronic psychoses include some specific ailments that may yield to person-specific interventions.

“It Seems the Fertility Clock Ticks for Men, Too” New York Times, 2007