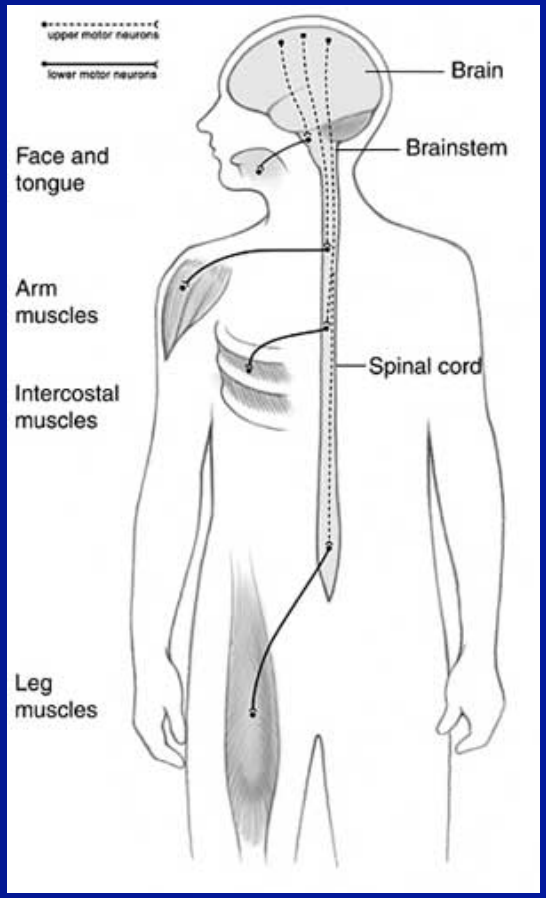
Amyotrophic lateral sclerosis (ALS)

What is amyotrophic lateral sclerosis?

- It is a progressive neurological disease that affects the control of muscle movement due to its damaging affects on motor neurons in the spinal cord and the brain



Picture from the Memory & Aging Center

Significance of the Name of this Disease

- A-myo-trophic comes from Greek
- “A” = no/negative
- “myo” = muscle
- “trophic” = nourishment
- “No Muscle Nourishment”

- Lateral = defines location of the nerve cells that signal and control the muscles

- Sclerosis = scarring and hardening in the degenerating region

From www.als.org

History

- Was discovered in 1850 by English scientist Augustus Waller who didn't know he had discovered ALS but saw nerve fibers that had extreme atrophy
- But 19 years later a French neurologist Jean-Martin Charcot took credit for it in publishing the disease in a scientific journal

Other common names for this disease:

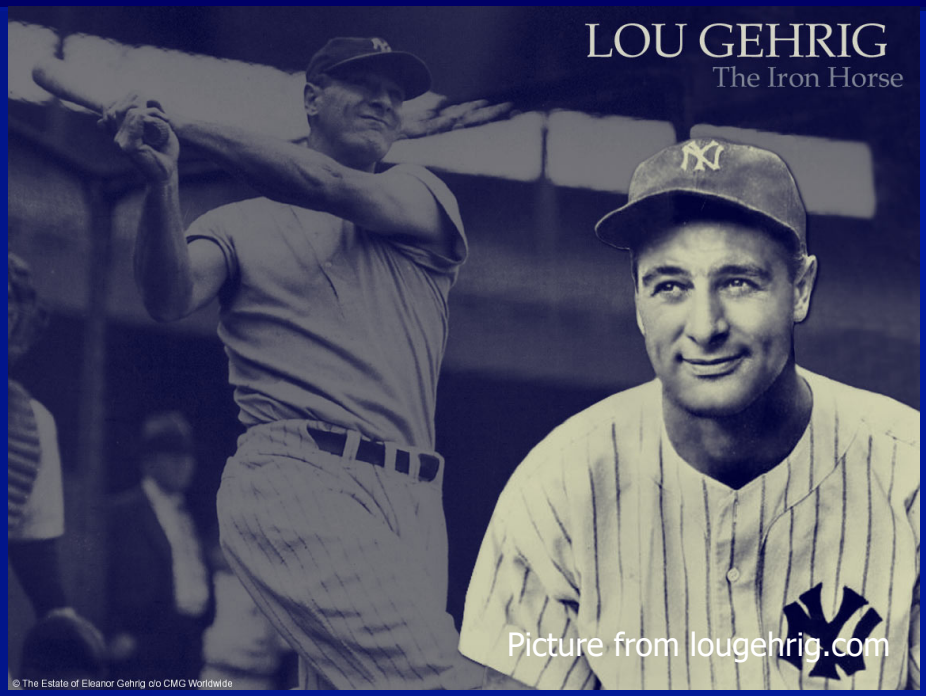
- Motor neuron disease
- Charcot's disease

Picture from the Neuromuscular website

- Lou Gehrig's disease

Who was Lou Gehrig?

- Lou Gehrig was a baseball player for the New York Yankees in the late 1920s and 1930s

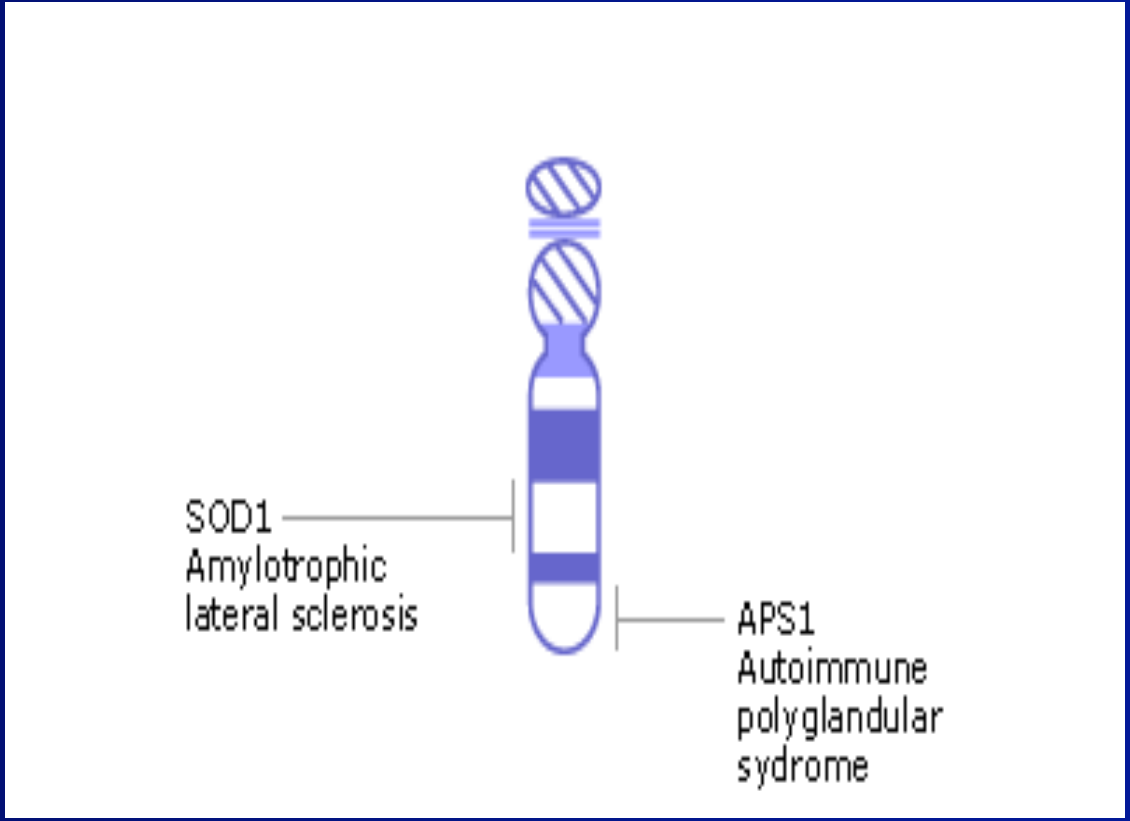



P-213-55
MILESTONES
OF THE CENTURY
Pathe News
01:38:24:12

What genes are related to ALS?

- Copper/zinc Superoxide dismutase 1 (SOD1)
- Heavy neurofilament subunit (NEFH)
- Peripherin (PRPH)
- Dynactin (DCTN1)

This disease affects SOD1 gene on chromosome 21

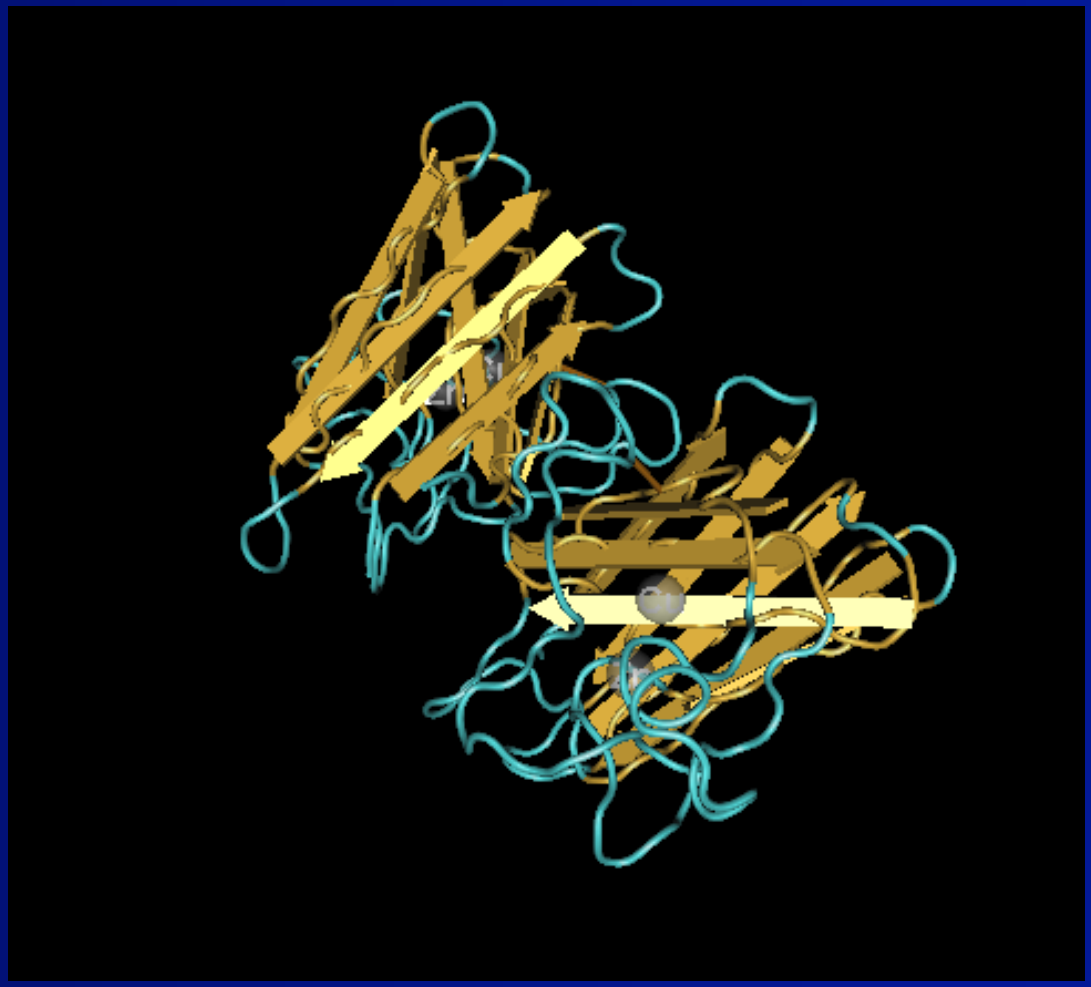


Mutations occurs at the SOD1 located on the long arm of Chromosome 21

Cu/Zn Superoxide dismutase 1 gene

- Codes for the protein Cu/Zn Superoxide dismutase 1
- Contains 5 exons and 4 introns
- mRNA is 981 base pairs long

Structure of SOD1 Protein



SOD1 protein

- Removes dangerous superoxide radicals by converting them to non-harmful substances

  $O2^- + O2^- + 2H+ \rightarrow O2 + H2O2$

- Protein contains 154 amino acids

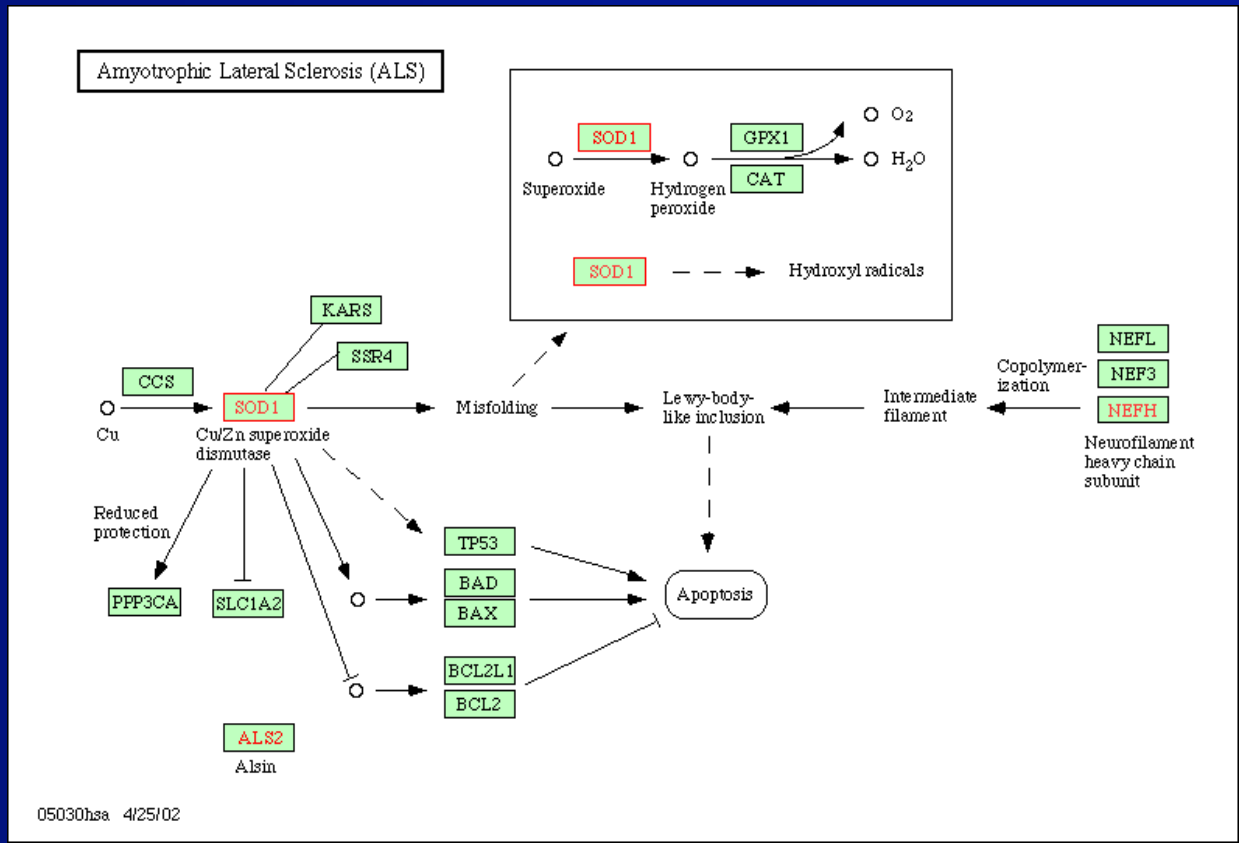
- Has one domain, SOD_Cu

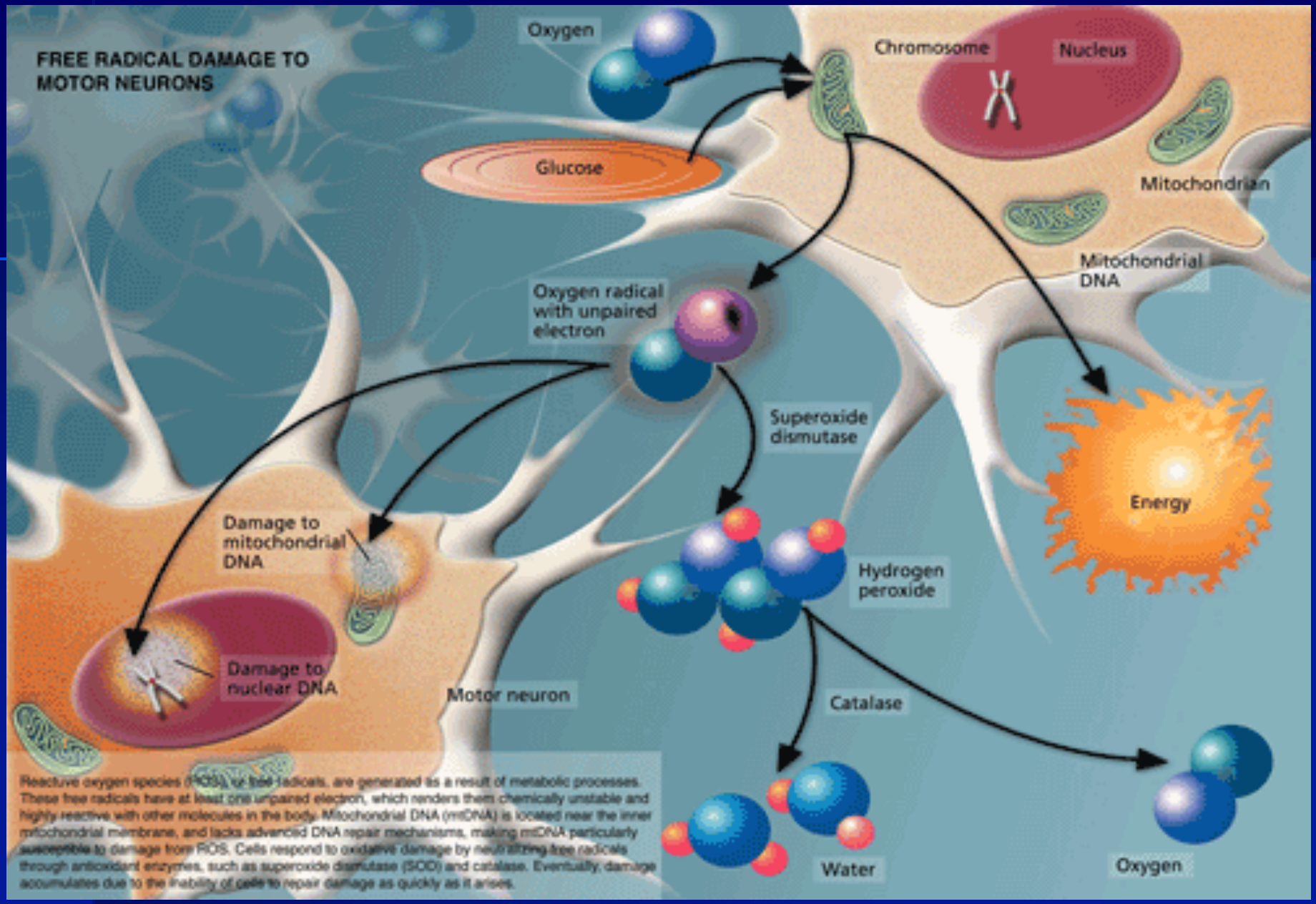
Mutations in SOD1 protein

- Several different mutations in this enzyme may all result in ALS, making the exact molecular cause of the disease difficult to ascertain

Mutations in SOD1 protein continued . . .

- Some mutations in SOD1 associated with ALS:
  - R4V
  - G93A
  - G37R
  - G16S





Picture from The ALS Society of Canada

Nature and Characteristics of ALS

- Forms:
  - Two types of ALS:
    - Sporadic – no family history
    - Familial – family history/background
  - 90% of the known cases are sporadic

ALS continued . . .

- Types of Familial
  - Autosomal dominant
  - Autosomal recessive
  - X-linked dominant
- Sporadic

Who Gets ALS?

- "According to the ALS CARE Database, 60% of the people with ALS in the database are men and 93% of patients in the database are caucasian."
- Normally occurs in people between 40 to 70 years of age
  - Also can occur in people in their 20's and 30's

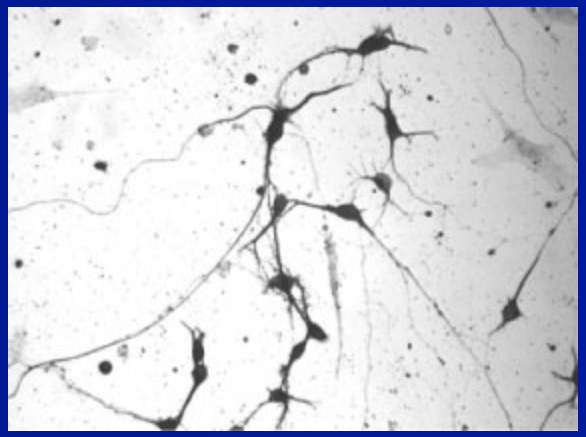
From The ALS Association

Cause of ALS

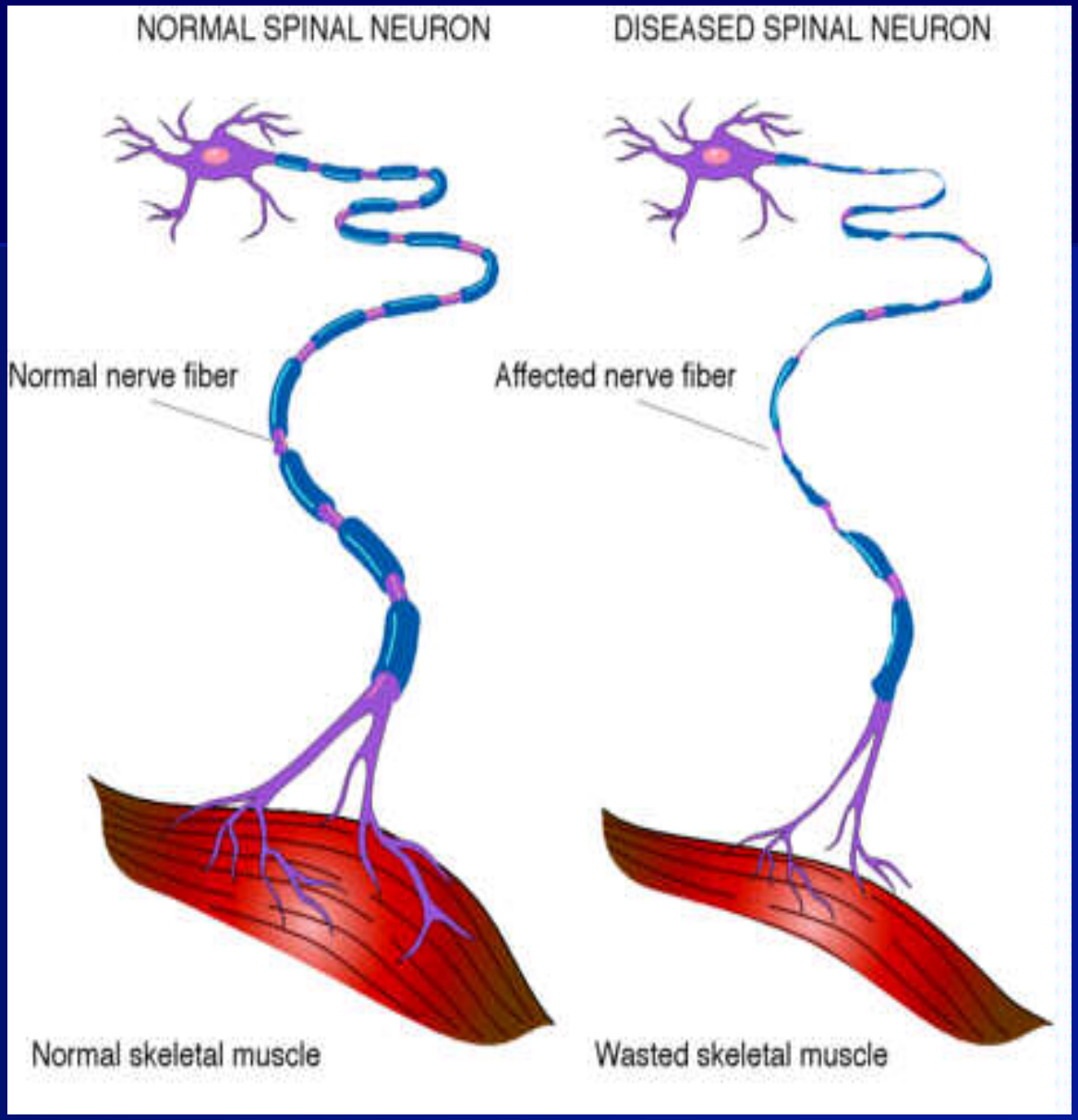
- Due to a mutation in SOD1, the superoxide radicals are not neutralized
- The radicals attack the motor neurons and degrade them
- Muscles are not able to be stimulated

Symptoms of ALS

- First signs and symptoms (frequently overlooked)
  - Twitching and cramping of muscles (especially in hands and feet)
  - Stiffness
  - Weakness (especially in hands, arms and legs)
  - Slurred speech



Picture taken from the National Institute of Aging


NORMAL SPINAL NEURON
DISEASED SPINAL NEURON
Normal nerve fiber
Affected nerve fiber
Normal skeletal muscle
Wasted skeletal muscle

Symptoms continued . . .

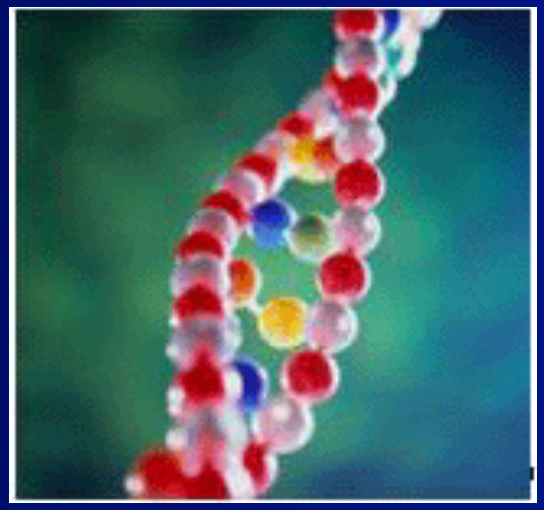
- Later signs and symptoms:
  - Difficulty chewing and swallowing
  - Shortness of breath
  - Muscle weakness due to wasting away of muscles
    - Causes muscles to become smaller
  - Respiratory failure
  - Paralysis

Picture from the ALS Association

- This picture from the Neuromuscular website shows the wasting away of a person's hands and arms

- Symptoms, or patterns of symptoms, are not the same for each ALS individual
- However, progressive muscle weakness and paralysis are universally experienced
- Since ALS attacks only motor neurons, the sense of sight, touch, hearing, taste, and smell are not affected
- Patients usually only live 3 to 5 years after they are diagnosed
- There are some cases; however, where individuals have lived 10 or more years

Diagnosing ALS



Picture from coolrunning.com

- 5,600 people in the US are diagnosed with ALS each year
- Blood tests, Urine tests, Spinal taps, x-rays, muscle or nerve biopsies, or a neurological examinations are administered

Signs and Symptoms

- Early symptoms
- Increasing muscle weakness *"especially in the arms and legs"*
- Difficulty speaking
- Trouble swallowing
- Problems with breathing
- Twitching
- Cramping of muscles (*mostly hands and feet*)

Signs and symptoms cont…

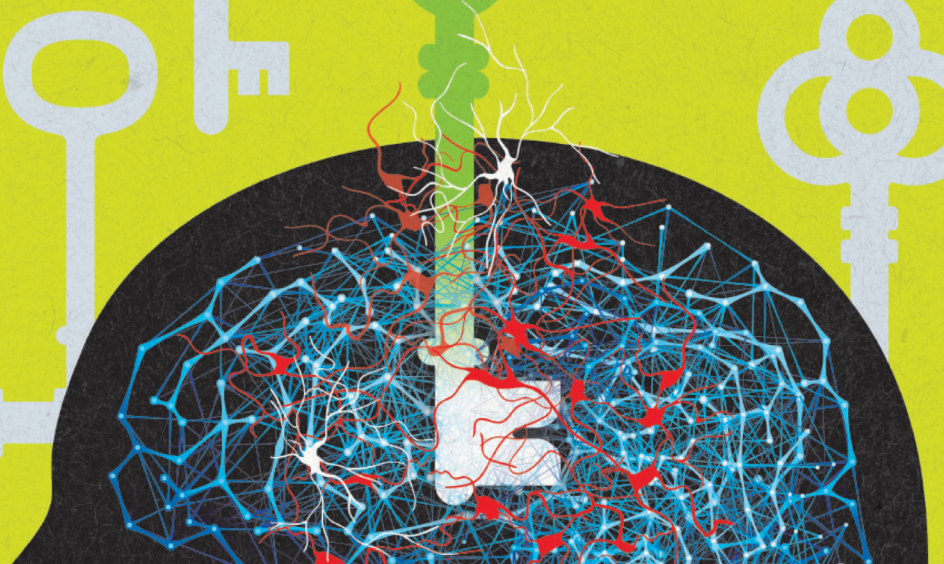
- Late Symptoms
- Extreme muscle atrophy
- Reflexes that are slow to non-existent
- Excessive drooling
- Babinski's sign: “the big toe dorsiflexes and the other toes fan out “
- Increased spasticity (muscle rigidity)
- Weight loss
- Choking
- Cardiac arrest due to respiratory arrest usually resulting in **death**


NEWS


itv NEWS
P80 HJP

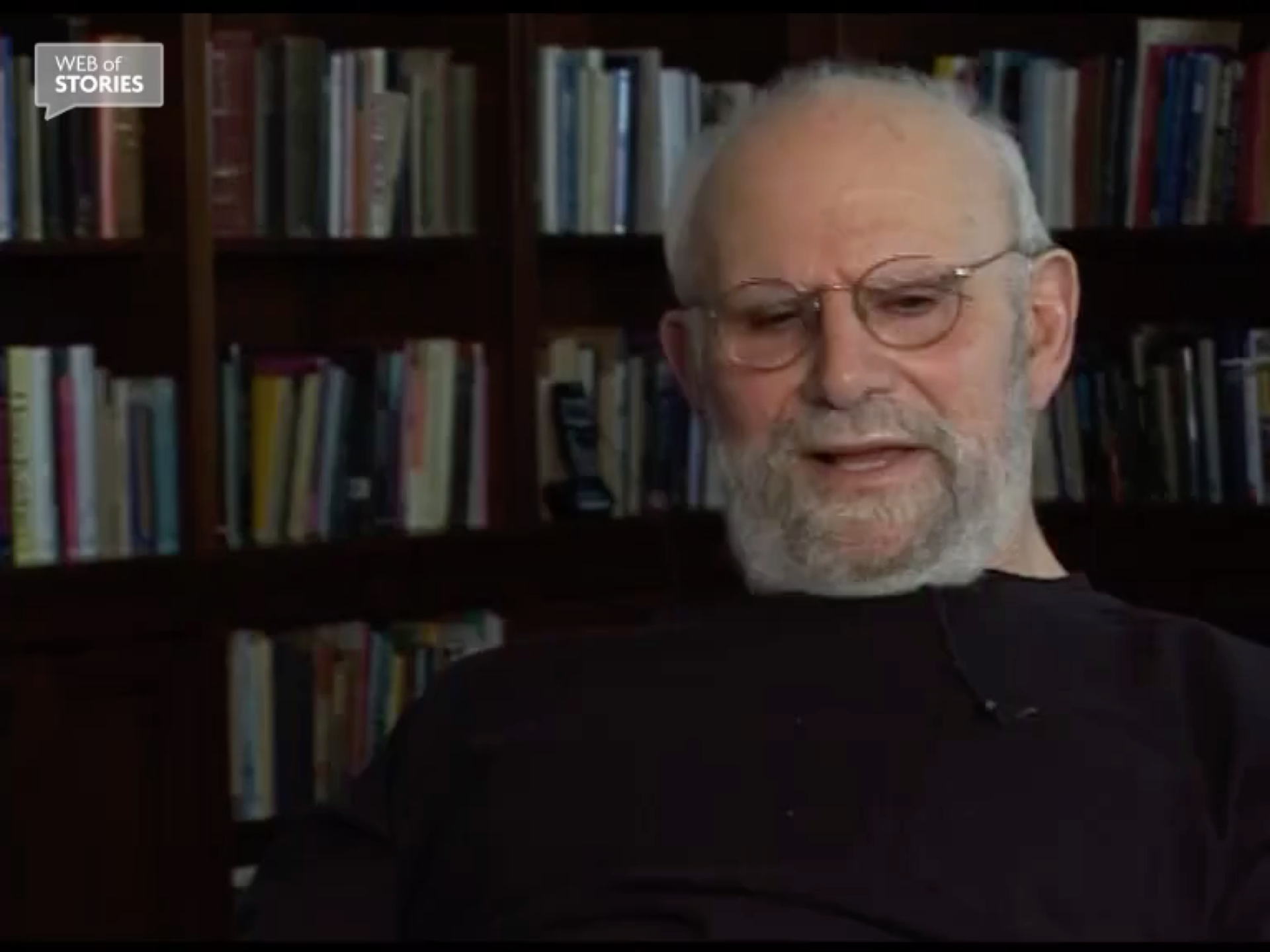
GUAM'S "SKELETON KEY" ENIGMA

By Steve Graff



ALS in GUAM
(1953)

Narrated by Leonard Kurland


WEB of
STORIES

The Umatac Cemetary (1995)

Narrated by Oliver Sacks

Timeline of Lytico-bodig

1904 **First official reports of lytico-bodig**

1940s Navy doctors and American neurologist Leonard T. Kurland, MD, begin to note the disproportionate impact of lytico-bodig disease in Umatac

1950 John Trojanowski spends a year on Guam as a young child

1954 **Lytico-bodig among Chamorro people is found to occur at 50 to 100 times the global rate of ALS and is the leading cause of death**

1955 NIH establishes a research center on Guam

1960s Consumption of cycad seeds suspected as cause of lytico-bodig

1970s Cycad hypothesis largely fades away by the end of the decade

1976 Consuming infected tissue suspected as cause of lytico-bodig

1982 Metal contamination hypothesis emerges

1983 Following decline in lytico-bodig cases, NIH closes its Guam research center

1985 **Lytico-bodig rate has declined to be near-comparable with mainland U.S. rate of ALS**

1987 Cycad hypothesis is resurrected with a controversial monkey study in *Science*

1991 Trojanowski and Lee discover tau tangles in Alzheimer's disease

1996 Trojanowski and Lee meet Schellenberg and begin to collaborate on lytico-bodig

1997 NIA awards a major grant to study lytico-bodig via interactions between aging, genetics, and environment

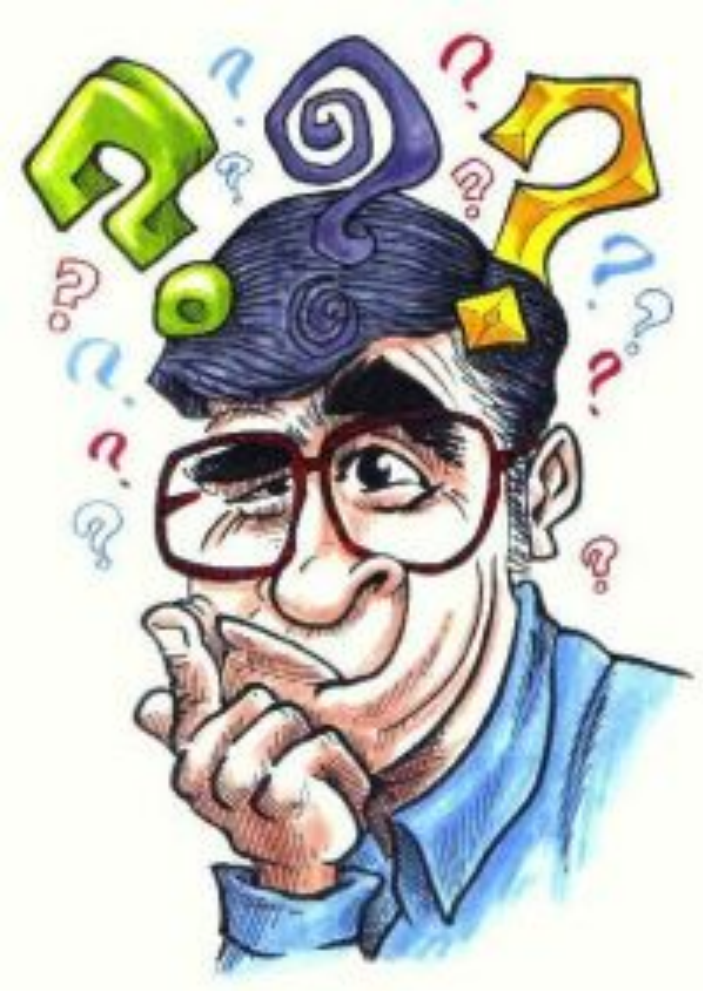
Medication for ALS

- Rilutek (brand name) / riluzole (generic) – slows progression of ALS
  - It is the only prescription drug for ALS
  - Approved in December 1995

From the MDA Publications

Picture from healthlit.org

Hypothesis



- The mechanisms that cause mutations in SOD1 that lead to ALS are unknown

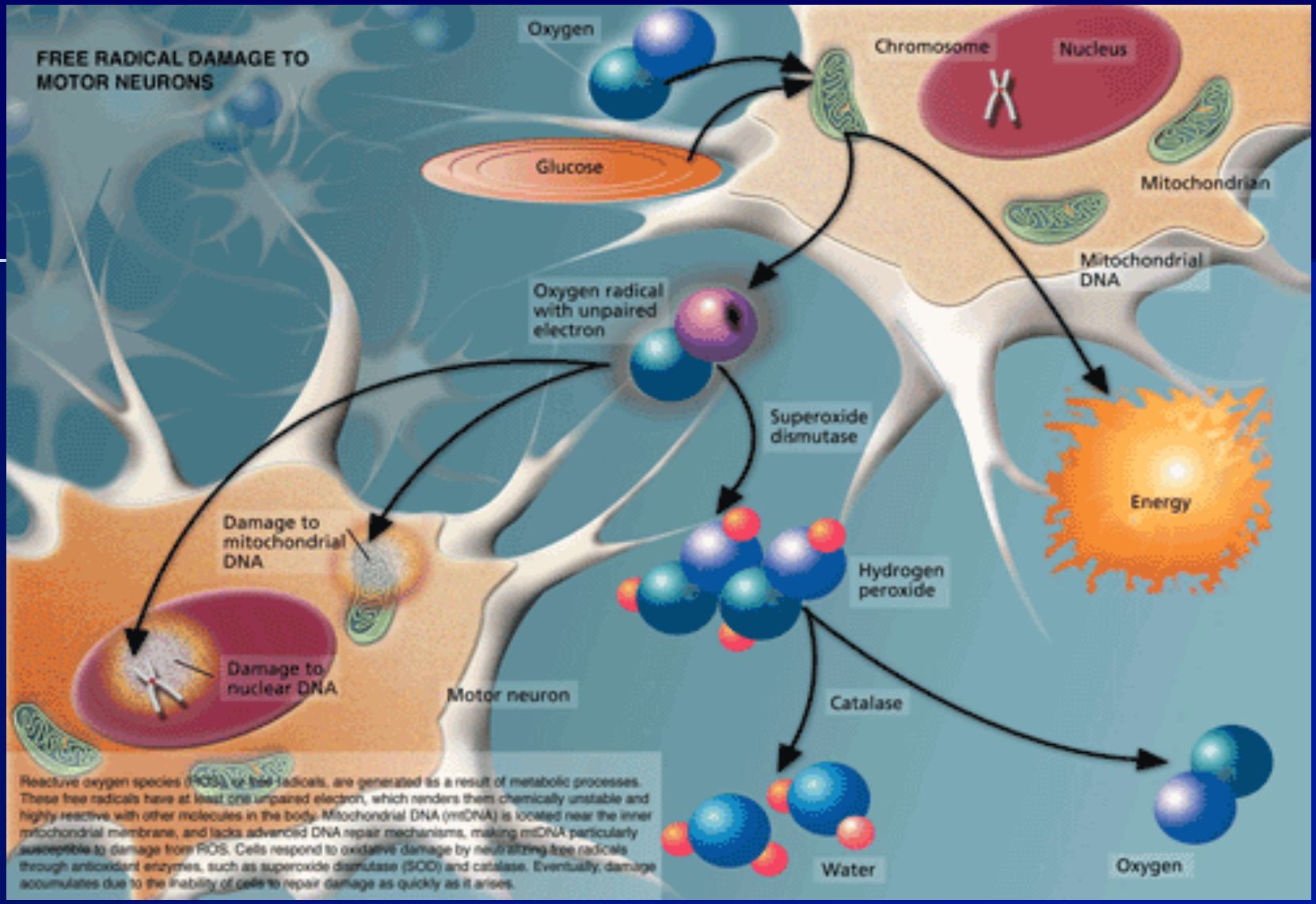
Hypothesis #1

- An increase or a decrease in the activity of SOD1 may cause ALS
  - We theorized that a decrease, rather than an increase, may be the cause of ALS.
  - Theory: decrease = produces more harmful free radicals
  - We searched NCBI in support for both an increase and a decrease in SOD1 activity

Support from NCBI

- One study conducted by Rosen found that increased levels of expression of SOD1 in mice would produce excessive levels of hydrogen peroxide

From OMIM



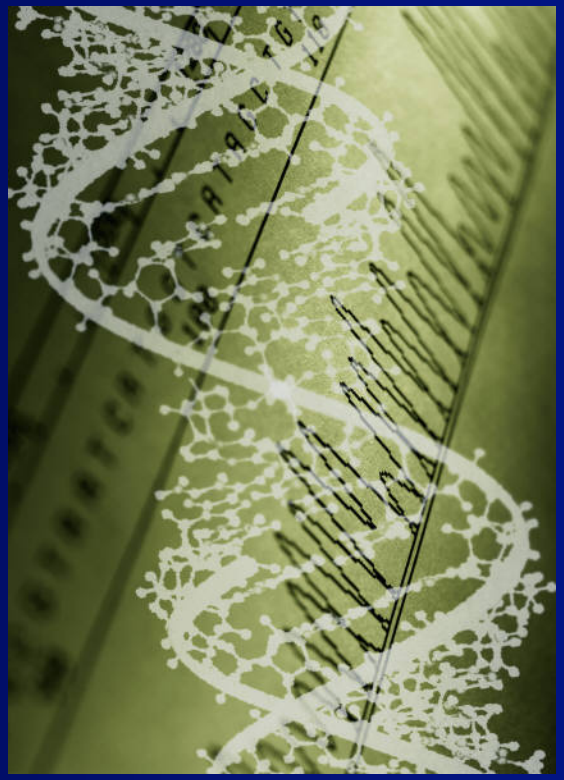
Picture from The ALS Society of Canada

Support continued . . .

- According to Kunst over-expression of normal SOD1 accelerates disease onset and progression
  - However, a decrease or increase in SOD1 activity is not sufficient to cause ALS in mice

From PubMed

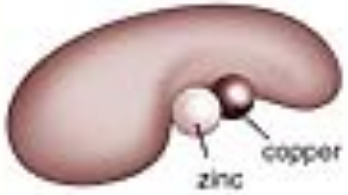
Hypothesis #2



- SOD1 may lose its ability to bind zinc (Zn), Copper (Cu), or both
  - This may cause SOD1 to lose its ability to process free radicals

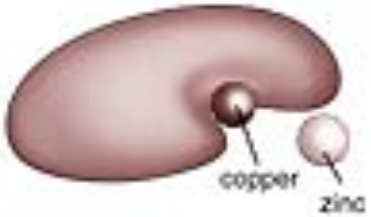
ZINC-SOD1 INTERACTION

Normal



The active SOD1 enzyme binds to both zinc and copper. → Free radicals are removed → Nerve cells are safe

SOD1-linked Familial ALS



The mutated version of SOD1 is no longer able to bind to zinc effectively. → Free radicals are produced → Nerve cells are lost

Sporadic ALS

The normal SOD1 *can* bind to zinc effectively, but there is no zinc available because it's bound to other cell proteins. → Free radicals are produced → Nerve cells are lost

From MDA Publications

Support from NCBI

- Zinc and Copper = normal
- Zinc removed = toxic
- Zinc and Copper removed = non-toxic
- Copper removed = not studied yet

- Zinc that is bound to SOD1 may stabilize the protein

From PubMed

Support continued . . .

- Zinc-deficient SOD1 produces more free radicals than it destroys
- SOD1 mutant can not bind zinc as strongly as normal SOD1